The Nervous System

PART XXVII

Chapter 590

Neurologic Evaluation

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HISTORY

A detailed history is the cornerstone of any neurologic assessment. Although parents may be the primary informants, most children older than 3-4 yr are capable of contributing to their history and should be questioned directly.

The history should begin with the chief complaint, as well as a determination of the complaint's relative significance within the context of normal development (see Chapters 9-16). The latter step is critical because a 13 mo old who cannot walk may be perfectly normal, whereas a 4 yr old who cannot walk might have a serious neurologic condition.

Next, the history of present illness should provide a chronological outline of the patient's symptoms, with attention paid to location, quality, intensity, duration, associated features, and alleviating or exacerbating factors. It is essential to perform a review of systems, because abnormalities of the central nervous system (CNS) often manifest with vague, nonfocal symptoms that may be misattributed to other organ systems (e.g., vomiting, constipation, urinary incontinence). A detailed history might suggest that vomiting is as a result of increased intracranial pressure (ICP) rather than gastritis or that constipation and urinary incontinence are caused by a spinal cord tumor rather than behavioral stool withholding. In addition, a systemic illness may produce CNS manifestations such as lupus erythematosus (seizures, psychosis, demyelination) or mitochondrial disorders (developmental delay, strokes, hypotonia).

Following the chief complaint and history of present illness, the physician should obtain a complete birth history, particularly if a congenital disorder is suspected. The birth history should begin with a review of the pregnancy, including specific questions about common complications, such as pregnancy-induced hypertension, preeclampsia, gestational diabetes, vaginal bleeding, infections, and falls. It is important to quantify any cigarette, alcohol, or drug (prescription, herbal, illicit) use. Inquiring about fetal movement might provide clues to an underlying diagnosis, because decreased or absent fetal activity can be associated with chromosomal anomalies and CNS or neuromuscular disorders. Finally, any abnormal ultrasound or amniocentesis results should be noted.

A labor history should address the gestational age at delivery and mode of delivery (spontaneous vaginal, vacuum- or forceps-assisted, cesarean section) and should comment on the presence or absence of fetal distress. If delivery was by cesarean section, it is essential to record the indication for surgery.

The birth weight, length, and head circumference provide useful information about the duration of a given problem, as well as insights into the uterine environment. Parents can usually provide a reliable history of their child's postnatal course; however, if the patient was resuscitated or had a complicated hospital stay, it is often helpful to obtain the hospital records. The physician should inquire about the infant's general well-being, feeding and sleeping patterns, activity level, and the nature of the infant's cry. If the infant had jaundice, it is important to determine both the degree of jaundice and how it was managed. Historical markers of neurologic dysfunction include full-term infants who are unable to breathe spontaneously; have poor, uncoordinated sucks; need an inordinate amount of time to feed; or require gavage feeding. Again, it is important to consider the developmental context, because all of these issues would be expected in premature infants, particularly those with a very-low birthweight. Double-checking the state newborn screening results may provide a clue to abnormal neurologic manifestation in an infant.

The most important component of a neurologic history is the **developmental assessment** (see Chapters 9-14 and 16). Careful evaluation of a child's social, cognitive, language, fine motor, and gross motor skills is required to distinguish normal development from either isolated or global (i.e., in 2 or more domains) developmental delay. An abnormality in development from birth suggests an intrauterine or perinatal cause, but a loss of skills **(regression)** over time strongly suggests an underlying degenerative disease of the CNS, such as an inborn error of metabolism. The ability of parents to recall the precise timing of their child's developmental milestones is extremely variable. It is often helpful to request old photographs of the child or to review the baby book, where the milestones may have been dutifully recorded. In general, parents are aware when their child has a developmental problem, and the physician should show appropriate concern. Table 590-1 outlines the upper limits of normal for attaining specific developmental milestones. Chapter 16 includes a comprehensive review of developmental screening tests and their interpretation.

Family history is extremely important in the neurologic evaluation of a child. Most parents are extremely cooperative in securing medical information about family members, particularly if it might have relevance for their child. The history should document the age and history of neurologic disease, including developmental delay, epilepsy, migraine, stroke, and inherited disorders, for all 1st- and 2nd-degree relatives. It is important to inquire directly about miscarriages or fetal deaths in utero and to document the sex of the embryo or fetus, as well as the gestational age at the time of demise. When available, the results of postmortem examinations should be obtained, as they can have a direct bearing on the patient's condition. The parents should be questioned about their ethnic backgrounds, because some genetic disorders occur more commonly within specific populations (e.g., Tay-Sachs disease in the Ashkenazi Jewish population). They should also be asked if there is any chance that they could be related to each other, because the incidence of metabolic and degenerative disorders of the CNS is increased significantly in children of **consanguineous** marriages.

The social history should detail the child's current living environment, as well as the child's relationship with other family members. It is important to inquire about recent stressors, such as divorce, remarriage, birth of a sibling, or death of a loved one, because they can affect the child's behavior. If the child is in daycare or school, one should document the child's academic and social performance, paying particular attention to any abrupt changes. Academic performance can be assessed by asking about the child's latest report card, and peer relationships can be evaluated by having the child name his or her "best friends." Any child who is unable to name at least 2 or 3 playmates might have abnormal social development. In some cases, discussions with the daycare worker or teacher provide useful ancillary data.

NEUROLOGIC EXAMINATION

The neurologic examination begins at the outset of the interview. Indirect observation of the child's appearance and movements can yield valuable information about the presence of an underlying disorder. For instance, it may be obvious that the child has dysmorphic facies, an

Table 590-1 Screening Scheme for Developmental Delay: Upper Range

AGE (mo)	GROSS MOTOR	FINE MOTOR	SOCIAL SKILLS	LANGUAGE
3	Supports weight on forearms	Opens hands spontaneously	Smiles appropriately	Coos, laughs
6	Sits momentarily	Transfers objects	Shows likes and dislikes	Babbles
9	Pulls to stand	Pincer grasp	Plays pat-a-cake, peek-a-boo	Imitates sounds
12	Walks with 1 hand held	Releases an object on command	Comes when called	1-2 meaningful words
18	Walks upstairs with assistance	Feeds from a spoon	Mimics actions of others	At least 6 words
24	Runs	Builds a tower of 6 blocks	Plays with others	2-3–word sentences

unusual posture, or an abnormality of motor function manifested by a hemiparesis or gait disturbance. The child's behavior while playing and interacting with his or her parents may also be telling. A normal child usually plays independently early in the visit, but then engages in the interview process. A child with attention-deficit/hyperactivity disorder might display impulsive behavior in the examining room, and a child with neurologic impairment might exhibit complete lack of awareness of the environment. Finally, note should be made of any unusual odors about the patient, because some metabolic disorders produce characteristic scents (e.g., the "musty" smell of phenylketonuria or the "sweaty feet" smell of isovaleric acidemia). If such an odor is present, it is important to determine whether it is persistent or transient, occurring only with illnesses.

The examination should be conducted in a nonthreatening, child-friendly setting. The child should be allowed to sit where the child is most comfortable, whether it be on a parent's lap or on the floor of the examination room. The physician should approach the child slowly, reserving any invasive or painful tests (e.g., measurement of head circumference, gag reflex) for the end of the examination. In the end, the more that the examination seems like a game, the more the child will cooperate. Because the neurologic examination of an infant requires a somewhat modified approach from that of an older child, the 2 groups are considered separately (see Chapters 9, 10, and 94 vs Chapters 11-14).

Mental Status

Age aside, the neurologic examination should include an assessment of the patient's mental status in terms of both level of arousal and interaction with the environment. Premature infants born at <28 wk of gestation do not have consistent periods of alertness, whereas slightly older infants arouse from sleep with gentle physical stimulation. Sleep–wake patterns are well developed at term. Because the level of alertness of a neonate depends on many factors, including the time of the last feeding, room temperature, and gestational age, serial examinations are critical when evaluating for changes in neurologic function. Older children's mental status can be assessed by watching them play. Having them tell a story, draw a picture, or complete a puzzle can also be helpful in assessing cognitive function. Memory can be evaluated informally as patients recount their personal information, as well as more formally by asking them to register and recall 3 objects or perform a digit span.

Head

Correct measurement of the **head circumference** is important. It should be performed at every visit for patients younger than 3 yr and should be recorded on a suitable head growth chart. To measure, a nondistensible plastic measuring tape is placed over the mid-forehead and extended circumferentially to include the most prominent portion of the occiput. If the patient's head circumference is abnormal, it is important to document the head circumferences of the parents and siblings. Errors in the measurement of a newborn skull are common owing to scalp edema, overriding sutures, and the presence of cephalohematomas. The average rate of head growth in a healthy premature infant is 0.5 cm in the 1st 2 wk, 0.75 cm in the 3rd wk, and 1.0 cm in the 4th wk and every week thereafter until the 40th wk of development. The head circumference of an average term infant measures 34-35 cm at birth, 44 cm at 6 mo, and 47 cm at 1 yr of age (see Chapters 9 and 10).



Figure 590-1 Congenital hydrocephalus. Note the enlarged cranium and prominent scalp veins.

If the brain is not growing, the skull will not grow; therefore, a small head frequently reflects a small brain, or **microcephaly**. Conversely, a large head may be associated with a large brain, or **macrocephaly**, which is most commonly familial but may be from a disturbance of growth, neurocutaneous disorder (e.g., neurofibromatosis), chromosomal defect (e.g., Klinefelter syndrome), or storage disorder. Alternatively, the head size may be increased secondary to hydrocephalus (Fig. 590-1) or chronic subdural hemorrhages. In the latter case, the skull tends to assume a square or box-like shape, because the long-standing presence of fluid in the subdural space causes enlargement of the middle fossa.

The shape of the head should be documented carefully. Plagiocephaly, or flattening of the skull, can be seen in normal infants but may be particularly prominent in hypotonic or weak infants, who are less mobile. A variety of abnormal head shapes can be seen when cranial sutures fuse prematurely, as in the various forms of inherited **craniosynostosis** (see Chapter 591.12).

An infant has 2 **fontanels** at birth: a diamond-shaped anterior fontanel at the junction of the frontal and parietal bones that is open at birth, and a triangular posterior fontanel at the junction of the parietal and occipital bones that can admit the tip of a finger or may be closed at birth. If the posterior fontanel is open at birth, it should close over the ensuing 6-8 wk; its persistence suggests underlying hydrocephalus or congenital hypothyroidism. The anterior fontanel varies greatly in size, but it usually measures approximately 2 × 2 cm. The average time of closure is 18 mo, but the fontanel can close normally as early as 9 mo. A very small or absent anterior fontanel at birth might indicate craniosynostosis or microcephaly, whereas a very large fontanel can

signify a variety of problems. The fontanel is normally slightly depressed and pulsatile and is best evaluated by holding the infant upright while the infant is asleep or feeding. A bulging fontanel is a potential indicator of increased ICP, but vigorous crying can cause a protuberant fontanel in a normal infant.

Inspection of the head should include observation of the venous pattern, because increased ICP and thrombosis of the superior sagittal sinus can produce marked venous distention. Dysmorphic facial features can indicate a neurodevelopmental aberration. Likewise, cutaneous abnormalities, such as cutis aplasia or abnormal hair whorls, can suggest an underlying brain malformation or genetic disorder.

Palpation of a newborn's skull characteristically reveals **molding** of the skull accompanied by **overriding sutures**—a result of the pressures exerted on the skull during its descent through the pelvis. Marked overriding of the sutures beyond the early neonatal period is cause for alarm, because it suggests an underlying brain abnormality. Palpation additionally might reveal bony bridges between sutures **(craniosynostosis),** cranial defects, or, in premature infants, softening of the parietal bones **(craniotabes).**

Auscultation of the skull is an important adjunct to the neurologic examination. **Cranial bruits** may be noted over the anterior fontanel, temporal region, or orbits, and are best heard using the diaphragm of the stethoscope. Soft symmetric bruits may be discovered in normal children younger than 4 yr of age or in association with a febrile illness. Demonstration of a loud or localized bruit is usually significant and warrants further investigation, because they may be associated with severe anemia, increased ICP, or arteriovenous malformations of the middle cerebral artery or vein of Galen. It is important to exclude murmurs arising from the heart or great vessels, because they may be transmitted to the cranium.

Cranial Nerves

Olfactory Nerve (Cranial Nerve I)

Anosmia, loss of smell, most commonly occurs as a transient abnormality in association with an upper respiratory tract infection or allergies. Permanent causes of anosmia include head trauma with damage to the ethmoid bone or shearing of the olfactory nerve fibers as they cross the cribriform plate, tumors of the frontal lobe, intranasal drug use, and exposure to toxins (acrylates, methacrylates, cadmium). Occasionally, a child who recovers from purulent meningitis or develops hydrocephalus has a diminished sense of smell. Rarely, anosmia is congenital, in which case it can occur as an isolated deficit or as part of Kallmann syndrome, a familial disorder characterized by hypogonadotropic hypogonadism and congenital anosmia. Although not a routine component of the examination, smell can be tested reliably as early as the 32nd wk of gestation by presenting a stimulus and observing for an alerting response, withdrawal, or both. Care should be taken to use appropriate stimuli, such as coffee or peppermint, as opposed to strongly aromatic substances (e.g., ammonia inhalants) that stimulate the trigeminal nerve. Each nostril should be tested individually by pinching shut the opposite side.

Optic Nerve (Cranial Nerve II)

Assessment of the optic disc and retina is a critical component of the neurologic examination. Although the retina is best visualized by dilating the pupil, most physicians do not have ready access to mydriatic agents at the bedside; therefore, it may be necessary to consult an ophthalmologist in some cases. Mydriatics should not be administered to patients whose pupillary responses are being followed as a marker for impending herniation or to patients with cataracts. When mydriatics are used, both eyes should be dilated, because unilateral papillary fixation and dilation can cause confusion and worry in later examiners unaware of the pharmacologic intervention. Examination of an infant's retina may be facilitated by providing a nipple or soother and by turning the head to one side. The physician gently strokes the patient to maintain arousal, while examining the closer eye. An older child should be placed in the parent's lap and should be distracted by bright objects or toys. The color of the optic nerve is salmon-pink in a child but may be gray-white in a newborn, particularly if the newborn has fair coloring. This normal finding can cause confusion and can lead to the improper diagnosis of optic atrophy.

Disc edema refers to swelling of the optic disc, and **papilledema** specifically refers to swelling that is secondary to increased ICP. Papilledema rarely occurs in infancy because the skull sutures can separate to accommodate the expanding brain. In older children, papilledema may be graded according to the Frisen scale (Fig. 590-2). Disc edema must be differentiated from **papillitis**, or inflammation of the optic nerve. Both conditions manifest with enlargement of the blind spot, but visual acuity and color vision tend to be spared in early papilledema in contrast to what occurs in optic neuritis.

Retinal hemorrhages occur in 30-40% of all full-term newborn infants. The hemorrhages are more common after vaginal delivery than after Cesarean section and are not associated with birth injury or with neurologic complications. They disappear spontaneously by 1-2 wk of age. The presence of retinal hemorrhages beyond the early neonatal period should raise a concern for nonaccidental trauma.

Vision

At 28 wk of corrected gestational age, a premature infant blinks in response to a bright light, and at 32 wk, the infant maintains eye closure until the light source is removed. A normal 37 wk infant turns the head and eyes toward a soft light, and a term infant is able to fix on and follow a target, such as the examiner's face. **Optokinetic nystagmus** (OKN), which is conjugate nystagmus that occurs during attempted fixation on a series of rapidly moving objects, can also be used as a crude assessment of the visual system in infants. OKN is elicited by moving an OKN tape—usually a strip of material with alternating 2-inch black and white strips—across the patient's visual field. Although OKN responses can be tested monocularly in neonates, they do not become symmetric until 4-6 mo of age.

Visual fields can be tested in an infant or young child by advancing a brightly colored object from behind the patient's head into the peripheral visual field and noting when the patient first looks at the object. Suspension of the object by a string prevents the patient from focusing on the examiner's hand and arm. The examiner should be certain that the patient is responding to seeing, not hearing, the object.

Visual acuity in term infants approximates 20/150 and reaches the adult level of 20/20 by about 6 mo of age. Children who are too young to read the standard letters on a Snellen eye chart may learn the "E game," which entails pointing to indicate the direction that the E is facing. Children as young as 2.5-3 yr of age can identify the objects on a pediatric eye chart (Allen chart) at a distance of 15-20 ft.

The pupil reacts to light by 29-32 wk of corrected gestational age; however, the pupillary response is often difficult to evaluate, because premature infants resist eye opening and have poorly pigmented irises. Pupillary size, symmetry, and reactivity may be affected by drugs, space-occupying brain lesions, metabolic disorders, and abnormalities of the optic nerves and midbrain. A small pupil may be seen as part of the **Horner syndrome**—characterized by ipsilateral **ptosis** (droopy eyelid), **miosis** (constricted pupil), and **anhidrosis** (lack of sweating) of the face. Horner syndrome may be congenital or may be caused by a lesion of the sympathetic pathway in the hypothalamus, brainstem, cervical spinal cord, or sympathetic plexus. Localization of the lesion within the sympathetic nervous system may be obvious given the other signs present or may be uncertain. In the latter case, serial testing with cocaine drops followed by hydroxyamphetamine drops may be helpful.

During the examination of the pupil, any abnormalities of the iris should also be noted (e.g., heterochromia, Brushfield spots). The physician should also assess the posterior segment of the eye using the **red reflex** test, which is performed in a darkened room using a direct ophthalmoscope held close to the examiner's eye and 12-18 inches from the infant's eyes. If the posterior segment of the eye is normal, the examiner should see symmetric reddish-pink retinal reflections. The absence of any red reflex or the presence of a blunted reflex, white reflex (**leukocoria**), or red reflex with dark spots all signal pathology and should prompt referral to an ophthalmologist.

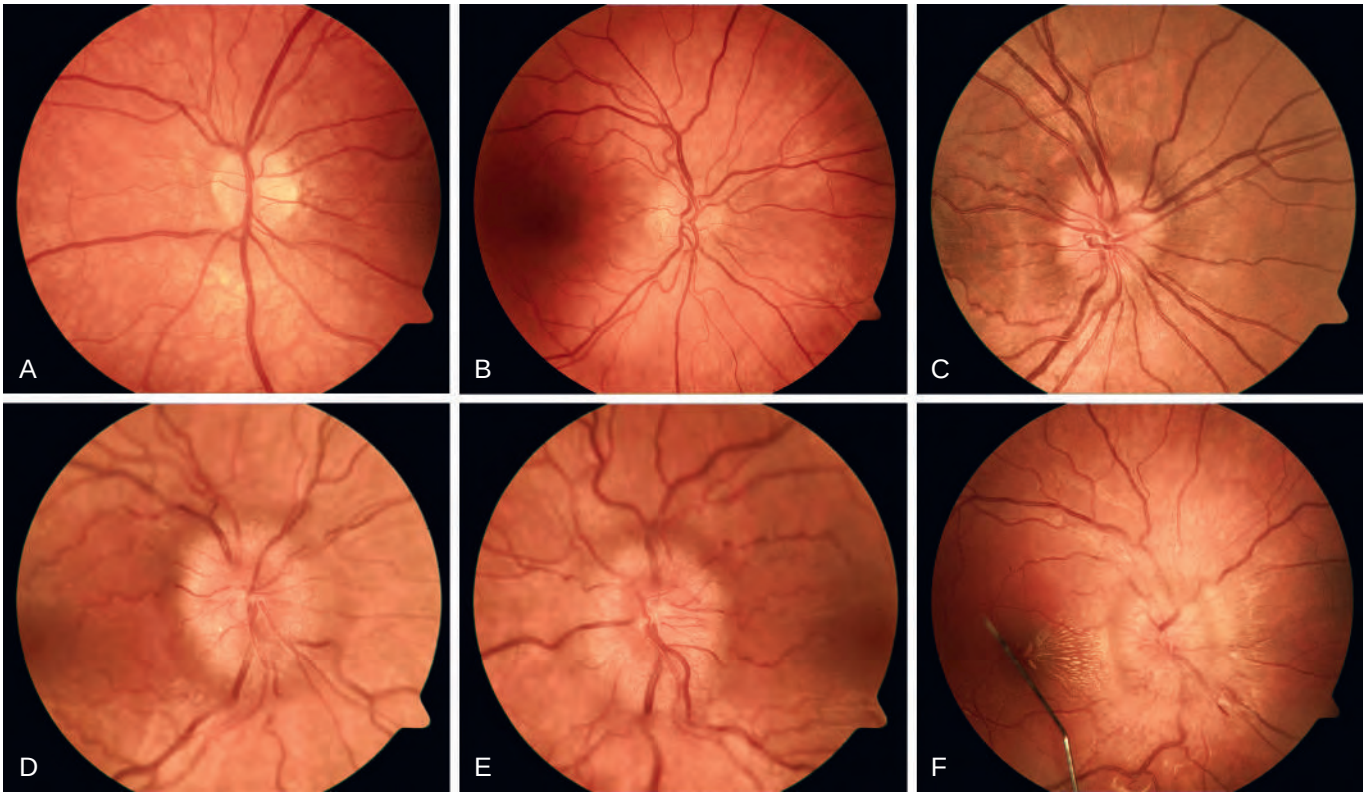


Figure 590-2 Stages of papilledema (Frisen scale). **A,** Stage 0: Normal optic disc. **B,** Stage 1: Very early papilledema with obscuration of the nasal border of the disc only, without elevation of the disc borders. **C,** Stage 2: Early papilledema showing obscuration of all borders, elevation of the nasal border, and a complete peripapillary halo. **D,** Stage 3: Moderate papilledema with elevation of all borders, increased diameter of the optic nerve head, obscuration of vessels at the disc margin, and a peripapillary halo with finger-like extensions. **E,** Stage 4: Marked papilledema characterized by elevation of the entire nerve head and total obscuration a segment of a major blood vessel on the disc. **F,** Stage 5: Severe papilledema with obscuration of all vessels and obliteration of the optic cup. Note also the nerve fiber layer hemorrhages and macular exudate. (***A-C*** *courtesy Dr. Deborah Friedman;* ***D-F*** *courtesy Flaum Eye Institute, University of Rochester.)*

Oculomotor (Cranial Nerve III), Trochlear (Cranial Nerve IV), and Abducens Nerves (Cranial Nerve VI)

The globe is moved by 6 extraocular muscles, which are innervated by the oculomotor, trochlear, and abducens nerves. These muscles and nerves can be assessed by having the patient follow an interesting toy or the examiner's finger in the 6 cardinal directions of gaze. The physician observes the range and nature (conjugate vs dysconjugate, smooth vs choppy or saccadic) of the eye movements, particularly noting the presence and direction of any abnormal eye movements. Premature infants older than 25 wk of gestational age and comatose patients can be evaluated using the oculocephalic (doll's eye) maneuver, in which the patient's head is quickly rotated to evoke reflex eye movements. If the brainstem is intact, rotating the patient's head to the right causes the eyes to move to the left and vice versa. Similarly, rapid flexion and extension of the head elicits vertical eye movement.

Disconjugate gaze can result from extraocular muscle weakness; cranial nerve (CN) III, IV, or VI palsies; or brainstem lesions that disrupt the medial longitudinal fasciculus. Infants who are younger than 2 mo old can have slightly disconjugate gaze at rest, with 1 eye horizontally displaced from the other by 1 or 2 mm **(strabismus)**. Vertical displacement of the eyes requires investigation, as it can indicate trochlear nerve (CN IV) palsy or **skew deviation** (supranuclear ocular malalignment that is often associated with lesions of the posterior fossa). Strabismus is discussed further in Chapter 623.

The oculomotor nerve innervates the superior, inferior, and medial recti, as well as the inferior oblique and the levator palpebrae superioris muscles. Complete paralysis of the oculomotor nerve causes ptosis, dilation of the pupil, displacement of the eye outward and downward, and impairment of adduction and elevation. The trochlear nerve supplies the superior oblique muscle, which depresses and intorts the globe during activities such as reading and walking downstairs. Patients with an isolated paralysis of the trochlear nerve often have a compensatory head tilt away from the affected side, which helps to alleviate their diplopia. The abducens nerve innervates the lateral rectus muscle; its paralysis causes medial deviation of the eye with an inability to abduct beyond the midline. Patients with increased ICP often respond positively when questioned about double vision (**diplopia**) and exhibit incomplete abduction of the eyes on lateral gaze as a result of partial VIth nerve palsies. This false-localizing sign occurs because CN VI has a long intracranial course, making it particularly susceptible to being stretched. **Internuclear ophthalmoplegia,** caused by a lesion in the medial longitudinal fasciculus of the brainstem, that functionally serves conjugate gaze by connecting CN VI on one side to CN III on the other, results in paralysis of medial rectus function in the adducting eye and nystagmus in the abducting eye.

When there is a subtle eye movement abnormality, the **red glass test** may be helpful in localizing the lesion. To perform this test, a red glass is placed over one of the patient's eyes and the patient is instructed to follow a white light in all directions of gaze. The child sees 1 red/white light in the direction of normal muscle function but notes a separation of the red and white images that is greatest in the plane of action of the affected muscle.

In addition to gaze palsies, the examiner might encounter a variety of adventitious movements. **Nystagmus** is an involuntary, rapid movement of the eye that may be subclassified as being **pendular**, in which the 2 phases have equal amplitude and velocity, or **jerk**, in which there is a fast and slow phase. Jerk nystagmus can be further characterized by the direction of its fast phase, which may be left-, right-, up-, or downbeating; rotatory; or mixed. Many patients have a few beats of nystagmus with extreme lateral gaze **(end-gaze nystagmus),** which is

of no consequence. Pathologic horizontal nystagmus is most often congenital, drug-induced (e.g., alcohol, anticonvulsants), or a result of vestibular system dysfunction. By contrast, vertical nystagmus is often associated with structural abnormalities of the brainstem and cerebellum. **Ocular bobbing** is characterized by a downward jerk followed by a slow drift back to primary position and is associated with pontine lesions. **Opsoclonus** describes involuntary, chaotic oscillations of the eyes, which are often seen in the setting of neuroblastoma or viral infection.

Trigeminal Nerve (Cranial Nerve V)

The 3 divisions of the trigeminal nerve—ophthalmic, maxillary, and mandibular—convey information about facial protopathic (pain, temperature) and epicritic (vibration, proprioception) sensation. Each modality should be tested and compared to the contralateral side. In patients who are uncooperative or comatose, the integrity of the trigeminal nerve can be assessed by the corneal reflex, elicited by touching the cornea with a small pledget of cotton and observing for symmetric eye closure, and nasal tickle, obtained by stimulating the nasal passage with a cotton swab and observing for symmetric grimace. An absent reflex may be because of a sensory defect (trigeminal nerve) or a motor deficit (facial nerve). The motor division of the trigeminal nerve can be tested by examining the masseter, pterygoid, and temporalis muscles during mastication, as well as by evaluation of the jaw jerk.

Facial Nerve (Cranial Nerve VII)

The facial nerve is a predominantly motor nerve that innervates the muscles of facial expression, buccinator, platysma, stapedius, stylohyoid, and posterior belly of the digastric. It also has a separate division, called the chorda tympani, that contains sensory, special sensory (taste), and parasympathetic fibers. Because the portion of the facial nucleus that innervates the upper face receives bilateral cortical input, lesions of the motor cortex or corticobulbar tract have little effect on upper face strength. Rather, such lesions manifest with flattening of the contralateral nasolabial fold or drooping of the corner of the mouth. Conversely, lower motor neuron or facial nerve lesions tend to involve upper and lower facial muscles equally. Facial strength can be evaluated by observing the patient's spontaneous movements and by asking the patient to mimic a series of facial movements (e.g., smiling, raising the eyebrows, inflating the cheeks). A facial nerve palsy may be congenital; idiopathic (**Bell palsy**); or secondary to trauma, demyelination (Guillain-Barré syndrome), infection (Lyme disease, herpes simplex virus, HIV), granulomatous disease, neoplasm, or meningeal inflammation or infiltration. Facial nerve lesions that are proximal to the junction with the chorda tympani will result in an inability to taste substances with the anterior two-thirds of the tongue. If necessary, taste can be tested by placing a solution of saline or glucose on 1 side of the extended tongue. Normal children can identify the test substance in <10 sec. Other findings that may be associated with facial nerve palsy include hyperacusis, resulting from stapedius muscle involvement, and impaired tearing.

Vestibulocochlear Nerve (Cranial Nerve VIII)

The vestibulocochlear nerve has 2 components within a single trunk: the vestibular nerve, which innervates the semicircular canals of the inner ear and is involved with equilibrium, coordination, and orientation in space, and the cochlear nerve, which innervates the cochlea and subserves hearing.

Dysfunction of the vestibular system results in **vertigo**, the sensation of environmental motion. On examination, patients with vestibular nerve dysfunction typically have nystagmus, in which the fast component is directed away from the affected nerve. With their arms outstretched and eyes closed, their limbs tend to drift toward the injured side. Likewise, if they march in place, they slowly pivot toward the lesion (**Fukuda stepping test**). On Romberg and tandem gait testing, they tend to fall toward the abnormal ear. Vestibular function can be further evaluated with **caloric testing**. Before testing, the tympanic membrane should be visualized to ensure that it is intact and unobstructed. In an obtunded or comatose patient, 30-50 mL of ice water is then delivered by syringe into the external auditory canal with the patient's head elevated 30 degrees. If the brainstem is intact, the eyes deviate toward the irrigated side. A much smaller quantity of ice water (2 mL) is used in awake, alert patients to avoid inducing nausea. In normal subjects, introduction of ice water produces eye deviation toward the stimulated labyrinth followed by nystagmus with the fast component away from the stimulated labyrinth.

Because hearing is integral to normal language development, the physician should inquire directly about hearing problems. Parents' concern is often a reliable indicator of hearing impairment and warrants a formal audiologic assessment with either audiometry or brainstem auditory evoked potential testing (see Chapter 637). Even in the absence of parents' concern, certain children warrant formal testing within the 1st mo of life, including those with a family history of early life or syndromic deafness or a personal history of prematurity, severe asphyxia, exposure to ototoxic drugs, hyperbilirubinemia, congenital anomalies of the head or neck, bacterial meningitis, and congenital TORCH (*t*oxoplasmosis, *o*ther infections, *r*ubella, *c*ytomegalovirus, *h*erpes simplex virus) infections. For all other infants and children, a simple bedside assessment of hearing is usually sufficient. Newborns might have subtle responses to auditory stimuli, such as changes in breathing, cessation of movement, or opening of the eyes and/or mouth. If the same stimulus is presented repeatedly, normal neonates cease to respond, a phenomenon known as *habituation*. By 3-4 mo of age, infants begin to orient to the source of sound. Hearing-impaired toddlers are visually alert and appropriately responsive to physical stimuli but might have more frequent temper tantrums and abnormal speech and language development.

Glossopharyngeal Nerve (Cranial Nerve IX)

The glossopharyngeal nerve conveys motor fibers to the stylopharyngeus muscle; general sensory fibers from the posterior third of the tongue, pharynx, tonsil, internal surface of the tympanic membrane, and skin of the external ear; special sensory (taste) fibers from the posterior third of the tongue; parasympathetic fibers to the parotid gland; and general visceral sensory fibers from the carotid bodies. The nerve is tested by stimulating 1 side of the lateral oropharynx or soft palate with a tongue blade and observing for symmetric elevation of the palate **(gag reflex).** An isolated lesion of CN IX is rare, because it runs in close proximity to CN X. Potential causes of injury and/or dysfunction include birth trauma, ischemia, mass lesions, motor neuron disease, retropharyngeal abscess, and Guillain-Barré syndrome.

Vagus Nerve (Cranial Nerve X)

The vagus nerve has 10 terminal branches: meningeal, auricular, pharyngeal, carotid body, superior laryngeal, recurrent laryngeal, cardiac, pulmonary, esophageal, and gastrointestinal. The pharyngeal, superior laryngeal, and recurrent laryngeal branches contain motor fibers that innervate all of the muscles of the pharynx and larynx, with the exception of the stylopharyngeus (CN IX) and tensor veli palatini (CN V) muscles. Thus, unilateral injury of the vagus nerve results in weakness of the ipsilateral soft palate and a hoarse voice; bilateral lesions can produce respiratory distress as a result of vocal cord paralysis, as well as nasal regurgitation of fluids, pooling of secretions, and an immobile, low-lying soft palate. Isolated lesions to the vagus nerve may be a complication of thoracotomies or may be seen in neonates with type II Chiari malformations. If such a lesion is suspected, it is important to visualize the vocal cords. In addition to motor information, the vagus nerve carries somatic afferents from the pharynx, larynx, ear canal, external surface of the tympanic membrane, and meninges of the posterior fossa; visceral afferents; taste fibers from the posterior pharynx; and preganglionic parasympathetics.

Accessory Nerve (Cranial Nerve XI)

The accessory nerve innervates the sternocleidomastoid (SCM) and trapezius muscles. The left SCM acts to turn the head to the right side and vice versa; acting together, the SCMs flex the neck. The trapezius

acts to elevate the shoulder. Lesions to the accessory nerve result in atrophy and paralysis of the ipsilateral SCM and trapezius muscles, with resultant depression of the shoulder. Because several cervical muscles are involved in head rotation, unilateral SCM paresis might not be evident unless the patient is asked to rotate the head against resistance. Skull base fractures or lesions, motor neuron disease, myotonic dystrophy, and myasthenia gravis commonly produce atrophy and weakness of these muscles; congenital torticollis is associated with SCM hypertrophy.

Hypoglossal Nerve (Cranial Nerve XII)

The hypoglossal nerve innervates the tongue. Examination of the tongue includes assessment of its bulk and strength, as well as observation for adventitious movements. Malfunction of the hypoglossal nucleus or nerve produces atrophy, weakness, and fasciculations of the tongue. If the injury is unilateral, the tongue deviates toward the side of the injury; if it is bilateral, tongue protrusion is not possible and the patient can have difficulty swallowing (**dysphagia**). Werdnig-Hoffmann disease (infantile spinal muscular atrophy, or spinal muscular atrophy type 1) and congenital anomalies in the region of the foramen magnum are the principal causes of hypoglossal nerve dysfunction.

Motor Examination

The motor examination includes assessment of muscle bulk, tone, and strength, as well as observation for involuntary movements that might indicate central or peripheral nervous system pathology.

Bulk

Decreased muscle bulk **(atrophy)** may be secondary to disuse or to diseases of the lower motor neuron, nerve root, peripheral nerve, or muscle. In most cases, neurogenic atrophy is more severe than myogenic atrophy. Increased muscle bulk **(hypertrophy)** is usually physiologic (e.g., body builders). **Pseudohypertrophy** refers to muscle tissue that has been replaced by fat and connective tissue, giving it a bulky appearance with a paradoxical reduction in strength, as in Duchenne muscular dystrophy.

Tone

Muscle tone, which is generated by an unconscious, continuous, partial contraction of muscle, creates resistance to passive movement of a joint. Tone varies greatly based on a patient's age and state. At 28 wk of gestation, all 4 extremities are extended and there is little resistance to passive movement. Flexor tone is visible in the lower extremities at 32 wk and is palpable in the upper extremities at 36 wk; a normal-term infant's posture is characterized by flexion of all 4 extremities.

There are 3 key tests for assessing postural tone in neonates: the traction response, vertical suspension, and horizontal suspension (Fig. 590-3; see Chapters 94 and 97). To evaluate the **traction response**, the physician grasps the infant's hands and gently pulls the infant to a sitting position. Normally, the infant's head lags slightly behind the infant's body and then falls forward upon reaching the sitting position. To test **vertical suspension**, the physician holds the infant by the axillae without gripping the thorax. The infant should remain suspended with the infant's lower extremities held in flexion; a hypotonic infant will slip through the physician's hands. With **horizontal suspension**, the physician holds the infant prone by placing a hand under the infant's abdomen. The head should rise and the limbs should flex, but a hypotonic infant will drape over the physician's hand, forming a U shape. Assessing tone in the extremities is accomplished by observing the infant's resting position and passively manipulating the infant's limbs. When the upper extremity of a normal-term infant is pulled gently across the chest, the elbow does not quite reach the mid-sternum **(scarf sign),** whereas the elbow of a hypotonic infant extends beyond the midline with ease. Measurement of the **popliteal angle** is a useful method for documenting tone in the lower extremities. The examiner flexes the hip and extends the knee. Normal-term infants allow



Figure 590-3 Normal tone in a full-term neonate. **A,** Flexed resting posture. **B,** Traction response. **C,** Vertical suspension. **D,** Horizontal suspension.

extension of the knee to approximately 80 degrees. Similarly, tone can be evaluated by flexing the hip and knee to 90 degrees and then internally rotating the leg, in which case the heel should not pass the umbilicus.

Abnormalities of tone include spasticity, rigidity, and hypotonia. (Paratonia, which is rarely seen in the pediatric population, is not discussed here.) **Spasticity** is characterized by an initial resistance to passive movement, followed by a sudden release, referred to as the **clasp-knife** phenomenon. Because spasticity results from upper motor neuron dysfunction, it disproportionately affects the upper-extremity flexors and lower-extremity extensors and tends to occur in conjunction with disuse atrophy, hyperactive deep tendon reflexes, and extensor plantar reflexes **(Babinski sign).** In infants, spasticity of the lower extremities results in scissoring of the legs upon vertical suspension. Older children can present with prolonged commando crawling or toe-walking. **Rigidity,** seen with lesions of the basal ganglia, is characterized by resistance to passive movement that is equal in the flexors and extensors regardless of the velocity of movement **(lead pipe).** Patients with either spasticity or rigidity might exhibit **opisthotonos**, defined as severe hyperextension of the spine caused by hypertonia of the paraspinal muscles (Fig. 590-4), although similar posturing can be seen in patients with Sandifer syndrome (gastroesophageal reflux or hiatal hernia associated with torsional dystonia). **Hypotonia** refers to abnormally diminished tone and is the most common abnormality of tone in neurologically compromised neonates. A hypotonic infant is floppy and often assumes a frog-leg posture at rest. Hypotonia can reflect pathology of the cerebral hemispheres, cerebellum, spinal cord, anterior horn cell, peripheral nerve, neuromuscular junction, or muscle.



Figure 590-4 Opisthotonus in a brain-injured infant.

Strength

Older children are usually able to cooperate with formal strength testing, in which case muscle power is graded on a scale of 0-5 as follows: 0 = no contraction; 1 = flicker or trace of contraction; 2 = active movement with gravity eliminated; 3 = active movement against gravity; 4 = active movement against gravity and resistance; 5 = normal power. An examination of muscle power should include all muscle groups, including the neck flexors and extensors and the muscles of respiration. It is important not only to assess individual muscle groups, but also to determine the pattern of weakness (i.e., proximal vs distal; segmental vs regional). Testing for **pronator drift** can be helpful in localizing the lesion in a patient with weakness. This test is accomplished by having the patient extend his or her arms away from the body with the palms facing upward and the eyes closed. *Together, pronation and downward drift of an arm indicate a lesion of the contralateral corticospinal tract.*

Because infants and young children are not able to participate in formal strength testing, they are best assessed with functional measures. Proximal and distal strength of the upper extremities can be tested by having the child reach overhead for a toy and by watching the child manipulate small objects. In infants younger than 2 mo old, the physician can also take advantage of the palmar grasp reflex in assessing distal power and the Moro reflex in assessing proximal power. Infants with decreased strength in the lower extremities tend to have diminished spontaneous activity in their legs and are unable to support their body weight when held upright. Older children may have difficulty climbing or descending steps, jumping, or hopping. They might also use their hands to "climb up" their legs when asked to rise from a prone position, a maneuver called **Gowers sign** (Fig. 590-5).

Involuntary Movements

Patients with lower motor neuron or peripheral nervous system lesions might have **fasciculations**, which are small, involuntary muscle contractions that result from the spontaneous discharge of a single motor unit and create the illusion of a "bag of worms" under the skin. Because most infants have abundant body fat, muscle fasciculations are best observed in the tongue in this age group.

Most other involuntary movements, including tics, dystonia, chorea, and athetosis, stem from disorders of the basal ganglia. Tremor seems



Figure 590-5 A-D, Gowers sign in a boy with hip girdle weakness because of Duchenne muscular dystrophy. When asked to rise from a prone position, the patient uses his hands to walk up his legs to compensate for proximal lower-extremity weakness.

Table 590-2 Timing of Selected Primitive Reflexes

REFLEX	ONSET	FULLY DEVELOPED	DURATION
Palmar grasp	28 wk gestation	32 wk gestation	2-3 mo postnatal
Rooting	32 wk gestation	36 wk gestation	Less prominent after 1 mo postnatal
Moro	28-32 wk gestation	37 wk gestation	5-6 mo postnatal
Tonic neck	35 wk gestation	1 mo postnatal	6-7 mo postnatal
Parachute	7-8 mo postnatal	10-11 mo postnatal	Remains throughout life

to be an exception, as it is thought to be mediated by cerebellothalamocortical pathways. Further detail on the individual movement disorders is provided in Chapter 597.

Sensory Examination

The sensory examination is difficult to perform on an infant or uncooperative child and has a relatively low yield in terms of the information that it provides. A gross assessment of sensory function can be achieved by distracting the patient with an interesting toy and then touching the patient with a cotton swab in different locations. Normal infants and children indicate an awareness of the stimulus by crying, withdrawing the extremity, or pausing briefly; however, with repeated testing, they lose interest in the stimulus and begin to ignore the examiner. It is critical, therefore, that any areas of concern are tested efficiently and, if necessary, reexamined at an appropriate time.

Fortunately, isolated disorders of the sensory system are less common in the very young pediatric population than in the adult population, so detailed sensory testing is rarely warranted. Furthermore, most patients who are old enough to voice a sensory complaint are also old enough to cooperate with formal testing of light touch, pain, temperature, vibration, proprioception, and corticosensation (e.g., stereognosis, 2-point discrimination, extinction to double simultaneous stimulation). A notable exception is when the physician suspects a spinal cord lesion in an infant or young child and needs to identify a sensory level. In such situations, observation might suggest a difference in color, temperature, or perspiration, with the skin cool and dry below the level of injury. Lightly touching the skin above the level can evoke a squirming movement or physical withdrawal. Other signs of spinal cord injury include decreased anal sphincter tone and strength and absence of the superficial abdominal, anal wink, and cremasteric reflexes.

Reflexes

Deep Tendon Reflexes and the Plantar Response

Deep tendon reflexes are readily elicited in most infants and children. In infants, it is important to position the head in the midline when assessing reflexes, because turning the head to 1 side can alter reflex tone. Reflexes are graded from 0 (absent) to 4+ (markedly hyperactive), with 2+ being normal. Reflexes that are 1+ or 3+ can be normal as long as they are symmetrical. Sustained clonus is always pathologic, but infants younger than 3 mo old can have 5-10 beats of clonus, and older children can have 1-2 beats of clonus, provided that it is symmetrical.

The ankle jerk is hardest to elicit, but it can usually be obtained by passively dorsiflexing the foot and then tapping on either the Achilles tendon or the ball of the foot. The knee jerk is evoked by tapping the patellar tendon. If this reflex is exaggerated, extension of the knee may be accompanied by contraction of the contralateral adductors **(crossed adductor response).** Hypoactive reflexes reflect lower motor neuron or cerebellar dysfunction, whereas hyperactive reflexes are consistent with upper motor neuron disease. The plantar response is obtained by stimulation of the lateral aspect of the sole of the foot, beginning at the heel and extending to the base of the toes. The **Babinski sign,** indicating an upper motor neuron lesion, is characterized by extension of the great toe and fanning of the remaining toes. Too vigorous stimulation may produce withdrawal, which may be misinterpreted as a Babinski sign. Plantar responses have limited diagnostic utility in neonates, because they are mediated by several competing reflexes and can be either flexor or extensor, depending on how the foot is positioned. Asymmetry of the reflexes or plantar response is a useful lateralizing sign in infants and children.

Primitive Reflexes

Primitive reflexes appear and disappear at specific times during development (Table 590-2), and their absence or persistence beyond those times signifies CNS dysfunction. Although many primitive reflexes have been described, the Moro, grasp, tonic neck, and parachute reflexes are the most clinically relevant. The **Moro reflex** is elicited by supporting the infant in a semierect position and then allowing the infant's head to fall backwards onto the examiner's hand. A normal response consists of symmetric extension and abduction of the fingers and upper extremities, followed by flexion of the upper extremities and an audible cry. An asymmetric response can signify a fractured clavicle, brachial plexus injury, or hemiparesis. Absence of the Moro reflex in a term newborn is ominous, suggesting significant dysfunction of the CNS. The **grasp response** is elicited by placing a finger in the open palm of each hand; by 37 wk of gestation, the reflex is strong enough that the examiner can lift the infant from the bed with gentle traction. The **tonic neck reflex** is produced by manually rotating the infant's head to 1 side and observing for the characteristic fencing posture (extension of the arm on the side to which the face is rotated and flexion of the contralateral arm). An obligatory tonic neck response, in which the infant becomes "stuck" in the fencing posture, is always abnormal and implies a CNS disorder. The **parachute reflex**, which occurs in slightly older infants, can be evoked by holding the infant's trunk and then suddenly lowering the infant as if he or she were falling. The arms will spontaneously extend to break the infant's fall, making this reflex a prerequisite to walking.

Coordination

Ataxia refers to a disturbance in the smooth performance of voluntary motor acts and is usually the result of cerebellar dysfunction. Lesions to the cerebellar vermis result in unsteadiness while sitting or standing **(truncal ataxia).** Affected patients might have a wide-based gait or may be unable to perform tandem gait testing. Lesions of the cerebellar hemispheres cause appendicular ataxia, which may be apparent as the patient reaches for objects and performs finger-to-nose and heel-to-shin movements. Other features of cerebellar dysfunction include errors in judging distance **(dysmetria),** inability to inhibit a muscular action **(rebound),** impaired performance of rapid alternating movements **(dysdiadochokinesia),** intention tremor, nystagmus, scanning dysarthria, hypotonia, and decreased deep tendon reflexes. Acute ataxia suggests an infectious or postinfectious, endocrinologic, toxic, traumatic, vascular, or psychogenic process, and chronic symptoms suggest a metabolic, neoplastic, or degenerative process.

Station and Gait

Observation of a child's station and gait is an important aspect of the neurologic examination. Normal children can stand with their feet close together without swaying; however, children who are unsteady may sway or even fall. On gait testing, the heels should strike either side of an imaginary line, but children with poor balance tend to walk with their legs farther apart to create a more stable base. Tandem gait

testing forces patients to have a narrow base, which highlights subtle balance difficulties.

There are a variety of abnormal gaits, many of which are associated with a specific underlying etiology. Patients with a **spastic** gait appear stiff-legged like a soldier. They may walk on tiptoe as a result of tightness or contractures of the Achilles tendons, and their legs may scissor as they walk. A **hemiparetic** gait is associated with spasticity and circumduction of the leg, as well as decreased arm swing on the affected side. **Cerebellar ataxia** results in a wide-based, reeling gait like a drunk person, whereas **sensory ataxia** results in a wide-based **steppage gait,** in which the patient lifts the legs up higher than usual in the swing phase and then slaps the foot down. A **myopathic,** or waddling, gait is associated with hip girdle weakness. Affected children often develop a compensatory lordosis and have other signs of proximal muscle weakness, such as difficulty climbing stairs. During gait testing, the examiner might also note hypotonia or weakness of the lower extremities; extrapyramidal movements, such as dystonia or chorea; or orthopedic deformities, such as pelvic tilt, genu recurvatum, varus or valgus deformities of the knee, pes cavus (high arches) or pes planus (flat feet), and scoliosis.

GENERAL EXAMINATION

Examination of other organ systems is essential because myriad systemic diseases affect the nervous system. Dysmorphic features can indicate a genetic syndrome (see Chapter 108). Heart murmurs may be associated with rheumatic fever (Sydenham chorea), cardiac rhabdomyoma (tuberous sclerosis), cyanotic heart disease (cerebral abscess or thrombosis), and endocarditis (cerebral vascular occlusion). Hepatosplenomegaly can suggest an inborn error of metabolism, storage disease, HIV, or malignancy. Cutaneous lesions may be a feature of a neurocutaneous syndrome (see Chapter 596).

SPECIAL DIAGNOSTIC PROCEDURES

Lumbar Puncture and Cerebrospinal Fluid Examination

Examination of the cerebrospinal fluid (CSF) and measurement of the pressure it creates in the subarachnoid space are essential in confirming the diagnosis of meningitis, encephalitis, and idiopathic intracranial hypertension (previously referred to as pseudotumor cerebri), and it is often helpful in assessing subarachnoid hemorrhage; demyelinating, degenerative, and collagen vascular diseases; and intracranial neoplasms. Having an experienced assistant who can position, restrain, and comfort the patient is critical to the success of the procedure.

The patient should be situated in a lateral decubitus or seated position with the neck and legs flexed to enlarge the intervertebral spaces. As a rule, sick neonates should be maintained in a seated position to prevent problems with ventilation and perfusion. Regardless of the position chosen, it is important to make sure that the patient's shoulders and hips are straight to prevent rotating the spine.

Once the patient is situated, the physician identifies the appropriate interspace by drawing an imaginary line from the iliac crest downward perpendicular to the vertebral column. In adults, lumbar punctures are usually performed in the L3-L4 or L4-L5 interspaces. Next, the physician dons a mask, gown, and sterile gloves. The skin is thoroughly prepared with a cleansing agent, and sterile drapes are applied. The skin and underlying tissues are anesthetized by injecting a local anesthetic (e.g., 1% lidocaine) at the time of the procedure or by applying a eutectic mixture of lidocaine and prilocaine (EMLA) to the skin 30 minutes before the procedure. A 22-gauge, 1.5-3.0 in, sharp, beveled spinal needle with a properly fitting stylet is introduced in the midsagittal plane and directed slightly cephalad. The physician should pause frequently, remove the stylet, and assess for CSF flow. Although a pop can occur as the needle penetrates the dura, it is more common to experience a subtle change in resistance.

Once CSF has been detected, a manometer and 3-way stopcock can be attached to the spinal needle to obtain an opening pressure. If the patient was seated as the spinal needle was introduced, the patient should be moved carefully to a **lateral decubitus position** with the head and legs extended before the manometer is attached. Normal opening pressures are 90-120 mm H_2O in newborns, 60-180 mm H_2O in young children, and 12-120 mm H_2O in older children and adults. The 90th percentile in children has been reported to be 250 mm of H_2O. The most common cause of an elevated opening pressure is an agitated patient. Sedation and high body mass index can also increase the opening pressure.

Contraindications to performing a lumbar puncture include suspected mass lesion of the brain, especially in the posterior fossa or above the tentorium and causing shift of the midline; suspected mass lesion of the spinal cord; symptoms and signs of impending cerebral herniation in a child with probable meningitis; critical illness (on rare occasions); skin infection at the site of the lumbar puncture; and thrombocytopenia with a platelet count $<20 \times 10^9$/L. If disc edema or focal findings suggest a mass lesion, a head CT should be obtained before proceeding with lumbar puncture to prevent uncal or cerebellar herniation as the CSF is removed. In the absence of these findings, routine head imaging is not warranted. The physician should also be alert to clinical signs of impending herniation, including alterations in the respiratory pattern (e.g., hyperventilation; Cheyne-Stokes respirations, ataxic respirations, respiratory arrest), abnormalities of pupil size and reactivity, loss of brainstem reflexes, and decorticate or decerebrate posturing. If any of these signs are present or the child is so ill that the lumbar puncture might induce cardiorespiratory arrest, blood cultures should be drawn and supportive care, including antibiotics, should be initiated. Once the patient has stabilized, it may be possible to perform a lumbar puncture safely.

Normal CSF contains up to 5/mm^3 white blood cells, and a newborn can have as many as 15/mm^3. Polymorphonuclear cells are always abnormal in a child, but 1-2/mm^3 may be present in a normal neonate. An elevated polymorphonuclear count suggests bacterial meningitis or the early phase of aseptic meningitis (see Chapter 603). CSF lymphocytosis can be seen in aseptic, tuberculous, or fungal meningitis; demyelinating diseases; brain or spinal cord tumor; immunologic disorders, including collagen vascular diseases; and chemical irritation (following myelogram, intrathecal methotrexate).

Normal CSF contains no red blood cells; thus, their presence indicates a traumatic tap or a subarachnoid hemorrhage. Progressive clearing of the blood between the first and last samples indicates a traumatic tap. Bloody CSF should be centrifuged immediately. A clear supernatant is consistent with a bloody tap, whereas **xanthochromia** (yellow color that results from the degradation of hemoglobin) suggests a subarachnoid hemorrhage. Xanthochromia may be absent in bleeds <12 hr old, particularly when laboratories rely on visual inspection rather than spectroscopy. Xanthochromia can also occur in the setting of hyperbilirubinemia, carotenemia, and markedly elevated CSF protein.

The normal CSF protein is 10-40 mg/dL in a child and as high as 120 mg/dL in a neonate. The CSF protein falls to the normal childhood range by 3 mo of age. The CSF protein may be elevated in many processes, including infectious, immunologic, vascular, and degenerative diseases, blockage of CSF flow, as well as tumors of the brain (primary CNS tumors, systemic tumors metastatic to the CNS, infiltrative acute lymphoblastic leukemia) and spinal cord. With a traumatic tap, the CSF protein is increased by approximately 1 mg/dL for every 1,000 red blood cells/mm^3. Elevation of CSF immunoglobulin G, which normally represents approximately 10% of the total protein, is observed in subacute sclerosing panencephalitis, in postinfectious encephalomyelitis, and in some cases of multiple sclerosis. If the diagnosis of multiple sclerosis is suspected, the CSF should be tested for the presence of oligoclonal bands.

The CSF glucose content is approximately 60% of the blood glucose in a healthy child. To prevent a spuriously elevated blood:CSF glucose ratio in a case of suspected meningitis, it is advisable to collect the blood glucose before the lumbar puncture when the child is relatively calm. Hypoglycorrhachia is found in association with diffuse meningeal disease, particularly bacterial and tubercular meningitis. Widespread neoplastic involvement of the meninges, subarachnoid hemorrhage, disorders involving the glucose transporter protein type 1, fungal meningitis, and, occasionally, aseptic meningitis can produce low CSF glucose as well.

A Gram stain of the CSF is essential if there is a suspicion for bacterial meningitis; an acid-fast stain and India ink preparation can be used to assess for tuberculous and fungal meningitis, respectively. CSF is then plated on different culture media depending on the suspected pathogen. When indicated by the clinical presentation, it can also be helpful to assess for the presence of specific antigens (e.g., latex agglutination for *Neisseria meningitidis*, *Haemophilus influenzae* type b, or *Streptococcus pneumoniae*) or to obtain antibody or polymerase chain reaction studies (e.g., herpes simplex virus-1 and -2, West Nile virus, enteroviruses). In noninfectious cases, levels of CSF metabolites, such as lactate, amino acids, and enolase, can provide clues to the underlying metabolic disease.

Neuroradiologic Procedures

Skull roentgenograms have limited diagnostic utility. They can demonstrate fractures, bony defects, intracranial calcifications, or indirect evidence of increased ICP. Acutely increased ICP causes separation of the sutures, whereas chronically increased ICP is associated with erosion of the posterior clinoid processes, enlargement of the sella turcica, and increased convolutional markings.

Cranial ultrasonography is the imaging method of choice for detecting intracranial hemorrhage, periventricular leukomalacia, and hydrocephalus in infants with patent anterior fontanels. Ultrasound is less sensitive than either CT or MRI for detecting hypoxic–ischemic injury, but the use of color Doppler or power Doppler sonography, both of which show changes in regional cerebral blood flow, improve its sensitivity. In general, ultrasound is not a useful technique in older children, although it can be helpful intraoperatively when placing shunts, locating small tumors, and performing needle biopsies.

CT is a valuable diagnostic tool in the evaluation of many neurologic emergencies, as well as some nonemergent conditions. It is a noninvasive, rapid procedure that can usually be performed without sedation. CT scans use conventional x-ray techniques, meaning that they produce ionizing radiation. Because children younger than 10 yr of age are several times more sensitive to radiation than adults, it is important to consider the whether imaging is actually indicated and, if it is, whether an ultrasound or MRI might be the more appropriate study. In the emergency setting, a noncontrast CT scan can demonstrate skull fractures, pneumocephalus, intracranial hemorrhages, hydrocephalus, and impending herniation. If the noncontrast scan reveals an abnormality and an MRI cannot be performed in a timely fashion, nonionic contrast should be used to highlight areas of breakdown in the blood–brain barrier (e.g., abscesses, tumors) and/or collections of abnormal blood vessels (e.g., arteriovenous malformations). CT is less useful for diagnosing acute infarcts in children, because radiographic changes might not be apparent for up to 24 hr. Some subtle signs of early (<24 hr) infarction include sulcal effacement, blurring of the gray–white junction, and the hyperdense middle cerebral artery sign (increased attenuation in the middle cerebral artery that is often associated with thrombosis). In the routine setting, CT imaging can be used to demonstrate intracranial calcifications or, with the addition of 3-dimensional reformatting, to evaluate patients with craniofacial abnormalities or craniosynostosis. Although other pathologic processes may be visible on CT scan, *MR is generally preferred because it provides a more-detailed view of the anatomy without exposure to ionizing radiation* (Table 590-3).

CT angiography is a useful tool for visualizing vascular structures and is accomplished by administering a tight bolus of iodinated contrast through a large-bore intravenous catheter and then acquiring CT images as the contrast passes through the arteries.

MRI is a noninvasive procedure that is well suited for detecting a variety of abnormalities, including those of the posterior fossa and spinal cord. MR scans are highly susceptible to patient motion artifact; consequently, many children younger than age 8 yr require sedation to ensure an adequate study. (The need for sedation is beginning to change in some centers as MRI technology improves and allows for faster performance of studies.) Because the American Academy of Pediatrics recommends that infants be kept nothing by mouth (NPO) for 4 hr or longer and older children for 6 hr or longer before deep sedation, it is often difficult to obtain an MRI on an infant or young child in the acute setting. MRI can be used to evaluate for congenital or acquired brain lesions, migrational defects, dysmyelination or demyelination, posttraumatic gliosis, neoplasms, cerebral edema, and acute stroke (see Table 590-3). Paramagnetic MR contrast agents (e.g., gadolinium-diethylenetriaminepentaacetic acid [DTPA]) are efficacious in identifying areas of disruption in the blood–brain barrier, such as those occurring in primary and metastatic brain tumors, meningitis, cerebritis, abscesses, and active demyelination. **MR angiography** and **MR venography** provide detailed images of major intracranial vasculature structures and assist in the diagnosis of conditions such as stroke, vascular malformations, and cerebral venous sinus thrombosis. MR angiography is the procedure of choice for infants and young children owing to the lack of ionizing radiation and contrast; however, CT angiography may be preferable in older children because it is faster and can eliminate the need for sedation; it is particularly useful for looking at blood vessels in the neck, where there is less interference from bone artifact than in the skull-encased brain.

Functional MRI is a noninvasive technique used to map neuronal activity during specific cognitive states and/or sensorimotor functions. Data are usually based on blood oxygenation, although they can also be based on local cerebral blood volume or flow. Functional MRI is useful for presurgical localization of critical brain functions and has several advantages over other functional imaging techniques. Specifically, functional MRI produces high-resolution images without exposure to ionizing radiation or contrast, and it allows coregistration of functional and structural images.

Proton MR spectroscopy (MRS) is a molecular imaging technique in which the unique neurochemical profile of a preselected brain region is displayed in the form of a spectrum. Many metabolites can be detected, the most common of which are *N*-acetylaspartate, creatine and phosphocreatine, choline, myoinositol, and lactate. Changes in the spectral pattern of a given area can yield clues to the underlying pathology, making MRS useful in the diagnosis of inborn errors of metabolism, as well as the preoperative and posttherapeutic assessment of intracranial tumors. MRS can also detect areas of cortical dysplasia in patients with epilepsy, because these patients have low *N*-acetylaspartate:creatine ratios. Finally, MRS may be useful in detecting hypoxic–ischemic injury in newborns in the 1st day of life, because the lactate peak enlarges and the *N*-acetylaspartate peak diminishes before MRI sequences become abnormal.

Catheter angiography is the gold standard for diagnosing vascular disorders of the CNS, such as arteriovenous malformations, aneurysms, arterial occlusions, and vasculitis. A 4-vessel study is accomplished by introducing a catheter into the femoral artery and then injecting contrast media into each of the internal carotid and vertebral arteries. Because catheter angiography is invasive and requires general anesthesia, it is typically reserved for treatment planning of endovascular or open procedures and for cases in which noninvasive imaging results are not diagnostic.

Positron emission tomography provides unique information on brain metabolism and perfusion by measuring blood flow, oxygen uptake, and/or glucose consumption. Positron emission tomography is an expensive technique that is gaining a following in some pediatric centers, particularly those with active epilepsy surgery programs. **Single-photon emission CT** using ^{99m}Tc hexamethylpropyleneamine oxime is a sensitive and inexpensive technique to study regional cerebral blood flow. Single-photon emission CT is particularly useful in assessing for vasculitis, herpes encephalitis, dysplastic cortex, and recurrent brain tumors. Positron emission tomography MRI is only available in a few pediatric centers in the United States; it provides better resolution and tissue definition than single-photon emission CT.

Electroencephalography

An electroencephalogram (EEG) provides a continuous recording of electrical activity between reference electrodes placed on the scalp. Although the genesis of the electrical activity is not certain, it likely originates from postsynaptic potentials in the dendrites of cortical neurons. Even with amplification of the electrical activity, not all potentials are recorded because there is a buffering effect of the scalp, muscles, bone, vessels, and subarachnoid fluid. EEG waves are

Table 590-3 Preferred Imaging Procedures in Neurologic Diseases

ISCHEMIC INFARCTION OR TRANSIENT ISCHEMIC ATTACK CT/CTA (head and neck) ± CT perfusion for patients who are unstable or are potential candidates for tissue plasminogen activator or other acute interventions Otherwise, MRI/MRA (head and neck) with and without gadolinium and with diffusion-weighted images If the examination findings localize to the anterior circulation, carotid ultrasound should be performed rather than neck CTA or MRA Obtain an MRV if the infarct does not follow an arterial distribution CT or MRI can detect infarcts more than 24 hr old, although MRI is generally preferred to avoid exposure to ionizing radiation	**HEADACHE** CT with and without contrast or MRI with and without gadolinium if a structural disorder is suspected (MRI is preferred in nonemergent situations as it does not involve ionizing radiation and provides a better view of the parenchyma)
INTRAPARENCHYMAL HEMORRHAGE CT if <24 hr; MRI if >24 hr MRI and MRA to assess for underlying vascular malformation, tumor, etc. Catheter angiography if MRA is nondiagnostic	**HEAD TRAUMA** CT without contrast initially MRI after initial assessment and treatment if clinically indicated. Diffusion tensor imaging and/or diffusion kurtosis sequences may be useful to detect subtle white matter abnormalities
ARTERIOVENOUS MALFORMATION CT for acute hemorrhage; MRI and MRA with and without gadolinium as early as possible Catheter angiography if noninvasive imaging is nondiagnostic	**EPILEPSY** MRI with and without gadolinium. Thin slices through the mesial temporal lobes may be helpful if a temporal focus is suspected PET Interictal SPECT
CEREBRAL ANEURYSM CT without contrast for acute subarachnoid hemorrhage MRA or CTA to identify the aneurysm Catheter angiography may be necessary in some cases TCD to detect vasospasm	**BRAIN TUMOR** MRI with and without gadolinium MRS PET
HYPOXIC–ISCHEMIC BRAIN INJURY Ultrasound in infants If ultrasound is negative or there is a discrepancy between the clinical course and the sonogram, obtain an MRI In older children, CT if unstable; otherwise, MRI MRS can show a lactate peak even in the absence of structural abnormalities and can be useful for prognostication purposes	**MULTIPLE SCLEROSIS** MRI with and without gadolinium Obtain sagittal FLAIR images
METABOLIC DISORDERS MRI, particularly T2-weighted and FLAIR images Diffusion-weighted images may be useful in distinguishing acute and chronic changes MRS, SPECT, and PET may be useful in certain disorders	**MENINGITIS OR ENCEPHALITIS** CT without and with contrast before lumbar puncture if there are signs of increased ICP on examination MRI with and without gadolinium after initial assessment and treatment for patients with complicated meningitis or encephalitis
HYDROCEPHALUS Ultrasound (in infants), CT with and without contrast, or MR with and without gadolinium for diagnosis of communicating hydrocephalus MR with and without gadolinium for diagnosis of noncommunicating hydrocephalus Ultrasound (in infants) or CT to follow ventricular size in response to treatment	**BRAIN ABSCESS** MRI with and without gadolinium Diffusion-weighted images and MRS can help to differentiate abscess from necrotic tumor If the patient is unstable, CT with and without contrast followed by MRI with and without contrast when feasible
	MOVEMENT DISORDERS MRI with and without gadolinium PET DaTscan (SPECT scan using ioflupane iodine-123 as the contrast agent for detecting dopamine transporters in suspected parkinsonian syndromes)

CTA, computed tomographic angiography; FLAIR, fluid-attenuated inversion recovery; ICP, intracranial pressure; MRA, magnetic resonance angiography; MRS, magnetic resonance spectroscopy; MRV, magnetic resonance venography; PET, positron emission tomography; SPECT, single-photon emission computed tomography; TCD, transcranial Doppler ultrasonography.

classified according to their frequency as delta (1-3/sec), theta (4-7/sec), alpha (8-12/sec), and beta (13-20/sec). These waves are altered by many factors, including age, level of alertness, eye closure, drugs, and disease states.

The normal waking EEG is characterized by the posterior dominant rhythm—a sinusoidal, 8-12 Hz rhythm that is most prominent over the occipital region in a state of relaxed wakefulness with the eyes closed. This rhythm first becomes apparent at 3-4 mo old, and most children have achieved the adult frequency of 8-12 Hz by age 8 yr.

Normal sleep is divided into 3 stages of non–rapid eye movement sleep—designated N1, N2, and N3—and rapid eye movement sleep. N1 corresponds to drowsiness, and N3 represents deep, restorative, slow-wave sleep. Rapid eye movement sleep is rarely captured during a routine EEG but may be seen on an overnight recording. The American Electroencephalography Society Guideline and Technical Standards states that "sleep recordings should be obtained whenever possible"; however, it appears that sleep deprivation—not sleep during the EEG—is what increases the yield of the study, particularly in children with 1 or more clinically diagnosed seizures and in children older than 3 yr of age.

EEG abnormalities can be divided into 2 general categories: epileptiform discharges and slowing. Epileptiform discharges are paroxysmal spikes or sharp waves, often followed by slow waves, which interrupt the background activity. They may be focal, multifocal, or generalized. Focal discharges are often associated with cerebral dysgenesis or irritative lesions, such as cysts, slow-growing tumors, or glial scar tissue; generalized discharges typically occur in children with structurally normal brains. Generalized discharges can occur as an epilepsy trait in children who have never had a seizure and, by themselves, are not an indication for treatment. Epileptiform activity may be enhanced by activation procedures, including hyperventilation and photic stimulation.

As with epileptiform discharges, slowing can be either focal or diffuse. Focal slowing should raise a concern for an underlying functional or structural abnormality, such as an infarct, hematoma, or tumor. Diffuse slowing is the hallmark of encephalopathy and is usually secondary to a widespread disease process or toxic–metabolic insult.

Long-term video EEG monitoring provides precise characterization of seizure types, which allows specific medical or surgical management. It facilitates more accurate differentiation of epileptic seizures

from paroxysmal events that mimic epilepsy, including psychogenic nonepileptiform attacks. Long-term EEG monitoring can also be useful during medication adjustments.

Evoked Potentials

An evoked potential is an electrical signal recorded from the CNS following the presentation of a specific visual, auditory, or sensory stimulus. Stimulation of the visual system by a flash or patterned stimulus, such as a black-and-white checkerboard, produces **visual evoked potentials** (VEPs), which are recorded over the occiput and averaged in a computer. Abnormal VEPs can result from lesions to the visual pathway anywhere from the retina to the visual cortex. Many demyelinating disorders and neurodegenerative diseases, such as Tay-Sachs, Krabbe, or Pelizaeus-Merzbacher disease, or neuronal ceroid lipofuscinoses, show characteristic VEP abnormalities. Flash VEPs can also be helpful in evaluating infants who have sustained an anoxic injury; however, detection of an evoked potential does not necessarily mean that the infant will have functional vision.

Brainstem auditory evoked responses (BAERs) provide an objective measure of hearing and are particularly useful in neonates and in children who have failed, or are uncooperative with, audiometric testing. BAERs are abnormal in many neurodegenerative diseases of childhood and are an important tool in evaluating patients with suspected tumors of the cerebellopontine angle. BAERs can be helpful in assessing brainstem function in comatose patients, because the waveforms are unaffected by drugs or by the level of consciousness; however, they are not accurate in predicting neurologic recovery and outcome.

Somatosensory evoked potentials (SSEPs) are obtained by stimulating a peripheral nerve (peroneal, median) and then recording the electrical response over the cervical region and contralateral parietal somatosensory cortex. SSEPs determine the functional integrity of the dorsal column–medial lemniscal system and are useful in monitoring spinal cord function during operative procedures for scoliosis, aortic coarctation, and myelomeningocele repair. SSEPs are abnormal in many neurodegenerative disorders and are the most accurate evoked potential in the assessment of neurologic outcome following a severe CNS insult.

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Chapter 591

Congenital Anomalies of the Central Nervous System

Stephen L. Kinsman and Michael V. Johnston

Central nervous system (CNS) malformations are grouped into neural tube defects and associated spinal cord malformations; encephaloceles; disorders of structure specification (gray matter structures, neuronal migration disorders, disorders of connectivity, and commissure and tract formation); disorders of the posterior fossa, brainstem, and cerebellum; disorders of brain growth and size; and disorders of skull growth and shape. Classification of these conditions into syndromic, nonsyndromic, and single-gene etiologies is also important. These disorders can also be seen as isolated findings or as being a consequence of environmental exposures. Elucidation of single-gene causes has outpaced our understanding of the epigenetic and environmental mechanisms causing these malformations.

These disorders are heterogeneous in their presentation. Common presentations and clinical problems include disorders of head size and/or shape; hydrocephalus; fetal ultrasonographic brain abnormalities; neonatal encephalopathy and seizures; developmental delay, cognitive impairment, and intellectual disability; hypotonia, motor impairment, and cerebral palsy; seizures, epilepsy, and drug-resistant epilepsy; cranial nerve dysfunction; and spinal cord dysfunction.

Bibliography is available at Expert Consult.

591.1 Neural Tube Defects

Stephen L. Kinsman and Michael V. Johnston

Neural tube defects (NTDs) account for the largest proportion of congenital anomalies of the CNS and result from failure of the neural tube to close spontaneously between the 3rd and 4th wk of in utero development. Although the precise cause of NTDs remains unknown, evidence suggests that many factors, including hyperthermia, drugs (valproic acid), malnutrition, low red cell folate levels, chemicals, maternal obesity or diabetes, and genetic determinants (mutations in folate-responsive or folate-dependent enzyme pathways) can adversely affect normal development of the CNS from the time of conception. In some cases, an abnormal maternal nutritional state or exposure to radiation before conception increases the likelihood of a congenital CNS malformation. The major NTDs include spina bifida occulta, meningocele, myelomeningocele, encephalocele, anencephaly, caudal regression syndrome, dermal sinus, tethered cord, syringomyelia, diastematomyelia, and lipoma involving the conus medullaris and/or filum terminale and the rare condition iniencephaly.

The human nervous system originates from the primitive ectoderm that also develops into the epidermis. The ectoderm, endoderm, and mesoderm form the three primary germ layers that are developed by the 3rd wk. The endoderm, particularly the notochordal plate and the intraembryonic mesoderm, induces the overlying ectoderm to develop the neural plate in the 3rd wk of development (Fig. 591-1*A*). Failure of normal induction is responsible for most of the NTDs, as well as disorders of prosencephalic development. Rapid growth of cells within the neural plate causes further invagination of the neural groove and differentiation of a conglomerate of cells, the neural crest, which migrate laterally on the surface of the neural tube (Fig. 591-1*B*). The notochordal plate becomes the centrally placed notochord, which acts as a foundation around which the vertebral column ultimately develops. With formation of the vertebral column, the notochord undergoes involution and becomes the nucleus pulposus of the intervertebral disks. The neural crest cells differentiate to form the peripheral nervous system, including the spinal and autonomic ganglia and the ganglia of cranial nerves V, VII, VIII, IX, and X. In addition, the neural crest forms the leptomeninges, as well as Schwann cells, which are responsible for myelination of the peripheral nervous system. The dura is thought to arise from the paraxial mesoderm. In the region of the embryo destined to become the head, similar patterns exist. In this region, the notochord is replaced by the prechordal mesoderm.

In the 3rd wk of embryonic development, invagination of the neural groove is completed and the neural tube is formed by separation from the overlying surface ectoderm (see Fig. 591-1*C*). Initial closure of the neural tube is accomplished in the area corresponding to the future junction of the spinal cord and medulla and moves rapidly both caudally and rostrally. For a brief period, the neural tube is open at both ends, and the neural canal communicates freely with the amniotic cavity (see Fig. 591-1*D*). Failure of closure of the neural tube allows excretion of fetal substances (α-fetoprotein [AFP], acetylcholinesterase) into the amniotic fluid, serving as biochemical markers for a NTD. Prenatal screening of maternal serum for AFP in the 16th-18th wk of gestation is an effective method for identifying pregnancies at risk for fetuses with NTDs in utero. Normally, the rostral end of the neural

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tube closes on the 23rd day and the caudal neuropore closes by a process of secondary neurulation by the 27th day of development, before the time that many women realize they are pregnant.

The embryonic neural tube consists of 3 zones: ventricular, mantle, and marginal (see Fig. 591-1*E*). The ependymal layer consists of pluripotential, pseudostratified, columnar neuroepithelial cells. Specific neuroepithelial cells differentiate into primitive neurons or neuroblasts that form the mantle layer. The marginal zone is formed from cells in the outer layer of the neuroepithelium, which ultimately becomes the white matter. Glioblasts, which act as the primitive supportive cells of the CNS, also arise from the neuroepithelial cells in the ependymal zone. They migrate to the mantle and marginal zones and become future astrocytes and oligodendrocytes. The importance of other pathways of progenitor cell generation and migration are also being elucidated. It is likely that microglia originate from mesenchymal cells at a later stage of fetal development when blood vessels begin to penetrate the developing nervous system.

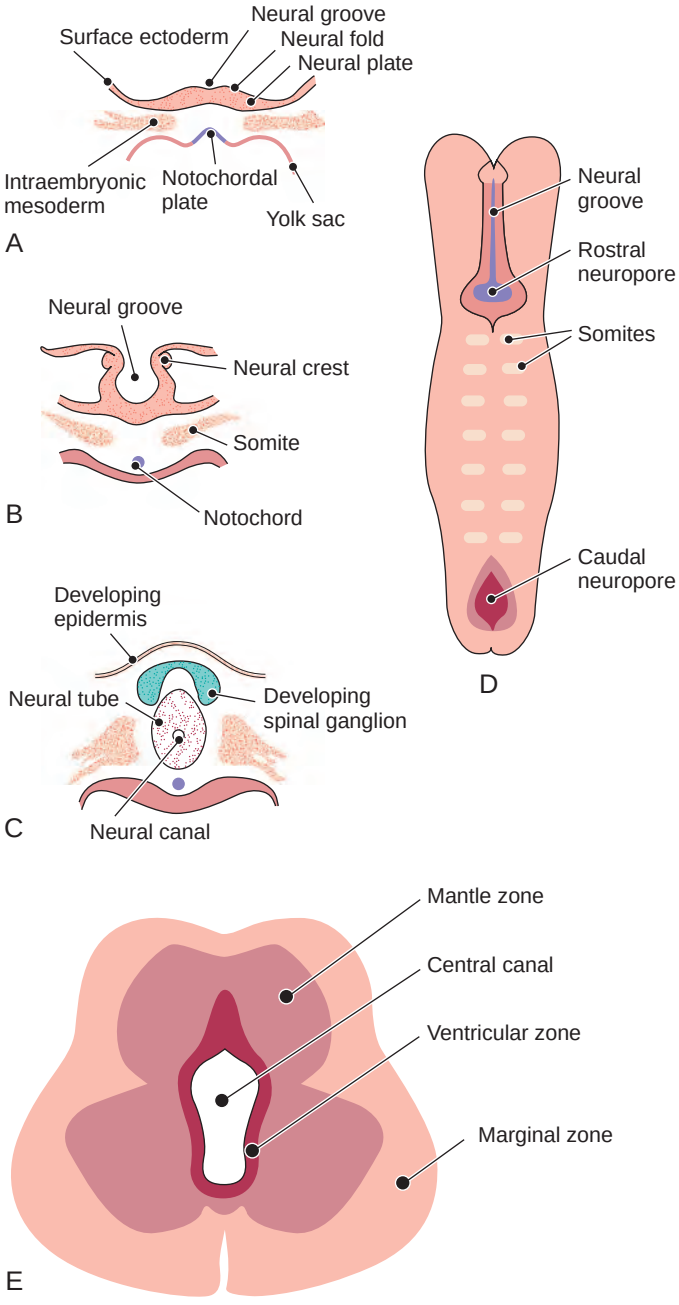


Figure 591-1 Diagrammatic illustration of the developing nervous system. **A,** Transverse sections of the neural plate during the 3rd wk. **B,** Formation of the neural groove and the neural crest. **C,** The neural tube is developed. **D,** Longitudinal drawing showing the initial closure of the neural tube in the central region. **E,** Cross-sectional drawing of the embryonic neural tube (primitive spinal cord).

591.2 Spina Bifida Occulta (Occult Spinal Dysraphism)

Stephen L. Kinsman and Michael V. Johnston

Spina bifida occulta is a common anomaly consisting of a midline defect of the vertebral bodies without protrusion of the spinal cord or meninges. Most patients are asymptomatic and lack neurologic signs, and the condition is usually of no consequence. Some consider the term *spina bifida occulta* to denote merely a posterior vertebral body fusion defect. This simple defect does not have an associated spinal cord malformation. Other clinically more significant forms of this closed spinal cord malformation are more correctly termed *occult spinal dysraphism*. In most of these cases, there are cutaneous manifestations such as a hemangioma, discoloration of the skin, pit, lump, dermal sinus, or hairy patch (Fig. 591-2). A spine roentgenogram in simple spina bifida occulta shows a defect in closure of the posterior vertebral arches and laminae, typically involving L5 and S1; there is no abnormality of the meninges, spinal cord, or nerve roots. Occult spinal dysraphism is often associated with more significant developmental abnormalities of the spinal cord, including syringomyelia, diastematomyelia, lipoma, fatty filum, dermal sinus, and/or a tethered cord. A spine x-ray in these cases might show bone defects or may be normal. All cases of occult spinal dysraphism are best investigated with MRI (Fig. 591-3). Initial screening in the neonate may include ultrasonography, but MRI is more accurate at any age.

A dermoid sinus usually forms a small skin opening, which leads into a narrow duct, sometimes indicated by protruding hairs, a hairy patch, or a vascular nevus. Dermoid sinuses occur in the midline at the sites where meningoceles or encephaloceles can occur: the lumbosacral region or occiput, respectively and occasionally in the cervical or thoracic area. Dermoid sinus tracts can pass through the dura, acting as a conduit for the spread of infection. Recurrent meningitis of occult origin should prompt careful examination for a small sinus tract in the posterior midline region, including the back of the head. Lower back sinuses are usually above the gluteal fold and are directed cephalad. Tethered spinal cord syndrome may also be an associated problem. Diastematomyelia commonly has bony abnormalities that require surgical intervention along with untethering of the spinal cord.

An approach to imaging of the spine in patients with cutaneous lesions is noted in Table 591-1.

Table 591-1 Cutaneous Lesions Associated with Occult Spinal Dysraphism

IMAGING INDICATED
Subcutaneous mass or lipoma
Hairy patch
Dermal sinus
Atypical dimples (deep, >5 mm, >25 mm from anal verge)
Vascular lesion, e.g., hemangioma or telangiectasia
Skin appendages or polypoid lesions, e.g., skin tags, tail-like appendages
Scar-like lesions
IMAGING UNCERTAIN
Hyperpigmented patches
Deviation of the gluteal fold
IMAGING NOT REQUIRED
Simple dimples (<5 mm, <25 mm from anal verge)
Coccygeal pits

From Williams H: Spinal sinuses, dimples, pits and patches: what lies beneath? Arch Dis Child Educ Pract Ed 91:ep75–ep80, 2006.

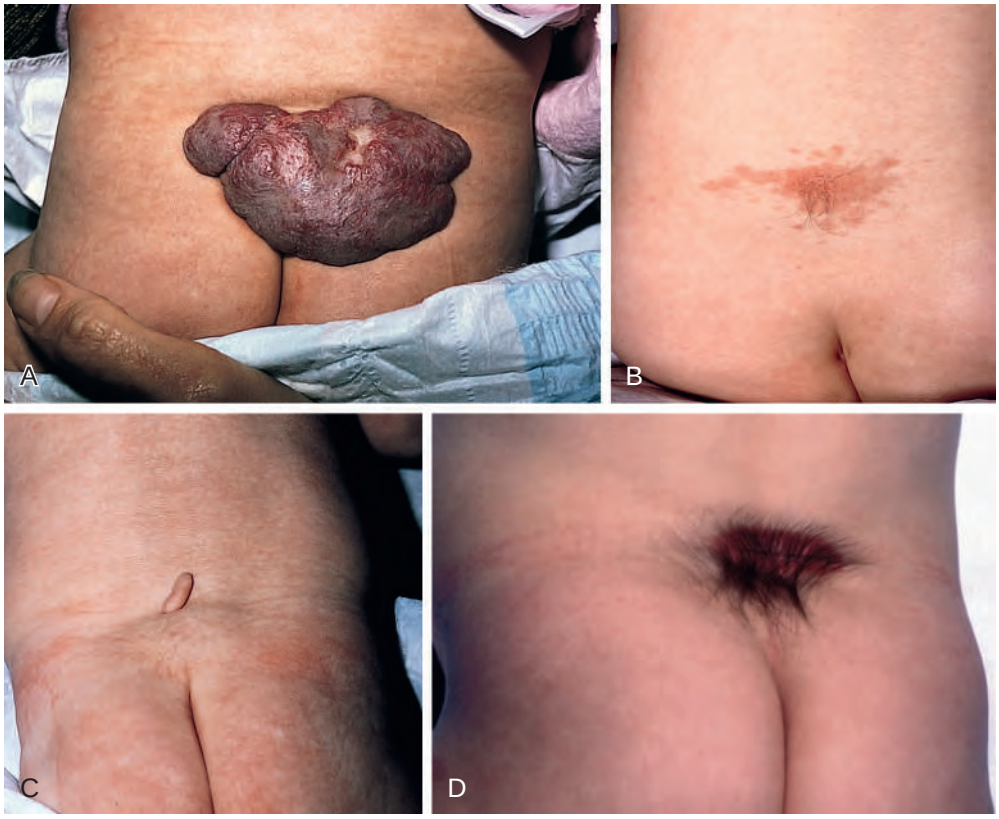


Figure 591-2 Clinical aspects of congenital median lumbosacral cutaneous lesions. **A,** Midline sacral hemangioma in a patient with an occult lipomyelomeningocele. **B,** Capillary malformation with a subtle patch of hypertrichosis in a patient with a dermal sinus. **C,** Human tail with underlying lipoma in an infant with lipomyelomeningocele. **D,** Midline area of hypertrichosis (faun tail) overlying a patch of hyperpigmentation. (**A-C** from Kos L, Drolet BA: Developmental abnormalities. In Eichenfield LF, Frieden IJ, Esterly NB, editors: *Neonatal dermatology*, ed 2, Philadelphia, 2008, WB Saunders. **D** from Spine and spinal cord: developmental disorders. In Schapira A, editor: *Neurology and clinical neuroscience*, Philadelphia, 2007, Mosby.)

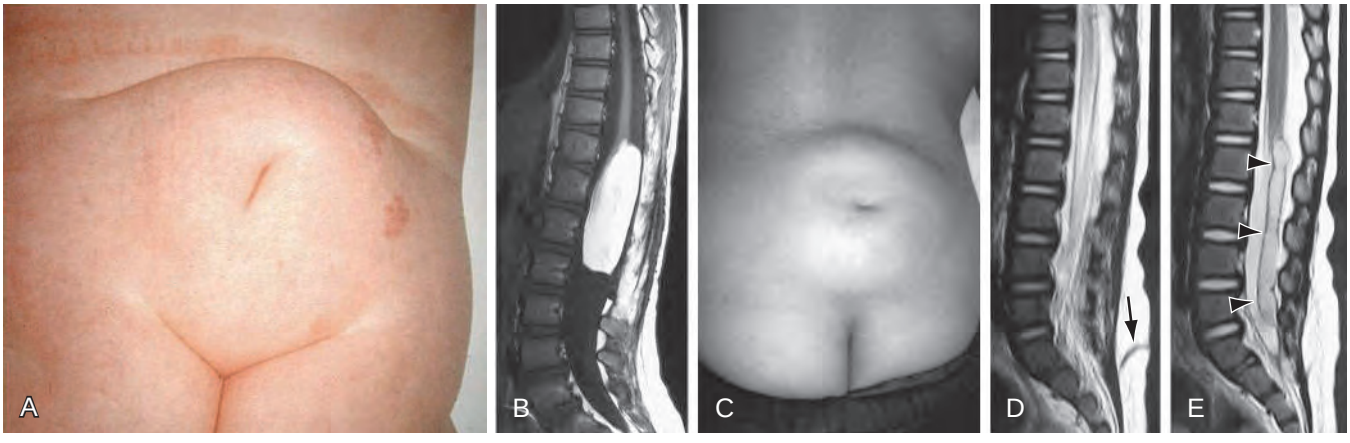


Figure 591-3 Clinical features and imaging findings associated with occult spinal dysraphism. **A,** Lumbosacral lipoma. The subcutaneous lipoma is in continuity with the spinal cord via a defect in the underlying muscles bone and dura. **B,** Sagittal T1-weighted image shows huge intradural lipoma, merging with the conus medullaris superiorly. **C,** Lipoma and central dermal sinus. **D** and **E,** Dermal sinus with dermoid on an 8 yr old girl. Slightly parasagittal T2-weighted image shows sacral dermal sinus coursing obliquely downward in subcutaneous fat *(arrow)* **(D).** Midsagittal T2-weighted image shows huge dermoid in the thecal sac *(arrowheads),* extending upward to the tip of the conus medullaris **(E).** The mass gives a slightly lower signal than cerebrospinal fluid and is outlined by a thin low-signal rim. (***A** from Thompson DNP: Spinal dysraphic anomalies: classification, presentation and management.* Paed Child Health *24:431–438, 2014, Fig. 4; **B, D,** and **E** from Rossi A, Biancheri R, Cama A, et al: Imaging in spine and spinal cord malformations,* Eur J Radiol *50(2):177–200, 2004, Fig. 9a; and **C,** from Jaiswal AK, Garg A, Mahapatra AK: Spinal ossifying lipoma,* J Clin Neurosci *12:714–717, 2005, Fig. 1.)*

591.3 Meningocele

Stephen L. Kinsman and Michael V. Johnston

A meningocele is formed when the meninges herniate through a defect in the posterior vertebral arches or the anterior sacrum. The spinal cord is usually normal and assumes a normal position in the spinal canal, although there may be tethering of the cord, syringomyelia, or diastematomyelia. A fluctuant midline mass that might transilluminate occurs along the vertebral column, usually in the lower back. Most meningoceles are well covered with skin and pose no immediate threat to the patient. Careful neurologic examination is mandatory. Orthopedic and urologic examination should also be considered. In asymptomatic children with normal neurologic findings and full-thickness skin covering the meningocele, surgery may be delayed or sometimes not performed.

Before surgical correction of the defect, the patient must be thoroughly examined with the use of plain x-rays, ultrasonography, and MRI to determine the extent of neural tissue involvement, if any, and associated anomalies, including diastematomyelia, lipoma, and possible clinically significant tethered spinal cord. Urologic evaluation usually includes cystometrogram to identify children with neurogenic bladder who are at risk for renal deterioration. Patients with leaking cerebrospinal fluid (CSF) or a thin skin covering should undergo immediate surgical treatment to prevent meningitis. A CT scan or MRI of the head is recommended for children with a meningocele because of the association with hydrocephalus in some cases. An anterior meningocele projects into the pelvis through a defect in the sacrum. Symptoms of constipation and bladder dysfunction develop due to the increasing size of the lesion. Female patients might have associated anomalies of the genital tract, including a rectovaginal fistula and vaginal septa. Plain x-rays demonstrate a defect in the sacrum, and CT scanning or MRI outlines the extent of the meningocele and any associated anomalies.

591.4 Myelomeningocele

Stephen L. Kinsman and Michael V. Johnston

Myelomeningocele represents the most severe form of dysraphism, a so-called aperta or open form, involving the vertebral column and spinal cord, which occurs with an incidence of approximately 1 in 4,000 live births.

ETIOLOGY

The cause of myelomeningocele is unknown, but as with all neural tube closure defects, including anencephaly, a genetic predisposition exists; the risk of recurrence after 1 affected child is 3-4% and increases to 10% with 2 prior affected children. Both epidemiologic evidence and the presence of substantial familial aggregation of anencephaly, myelomeningocele, and craniorachischisis indicate heredity, on a polygenic basis, as a significant contributor to the etiology of NTDs. Nutritional and environmental factors have a role in the etiology of myelomeningocele as well.

Folate is intricately involved in the prevention and etiology of NTDs. Folate functions in single-carbon transfer reactions and exists in many chemical forms. Folic acid (pteroylmonoglutamic acid), which is the most oxidized and stable form of folate, occurs rarely in food but is the form used in vitamin supplements and in fortified food products, particularly flour. Most naturally occurring folates (food folate) are pteroylpolyglutamates, which contain 1-6 additional glutamate molecules joined in a peptide linkage to the γ-carboxyl of glutamate. Folate coenzymes are involved in DNA synthesis, purine synthesis, generation of formate into the formate pool, and amino acid interconversion; the conversion of homocysteine to methionine provides methionine for the synthesis of *S*-adenosylmethionine (SAMe, an agent important for in vivo methylation). Mutations in the genes encoding the enzymes involved in homocysteine metabolism may play a role in the pathogenesis of meningomyelocele. These enzymes include 5,10-methylenetetrahydrofolate reductase, cystathionine β-synthase, and methionine synthase. An association between a thermolabile variant of 5,10-methylenetetrahydrofolate reductase and mothers of children with NTDs might account for up to 15% of preventable NTDs. Maternal periconceptional use of folic acid supplementation reduces the incidence of NTDs in pregnancies at risk by at least 50%. To be effective, folic acid supplementation should be initiated before conception and continued until at least the 12th wk of gestation, when neurulation is complete. The mechanisms by which folic acid prevents NTDs remain poorly understood.

PREVENTION

The U.S. Public Health Service has recommended that all women of childbearing age and who are capable of becoming pregnant take 0.4 mg of folic acid daily. If, however, a pregnancy is planned in high-risk women (previously affected child), supplementation should be started with 4 mg of folic acid daily, beginning 1 mo before the time of the planned conception. The modern diet provides about half the daily requirement of folic acid. To increase folic acid intake, fortification of flour, pasta, rice, and cornmeal with 0.15 mg folic acid per 100 g was mandated in the United States and Canada in 1998. The added folic acid is insufficient to maximize the prevention of preventable NTDs. Therefore, informative educational programs and folic acid vitamin supplementation remain essential for women planning a pregnancy and possibly for all women of childbearing age. In addition, women should also strive to consume food folate from a varied diet. Certain drugs, including drugs that antagonize folic acid, such as trimethoprim and the anticonvulsants carbamazepine, phenytoin, phenobarbital, and primidone, increase the risk of myelomeningocele. The anticonvulsant valproic acid causes NTDs in approximately 1-2% of pregnancies when administered during pregnancy. Some epilepsy clinicians recommend that all female patients of childbearing potential who take anticonvulsant medications also receive folic acid supplements. There may be a threshold for ideal red blood cell folate levels (900-1,000 nmol/L), which is associated with a markedly reduced risk of NTDs.

CLINICAL MANIFESTATIONS

Myelomeningocele produces dysfunction of many organs and structures, including the skeleton, skin, and gastrointestinal and genitourinary tracts, in addition to the peripheral nervous system and the CNS. A myelomeningocele may be located anywhere along the neuraxis, but the lumbosacral region accounts for at least 75% of the cases. The extent and degree of the neurologic deficit depend on the location of the myelomeningocele and the associated lesions. A lesion in the low sacral region causes bowel and bladder incontinence associated with anesthesia in the perineal area but with no impairment of motor function. Newborns with a defect in the midlumbar or high lumbothoracic region typically have either a sac-like cystic structure covered by a thin layer of partially epithelialized tissue (Fig. 591-4) or an exposed flat



Figure 591-4 A lumbar myelomeningocele is covered by a thin layer of skin.

neural placode without overlying tissues. When a cyst or membrane is present, remnants of neural tissue are visible beneath the membrane, which occasionally ruptures and leaks CSF.

Examination of the infant shows a flaccid paralysis of the lower extremities, an absence of deep tendon reflexes, a lack of response to touch and pain, and a high incidence of lower-extremity deformities (clubfeet, ankle and/or knee contractures, and subluxation of the hips). Some children have constant urinary dribbling and a relaxed anal sphincter. Other children do not leak urine and in fact have a high-pressure bladder and sphincter dyssynergy. Thus, a myelomeningocele above the midlumbar region tends to produce lower motor neuron signs because of abnormalities and disruption of the conus medullaris and above spinal cord structures.

Infants with myelomeningocele typically have increased neurologic deficit as the myelomeningocele extends higher into the thoracic region. These infants sometimes have an associated kyphotic gibbus that requires neonatal orthopedic correction. Patients with a myelomeningocele in the upper thoracic or cervical region usually have a very minimal neurologic deficit and, in most cases, do not have hydrocephalus. They can have neurogenic bladder and bowel.

Hydrocephalus in association with a type II Chiari malformation develops in at least 80% of patients with myelomeningocele. Generally, patients with sacral myelomeningocele have a very low risk of hydrocephalus. The possibility of hydrocephalus developing after the neonatal period should always be considered, no matter what the spinal level. Ventricular enlargement may be indolent and slow growing or may be rapid causing a bulging anterior fontanel, dilated scalp veins, setting-sun appearance of the eyes, irritability, and vomiting in association with an increased head circumference. Approximately 15% of infants with hydrocephalus and Chiari II malformation develop symptoms of hindbrain (brainstem) dysfunction, including difficulty feeding, choking, stridor, apnea, vocal cord paralysis, pooling of secretions, and spasticity of the upper extremities, which, if untreated, can lead to death. This Chiari crisis is caused by downward herniation of the medulla and cerebellar tonsils through the foramen magnum, as well as endogenous malformations in the cerebellum and brainstem, causing dysfunction.

TREATMENT

Management and supervision of a child and family with a myelomeningocele require a multidisciplinary team approach, including surgeons, other physicians, and therapists, with 1 individual (often a pediatrician) acting as the advocate and coordinator of the treatment program. The news that a newborn child has a devastating condition such as myelomeningocele causes parents to feel considerable grief and anger. They need time to learn about the condition and its associated complications and to reflect on the various procedures and treatment plans. A knowledgeable individual in an unhurried and nonthreatening setting must give the parents the facts, along with general prognostic information and management strategies and timelines. If possible, discussions with other parents of children with NTDs are helpful in resolving important questions and issues.

Surgery is often done within a day or so of birth but can be delayed for several days (except when there is a CSF leak) to allow the parents time to begin to adjust to the shock and to prepare for the multiple procedures and inevitable problems that lie ahead. Evaluation of other congenital anomalies and renal function can also be initiated before surgery. Most pediatric centers aggressively treat the majority of infants with myelomeningocele. After repair of a myelomeningocele, most infants require a shunting procedure for hydrocephalus. If symptoms or signs of hindbrain dysfunction appear, early surgical decompression of the posterior fossa is indicated. Clubfeet can require taping or casting, and dislocated hips may require operative procedures.

Careful evaluation and reassessment of the genitourinary system are some of the most important components of the management. Teaching the parents, and, ultimately, the patient, to regularly catheterize a neurogenic bladder is a crucial step in maintaining a low residual volume and bladder pressure that prevents urinary tract infections and reflux leading to pyelonephritis, hydronephrosis, and bladder damage. Latex-free catheters and gloves must be used to prevent development of latex allergy. Periodic urine cultures and assessment of renal function, including serum electrolytes and creatinine as well as renal scans, vesiculourethrograms, renal ultrasonography, and cystometrograms, are obtained according to the risk status and progress of the patient and the results of the physical examination. This approach to urinary tract management has greatly reduced the need for urologic diversionary procedures and significantly decreased the morbidity and mortality associated with progressive renal disease in these patients. Some children can become continent with surgical implantation of an artificial urinary sphincter (these are used less often) or bladder augmentation at a later age.

Although incontinence of fecal matter is common and is socially unacceptable during the school years, it does not pose the same organ-damaging risks as urinary dysfunction, but occasionally fecal impaction and/or megacolon develop. Many children can be bowel-trained with a regimen of timed enemas or suppositories that allows evacuation at a predetermined time once or twice a day. Special attention to low anorectal tone and enema administration and retention is often required. Appendicostomy for antegrade enemas may also be helpful (see Chapter 23.4).

Functional ambulation is the wish of each child and parent and may be possible, depending on the level of the lesion and on intact function of the iliopsoas muscles. Almost every child with a sacral or lumbosacral lesion obtains functional ambulation; approximately half the children with higher defects ambulate with the use of braces, other orthotic devices, and canes. Ambulation is often more difficult as adolescence approaches and body mass increases. Deterioration of ambulatory function, particularly during earlier years, should prompt referral for evaluation of tethered spinal cord and other neurosurgical issues.

In utero surgical closure of a spinal lesion has been successful in a few centers. Preliminary reports suggest a lower incidence of hindbrain abnormalities and hydrocephalus (fewer shunts) as well as improved motor outcomes. This suggests that the defects may be progressive in utero and that prenatal closure might prevent the development of further loss of function. In utero diagnosis is facilitated by maternal serum AFP screening and by fetal ultrasonography (see Chapter 96).

PROGNOSIS

For a child who is born with a myelomeningocele and who is treated aggressively, the mortality rate is 10-15%, and most deaths occur before age 4 yr, although life-threatening complications occur at all ages. At least 70% of survivors have normal intelligence, but learning problems and seizure disorders are more common than in the general population. Previous episodes of meningitis or ventriculitis adversely affect intellectual and cognitive function. Because myelomeningocele is a chronic disabling condition, periodic and consistent multidisciplinary follow-up is required for life. Renal dysfunction is one of the most important determinants of mortality.

Bibliography is available at Expert Consult.

591.5 Encephalocele

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Two major forms of dysraphism affect the skull, resulting in protrusion of tissue through a bony midline defect, called cranium bifidum. A cranial meningocele consists of a CSF-filled meningeal sac only, and a cranial encephalocele contains the sac plus cerebral cortex, cerebellum, or portions of the brainstem. Microscopic examination of the neural tissue within an encephalocele often reveals abnormalities. The cranial defect occurs most commonly in the occipital region at or

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below the inion, but in certain parts of the world, frontal or nasofrontal encephaloceles (transethmoidal, sphenoethmoidal, sphenomaxillary, sphenoorbital, transsphenoidal) are more common. Some frontal lesions are associated with a cleft lip and palate. These abnormalities are one-tenth as common as neural tube closure defects involving the spine. The etiology is presumed to be similar to that for anencephaly and myelomeningocele; examples of each are reported in the same family.

Infants with a cranial encephalocele are at increased risk for developing hydrocephalus because of **aqueductal stenosis**, **Chiari malformation**, or the **Dandy-Walker syndrome**. Examination might show a small sac with a pedunculated stalk or a large cyst-like structure that can exceed the size of the cranium. The lesion may be completely covered with skin, but areas of denuded lesion can occur and require urgent surgical management. Transillumination of the sac can indicate the presence of neural tissue. A plain x-ray of the skull and cervical spine is indicated to define the anatomy of the cranium and vertebrae. Ultrasonography is most helpful in determining the contents of the sac. MRI or CT further helps define the spectrum of the lesion. Children with a cranial meningocele generally have a good prognosis, whereas patients with an encephalocele are at risk for vision problems, microcephaly, intellectual disability, and seizures. Generally, children with neural tissue within the sac and associated hydrocephalus have the poorest prognosis.

Cranial encephalocele is often part of a syndrome. Meckel-Gruber syndrome is a rare autosomal recessive condition that is characterized by an occipital encephalocele, cleft lip or palate, microcephaly, microphthalmia, abnormal genitalia, polycystic kidneys, and polydactyly. Determination of maternal serum AFP levels and ultrasound measurement of the biparietal diameter, as well as identification of the encephalocele itself, can diagnose encephaloceles in utero. Fetal MRI can help define the extent of associated CNS anomalies and the degree of brain herniated into the encephalocele.

Bibliography is available at Expert Consult.

591.6 Anencephaly

Stephen L. Kinsman and Michael V. Johnston

An anencephalic infant presents a distinctive appearance with a large defect of the calvarium, meninges, and scalp associated with a rudimentary brain, which results from failure of closure of the rostral neuropore, the opening of the anterior neural tube. The primitive brain consists of portions of connective tissue, vessels, and neuroglia. The cerebral hemispheres and cerebellum are usually absent, and only a residue of the brainstem can be identified. The pituitary gland is hypoplastic, and the spinal cord pyramidal tracts are missing owing to the absence of the cerebral cortex. Additional anomalies include folding of the ears, cleft palate, and congenital heart defects in 10-20% of cases. Most anencephalic infants die within several days of birth.

The incidence of anencephaly approximates 1 in 1,000 live births; the greatest incidence is in Ireland, Wales, and Northern China. The recurrence risk is approximately 4% and increases to 10% if a couple has had 2 previously affected pregnancies. Many factors, in addition to genetics, are implicated as a cause of anencephaly, including low socioeconomic status, nutritional and vitamin deficiencies, and a large number of environmental and toxic factors. It is very likely that several noxious stimuli interact on a genetically susceptible host to produce anencephaly. The incidence of anencephaly has been decreasing since the 1990s. Approximately 50% of cases of anencephaly have associated polyhydramnios. Couples who have had an anencephalic infant should have successive pregnancies monitored, including amniocentesis, determination of AFP levels, and ultrasound examination between the 14th and 16th wk of gestation. Prenatal folic acid supplementation decreases the risk of this condition.

591.7 Disorders of Neuronal Migration

Stephen L. Kinsman and Michael V. Johnston

Disorders of neuronal migration can result in minor abnormalities with little or no clinical consequence (small heterotopia of neurons) or devastating abnormalities of CNS structure and/or function (intellectual disability, seizures, lissencephaly, and schizencephaly, particularly the open-lip form) (Fig. 591-5). One of the most important mechanisms in the control of neuronal migration is the radial glial fiber system that guides neurons to their proper site. Migrating neurons attach to the radial glial fiber and then disembark at predetermined sites to form, ultimately, the precisely designed 6-layered cerebral cortex. Another important mechanism is the tangential migration of progenitor neurons destined to become cortical interneurons. The severity and the extent of the disorder are related to numerous factors, including the timing of a particular insult and a host of environmental and genetic contributors. Some cortical malformations may be from somatic mutations, as exemplified by kinesin gene mutations in patients with pachygyria.

LISSENCEPHALY

Lissencephaly, or agyria, is a rare disorder that is characterized by the absence of cerebral convolutions and a poorly formed sylvian fissure, giving the appearance of a 3-4 mo fetal brain. The condition is probably a result of faulty neuroblast migration during early embryonic life and is usually associated with enlarged lateral ventricles and heterotopias in the white matter. In some forms, there is a 4-layered cortex, rather than the usual 6-layered one, with a thin rim of periventricular white matter and numerous gray heterotopias visible by microscopic examination. Milder forms of lissencephaly also exist.

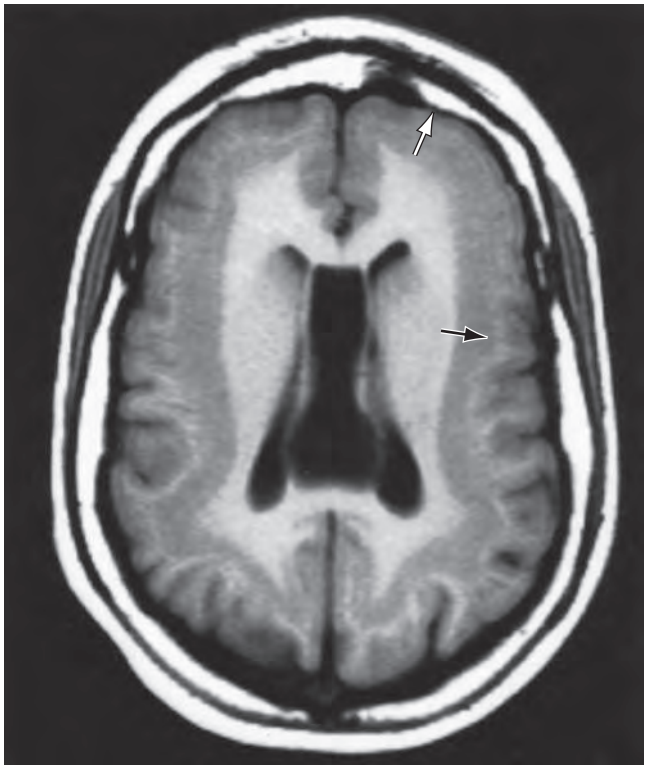


Figure 591-5 T1-weighted MRI scan demonstrating band heterotopia. A thin layer of white matter *(black arrow)* lies between the band of heterotopic gray matter and the cortical surface. Failure of cortical organization with lissencephaly is present in both frontal lobes *(white arrow)*.

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These infants present with failure to thrive, microcephaly, marked developmental delay, and a severe seizure disorder. Ocular abnormalities are common, including hypoplasia of the optic nerve and microphthalmia. Lissencephaly can occur as an isolated finding, but it is associated with Miller-Dieker syndrome in approximately 15% of cases. These children have characteristic facies, including a prominent forehead, bitemporal hollowing, anteverted nostrils, a prominent upper lip, and micrognathia. Approximately 70% of children with Miller-Dieker syndrome have visible or submicroscopic chromosomal deletions of 17p13.3.

The gene *LIS-1* (lissencephaly 1) that maps to chromosome region 17p13.3 is deleted in patients with Miller-Dieker syndrome. CT and MRI scans typically show a smooth brain with an absence of sulci (Fig. 591-6). *Doublecortin* is an X chromosome gene that causes lissencephaly when mutated in males and subcortical band heterotopia when mutated in females. Other important forms of lissencephaly include the Walker-Warburg variant and other cobblestone cortical malformations.

SCHIZENCEPHALY

Schizencephaly is the presence of unilateral or bilateral clefts within the cerebral hemispheres owing to an abnormality of morphogenesis (Fig. 591-7). The cleft may be fused or unfused and, if unilateral and large, may be confused with a porencephalic cyst. Not infrequently, the borders of the cleft are surrounded by abnormal brain, particularly microgyria. MRI is the study of choice for elucidating schizencephaly and associated malformations.

When the clefts are bilateral, many patients are severely intellectually challenged, with seizures that are difficult to control, and microcephalic, with spastic quadriparesis. Some cases of bilateral schizencephaly are associated with septooptic dysplasia and endocrinologic disorders. Unilateral schizencephaly is a common cause of congenital hemiparesis. It remains controversial whether genetic causes of schizencephaly exist. Some gene mutations are seen in cases of familial schizencephaly.

NEURONAL HETEROTOPIAS

Subtypes of neuronal heterotopias include periventricular nodular heterotopias, subcortical heterotopia (including band-type), and marginal glioneuronal heterotopias. Intractable seizures are a common feature. Several genes have been identified that are a cause of these conditions.

POLYMICROGYRIAS

Polymicrogyria is characterized by an augmentation of small convolutions separated by shallow enlarged sulci. Epilepsy, including drug-resistant forms, is a common feature. Truncation of the *KBP* gene has been implicated in a family with multiple members with polymicrogyria.



Figure 591-6 MRI of an infant with lissencephaly. Note the absence of cerebral sulci and the maldeveloped sylvian fissures associated with enlarged ventricles.

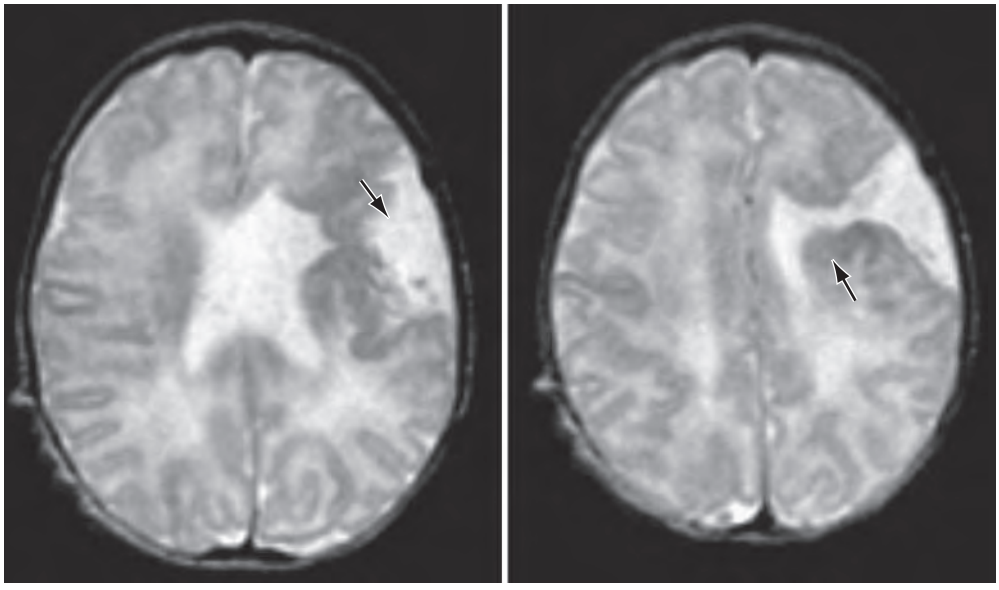


Figure 591-7 Unilateral schizencephaly shown on axial MR images of the brain. Example of an open-lip schizencephaly with a cleft communicating between the ventricle and the extraaxial cranial space *(arrow on left panel)*. Many of these clefts are lined with abnormal gray matter *(arrow on right panel)*.

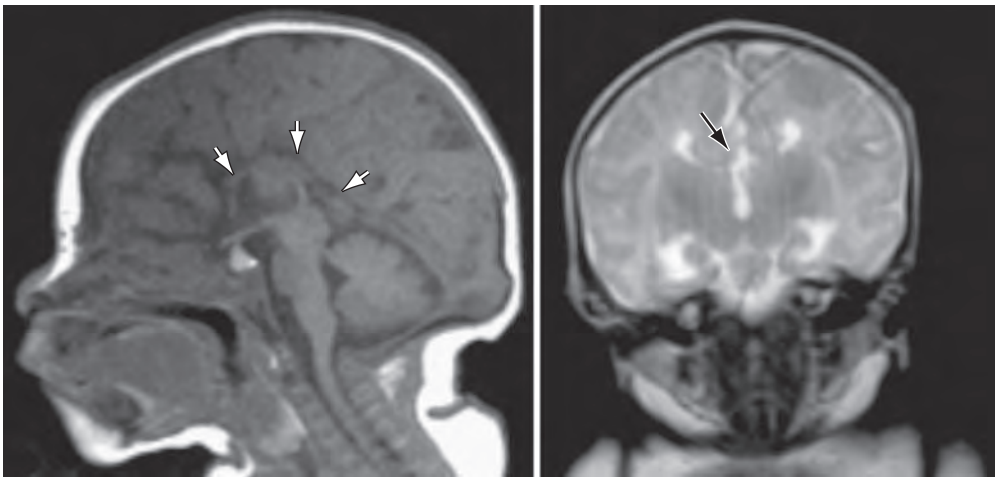


Figure 591-8 Agenesis of the corpus callosum shown on MR images of the brain. Sagittal *(left panel)* and coronal *(right panel)* views of an infant show the total absence of a midsagittal white matter structure *(left panel, arrows)*. The coronal view *(right panel)* demonstrates (despite some motion artifact) the absence of a structure bridging the 2 hemispheres *(area under arrow)*.

FOCAL CORTICAL DYSPLASIAS

Focal cortical dysplasias consist of abnormal cortical lamination in a discrete area of cortex. High-resolution, thin-section MRI can reveal these areas sometimes in the setting of drug-resistant epilepsy.

PORENCEPHALY

Porencephaly is the presence of cysts or cavities within the brain that result from developmental defects or acquired lesions, including infarction of tissue. True porencephalic cysts are most commonly located in the region of the sylvian fissure and typically communicate with the subarachnoid space, the ventricular system, or both. They represent developmental abnormalities of cell migration and are often associated with other malformations of the brain, including microcephaly, abnormal patterns of adjacent gyri, and encephalocele. Affected infants tend to have many problems, including intellectual disability, spastic hemiparesis or quadriparesis, optic atrophy, and seizures.

Several risk factors for porencephalic cyst formation have been identified, including hemorrhagic venous infarctions; various thrombophilias such as protein C deficiency and factor V Leiden mutations; perinatal alloimmune thrombocytopenia; von Willebrand disease; maternal warfarin use; maternal cocaine use; congenital infections; trauma such as amniocentesis; and maternal abdominal trauma. Mutations in the *COL4A1* gene have been described in cases of familial porencephaly.

Pseudoporencephalic cysts characteristically develop during the perinatal or postnatal period and result from abnormalities (infarction, hemorrhage) of arterial or venous circulation. These cysts tend to be unilateral, do not communicate with a fluid-filled cavity, and are not associated with abnormalities of cell migration or CNS malformations. Infants with pseudoporencephalic cysts present with hemiparesis and focal seizures in the 1st yr of life and sometimes present with neonatal encephalopathy or as a floppy newborn or infant.

Bibliography is available at Expert Consult.

591.8 Agenesis of the Corpus Callosum

Stephen L. Kinsman and Michael V. Johnston

Agenesis of the corpus callosum consists of a heterogeneous group of disorders that vary in expression from severe intellectual and neurologic abnormalities to the asymptomatic and normally intelligent patient (Fig. 591-8). The corpus callosum develops from the commissural plate that lies in proximity to the anterior neuropore. Either a direct insult to the commissural plate or disruption of the genetic signaling that specifies and organizes this area during early embryogenesis causes agenesis of the corpus callosum.

It is often said that the outcome of agenesis of the corpus callosum is dictated by *the company it keeps*. When agenesis of the corpus callosum is an isolated phenomenon, the patient may be normal. When it is accompanied by brain anomalies from cell migration defects, such as heterotopias, polymicrogyria, and pachygyria (broad, wide gyri), patients often have significant neurologic abnormalities, including intellectual disability, microcephaly, hemiparesis, diplegia, and seizures.

The anatomic features of agenesis of the corpus callosum are best depicted on MRI or CT scan and include widely separated frontal horns with an abnormally high position of the third ventricle between the lateral ventricles. MRI precisely outlines the extent of the corpus callosum defect.

Absence of the corpus callosum may be inherited as an X-linked recessive trait or as an autosomal dominant trait and on occasion as an autosomal recessive trait. The condition may be associated with specific chromosomal disorders, particularly trisomy 8 and trisomy 18. Single-gene mutations have also been identified, usually in association with other anomalies. Agenesis of the corpus callosum is also seen in some metabolic disorders (Table 591-2).

Aicardi syndrome represents a complex disorder that affects many systems and is typically associated with agenesis of the corpus callosum, distinctive chorioretinal lacunae, and infantile spasms. Patients are almost all female, suggesting a genetic abnormality of the X chromosome (it may be lethal in males during fetal life). Seizures become evident during the 1st few mo and are typically resistant to anticonvulsants. An electroencephalogram shows independent activity recorded from both hemispheres as a result of the absent corpus callosum and shows often hemihypsarrhythmia. All patients have severe intellectual disability and can have abnormal vertebrae that may be fused or only partially developed (hemivertebra). Abnormalities of the retina, including circumscribed pits or lacunae and coloboma of the optic disc, are the most characteristic findings of Aicardi syndrome.

Colpocephaly refers to an abnormal enlargement of the occipital horns of the ventricular system and can be identified as early as the fetal period. It is often associated with agenesis of the corpus callosum, but it can occur in isolation. It is also associated with microcephaly. It can also be seen in anatomic megalencephaly, such as is associated with Sotos syndrome.

HOLOPROSENCEPHALY

Holoprosencephaly is a developmental disorder of the brain that results from defective formation of the prosencephalon and

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Table 591-2 Disorders Associated with Agenesis of the Corpus Callosum*

DISORDER	SALIENT FEATURES
WITH IDENTIFIED GENES†	
Andermann syndrome *(KCC3)*	ACC, progressive neuropathy, and dementia
Donnai-Barrow syndrome *(LRP2)*	Diaphragmatic hernia, exomphalos, ACC, deafness
Frontonasal dysplasia *(ALX1)*	ACC, bilateral extreme microphthalmia, bilateral oblique facial cleft
XLAG *(ARX)*	Lissencephaly, ACC, intractable epilepsy
Microcephaly *(TBR2)*	ACC, polymicrogyria
Microcephaly with simplified gyral pattern and ACC *(WDR62)*	
Mowat-Wilson syndrome *(ZFHX1B)*	Hirschsprung disease, ACC
Pyridoxine-dependent epilepsy *(ALDH7A1)*	ACC, seizures, other brain malformations
Pyruvate dehydrogenase deficiency *(PDHA1, PDHB, PDHX)*	ACC with other brain changes
ACC with fatal lactic acidosis *(MRPS16)*	Complexes I and IV deficiency, ACC, brain malformations
HSAS/MASA syndromes *(L1CAM)*	Hydrocephalus, adducted thumbs, ACC, MR
ACC SEEN CONSISTENTLY (NO GENE YET IDENTIFIED)	
Acrocallosal syndrome	ACC, polydactyly, craniofacial changes, MR
Aicardi syndrome	ACC, chorioretinal lacunae, infantile spasms, MR
Chudley-McCullough syndrome	Hearing loss, hydrocephalus, ACC, colpocephaly
FG syndrome	MR, ACC, craniofacial changes, macrocephaly
Genitopatellar syndrome	Absent patellae, urogenital malformations, ACC
Temtamy syndrome	ACC, optic coloboma, craniofacial changes, MR
Toriello-Carey syndrome	ACC, craniofacial changes, cardiac defects, MR
Vici syndrome	ACC, albinism, recurrent infections, MR
ACC SEEN OCCASIONALLY (PARTIAL LIST)‡	
ACC with spastic paraparesis *(SPG11; SPG15)*	Progressive spasticity and neuropathy, thin corpus callosum
Craniofrontonasal syndrome	Coronal craniosynostosis, facial asymmetry, bifid nose
Fryns syndrome	CDH, pulmonary hypoplasia, craniofacial changes
Marden-Walker syndrome	Blepharophimosis, micrognathia, contractures, ACC
Meckel-Gruber syndrome	Encephalocele, polydactyly, polycystic kidneys
Nonketotic hyperglycinemia *(GLDC, GCST, GCSH)*	ACC, cerebral and cerebellar atrophy, myoclonus, progressive encephalopathy
Microphthalmia with linear skin defects	Microphthalmia, linear skin markings, seizures
Opitz G syndrome	Pharyngeal cleft, craniofacial changes, ACC, MR
Orofaciodigital syndrome	Tongue hamartoma, microretrognathia, clinodactyly
Pyruvate decarboxylase deficiency	Lactic acidosis, seizures, severe MR and spasticity
Rubinstein-Taybi syndrome	Broad thumbs and great toes, MR, microcephaly
Septooptic dysplasia (de Morsier syndrome)	Hypoplasia of septum pellucidum and optic chiasm
Sotos syndrome	Physical overgrowth, MR, craniofacial changes
Warburg micro syndrome	Microcephaly, microphthalmia, microgenitalia, MR
Wolf-Hirschhorn syndrome	Microcephaly, seizures, cardiac defects, 4p–

*Reliable incidence data are unavailable for these very rare syndromes.

†Gene symbols in parentheses.

‡Many of these also may consistently have a thin of dysplastic corpus callosum, such as Sotos' syndrome or agenesis of the corpus callosum (ACC) with spastic paraparesis (SPG11). The overlap between ACC and these conditions is still under investigation. Other gene symbols are omitted from this section.

4p–, deletion of the terminal region of the short arm of chromosome 4, defines the genotype for Wolf-Hirschhorn patients; ACC, agenesis of the corpus callosum; ARX, Aristaless-related homeobox gene; CDH, congenital diaphragmatic hernia; HSAS/MASA, X-linked hydrocephalus/mental retardation, aphasia, shuffling gait, and adducted thumbs; KCC3, KCl cotransporter 3; L1CAM, L1 cell adhesion molecule; MR, mental retardation; MRPS16, mitochondrial ribosomal protein S16; SPG11, spastic paraplegia 11; XLAG, X-linked lissencephaly with absent corpus callosum and ambiguous genitalia; ZFHX1B, zinc finger homeobox 1b.

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inadequate induction of forebrain structures. The abnormality, which represents a spectrum of severity, is classified into 3 groups: alobar, semilobar, and lobar, depending on the degree of the cleavage abnormality (Fig. 591-9). A fourth type, the middle interhemispheric fusion variant or syntelencephaly, involves a segmental area of noncleavage, actually a nonseparation, of the posterior frontal and parietal lobes. Facial abnormalities, including cyclopia, synophthalmia, cebocephaly, single nostril, choanal atresia, solitary central incisor tooth, and premaxillary agenesis are common in severe cases, because the prechordal mesoderm that induces the ventral prosencephalon is also responsible for induction of the median facial structures. Milder facial abnormalities are seen in milder forms. Alobar holoprosencephaly is characterized by a single ventricle, an absent falx, and nonseparated deep cerebral nuclei. Care must be taken not to overdiagnose holoprosencephaly based on ventricular abnormalities alone. Evidence of nonseparated midline deep-brain structures, such as caudate, putamen, globus pallidus, and hypothalamus, is the critical element for diagnosis.

Affected children with the alobar type have high mortality rates, but some live for years. Mortality and morbidity with milder types are more variable, and morbidity is less severe. Care must be taken not to prognosticate severe outcomes in all cases. The incidence of holoprosencephaly ranges from 1 in 5,000-16,000 live births. A prenatal diagnosis can be confirmed by ultrasonography after the 10th wk of gestation for more severe types, but fetal MRI at later gestational ages gives far greater anatomic, and therefore diagnostic, precision.

The cause of holoprosencephaly is often not identified. There appears to be an association with maternal diabetes. Chromosomal abnormalities, including deletions of chromosomes 7q and 3p, 21q, 2p, 18p, and 13q, as well as trisomy 13 and 18, account for upwards of 50% of all cases. Mutations in the *sonic hedgehog* gene at 7q have been shown to cause holoprosencephaly. *Gene Reviews* lists 14 single-gene causes. Clinically, it is important to look for associated anomalies, because many syndromes are associated with holoprosencephaly.

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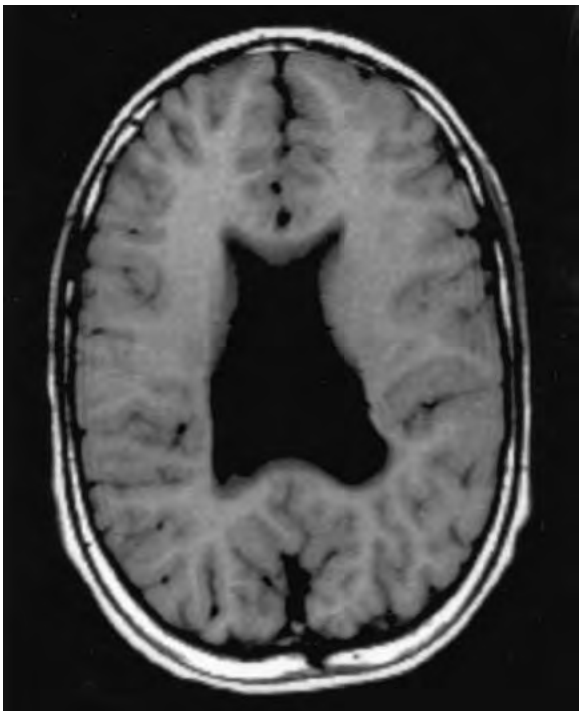


Figure 591-9 Lobar holoprosencephaly. T1-weighted MRI scan demonstrates failure of separation of the hemispheres and a persistent fused ventricle.

591.9 Agenesis of the Cranial Nerves and Dysgenesis of the Posterior Fossa

Stephen L. Kinsman and Michael V. Johnston

Classification of disorders of cranial nerve, brainstem, and cerebellum development remains anatomic, but future classification systems will likely be based on the molecular biology of brain development based on the genes involved and the roles they play in orchestrating brain architecture.

CONGENITAL CRANIAL DYSINNERVATION DISORDERS

Absence of the cranial nerves or the corresponding central nuclei has been described in several conditions and includes the optic nerve defects, congenital ptosis, Marcus Gunn phenomenon (sucking jaw movements causing simultaneous eyelid blinking; this congenital synkinesis results from abnormal innervation of the trigeminal and oculomotor nerves), trigeminal and auditory nerves defects, and cranial nerves IX, X, XI, and XII defects. Increased understanding of these disorders and their genetic causes has led to the term *congenital cranial dysinnervation disorders*.

Optic nerve hypoplasia can occur in isolation or as part of the septooptic dysplasia complex (de Morsier syndrome). Septooptic dysplasia can be caused by a mutation in the *HESX1* gene.

Möbius syndrome is characterized by bilateral facial weakness, which is often associated with paralysis of the abducens nerve. Hypoplasia or agenesis of brainstem nuclei, as well as absent or decreased numbers of muscle fibers, has been reported. Affected infants present in the newborn period with facial weakness, causing feeding difficulties owing to a poor suck. The immobile, dull facies might give the incorrect impression of intellectual impairment; the prognosis for normal development is excellent in most cases. The facial appearance of Möbius syndrome has been improved by facial surgery.

Duane retraction syndrome is characterized by congenital limitation of horizontal globe movement and some globe retraction on attempted adduction and is believed to be the result of abnormal innervation by the oculomotor nerve of the lateral rectus muscle. Abnormalities of cranial nerve development have been demonstrated in this condition.

Less common than Duane retraction syndrome and Möbius syndrome are the group of disorders known as **congenital fibrosis of the extraocular muscles**. Congenital fibrosis of the extraocular muscles is characterized by severe restriction of eye movements and ptosis from abnormal oculomotor and trochlear nerve development and/or from abnormalities of extraocular muscle innervation.

BRAINSTEM AND CEREBELLAR DISORDERS

Disorders of the posterior fossa structures include abnormalities of not only the brainstem and cerebellum, but also the CSF spaces. Commonly encountered malformations include Chiari malformation, Dandy-Walker malformation, arachnoid cysts, mega cisterna magna, persisting Blake pouch, Joubert syndrome, rhombencephalosynapsis, Lhermitte-Duclos disease, and the pontocerebellar hypoplasias.

Chiari malformation is the most common malformation of the posterior fossa and hindbrain. It consists of herniation of the cerebellar tonsils though the foramen magnum. Often, there is also an associated developmental abnormality of the bones of the skull base leading to a small posterior fossa. Cases can be either asymptomatic or symptomatic. When symptoms develop, they often do not do so until late childhood. Symptoms include headaches that are worse with straining and other maneuvers that increase intracranial pressure. Symptoms of brainstem compression such as diplopia, oropharyngeal dysfunction, spasticity, tinnitus, and vertigo can occur. Obstructive hydrocephalus and/or syringomyelia can also occur.

Dandy-Walker malformation is part of a continuum of posterior fossa anomalies that include cystic dilation of the fourth ventricle, hypoplasia of the cerebellar vermis, hydrocephalus, and an enlarged posterior fossa with elevation of the lateral venous sinuses and the tentorium. Extracranial anomalies are also seen. Variable degrees of neurologic impairment are usually present. The etiology of Dandy-Walker malformation includes chromosomal abnormalities, single gene disorders, and exposure to teratogens.

Arachnoid cysts of the posterior fossa can be associated with hydrocephalus. Mega cisterna magna is characterized by an enlarged CSF space inferior and dorsal to the cerebellar vermis and when present in isolation may be considered a normal variant. Persisting Blake pouch is a cyst that obstructs the subarachnoid space and is associated with hydrocephalus.

Joubert syndrome is an autosomal recessive disorder (ciliopathy) with significant genetic heterogeneity that is associated with cerebellar vermis hypoplasia and the pontomesencephalic **molar tooth sign** (a deepening of the interpeduncular fossa with thick and straight superior cerebellar peduncles) (Fig. 591-10). It is associated with hypotonia, ataxia (as toddler), characteristic breathing abnormalities including episodic apnea and hyperpnea (which improves with age), global developmental delay, nystagmus, strabismus, ptosis, and oculomotor apraxia. There can be many associated systemic features (Joubert syndrome and related disorders) including progressive retinal dysplasia (Leber congenital amaurosis), coloboma, congenital heart disease, microcystic kidney disease, liver fibrosis, polydactyly, tongue protrusion, and soft tissue tumors of the tongue (Fig. 591-11).

Rhombencephalosynapsis is an absent or small vermis associated with a nonseparation or fusion of the deep midline cerebellar structures. Ventriculomegaly or hydrocephalus is often seen. There is variable clinical presentation from normal to cognitive and language impairments, epilepsy, and spasticity. **Lhermitte-Duclos** disease is a dysplastic gangliocytoma of the cerebellum leading to focal enlargement of the cerebellum and macrocephaly, cerebellar signs, and seizures.

Pontocerebellar hypoplasias are a group of disorders characterized by impairment of cerebellar and pontine development together with histopathologic features of neuronal death and glial replacement. Clinical features tend to be nonspecific and include hypotonia, feeding difficulties, developmental delay, and breathing difficulties. Classification, associations, and causes include type I (with features of anterior

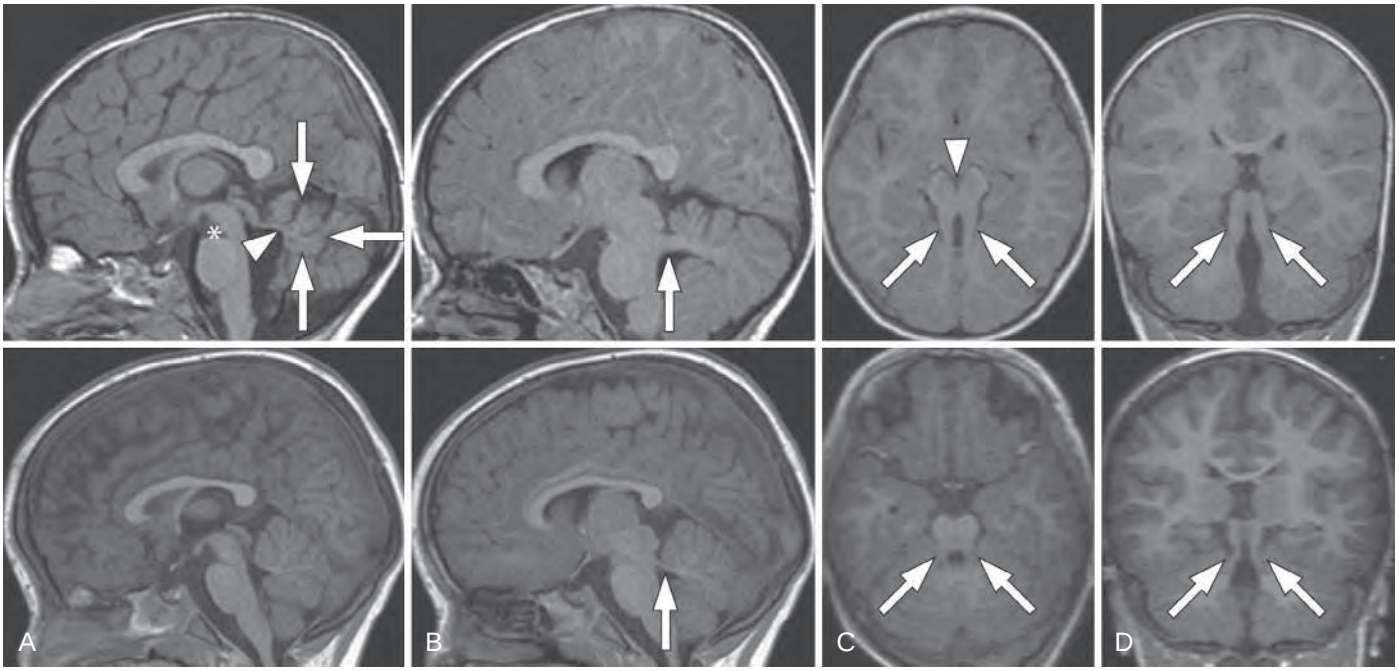


Figure 591-10 Neuroimaging findings in a 2-yr-old child with pure Joubert syndrome *(upper panels)* compared to a healthy control *(lower panels).* **A,** Parasagittal T1-weighted image shows the thickened, elongated, and horizontally orientated superior cerebellar peduncles *(white arrow).* **B,** Midsagittal T1-weighted image demonstrates a moderate hypoplasia and dysplasia of the cerebellar vermis *(white arrows)* with secondary distortion and enlargement of the fourth ventricle with rostral shifting of the fastigium *(white arrowhead).* A deepened interpeduncular fossa is also noted. **C,** Axial T1-weighted image at the level of the pontomesencephalic junction shows the molar tooth sign with a deepened interpeduncular fossa *(white arrowhead)* and elongated, thickened, and horizontally orientated superior cerebellar peduncles *(white arrows).* Additionally, the cerebellar vermis appears to be hypoplastic and its remnants dysplastic. **D,** Coronal T1-weighted image reveals the thickened superior cerebellar peduncles *(white arrows). (From Romani M, Micalizzi A, Valente EM: Joubert syndrome: congenital cerebellar ataxia with the molar tooth.* Lancet Neurol *12:894–905, 2013, Fig. 1.)*

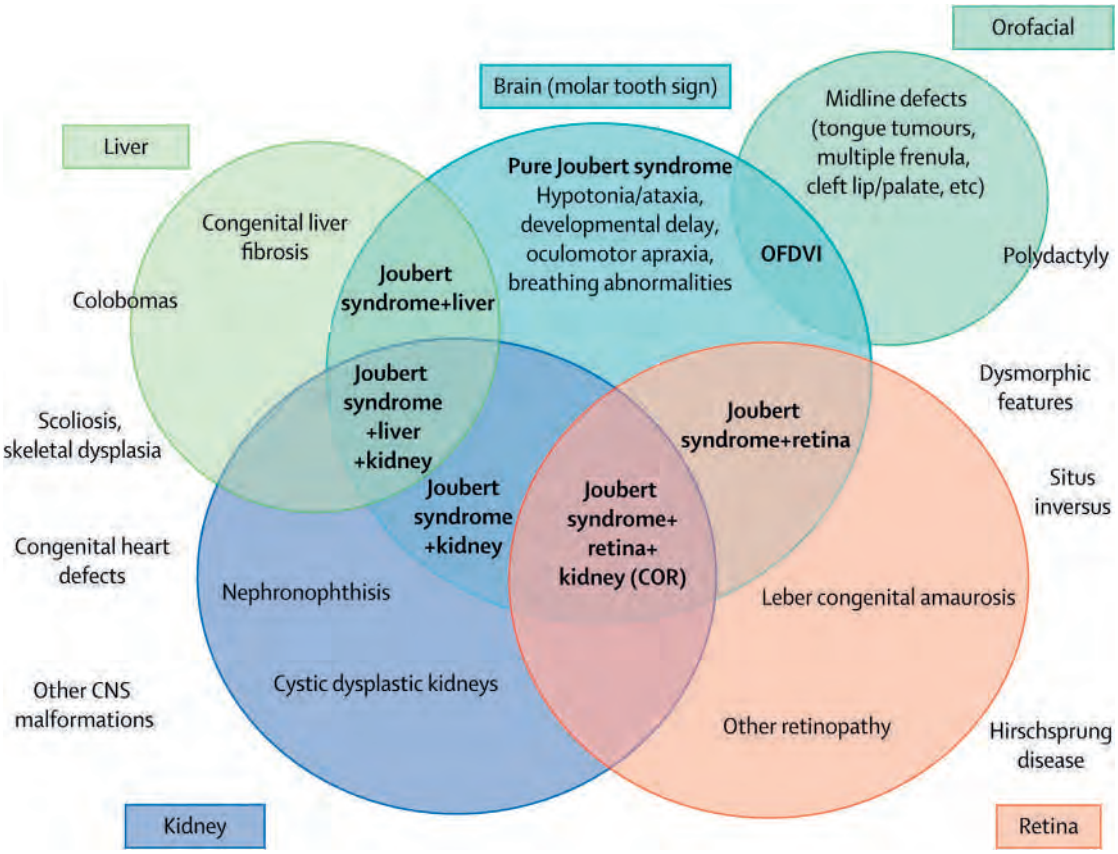


Figure 591-11 Spectrum of organ involvement in Joubert syndrome and classification in clinical subgroups *(in bold).* Chorioretinal colobomas are more frequently found in the subgroup of Joubert syndrome with liver involvement but can be present also in other subgroups. Similarly, polydactyly (especially if preaxial or mesoaxial) is invariably present in the Orofaciodigital type VI subgroup, but postaxial polydactyly is frequently observed also in association with other Joubert syndrome phenotypes. Other clinical features outside the circles occur more rarely, without a specific association to a clinical subgroup. *CNS,* central nervous system; *COR,* cerebello oculorenal; K, kidney involvement; L, liver involvement; MTS, molar tooth sign; *OFDVI,* orofaciodigital type VI syndrome. *(From Romani M, Micalizzi A, Valente EM: Joubert syndrome: congenital cerebellar ataxia with the molar tooth.* Lancet Neurol *12:894–905, 2013, Fig. 3.)*

horn cell involvement), type II (with extrapyramidal features, seizures, and acquired microcephaly), Walker-Warburg syndrome, muscle-eye-brain disease, congenital disorders of glycosylation type 1A, mitochondrial cytopathies, teratogen exposure, congenital cytomegalovirus infection, 3-methylglutaconic aciduria, PEHO syndrome (progressive encephalopathy with edema, hypsarrhythmia, and optic atrophy), autosomal recessive cerebellar hypoplasia in the Hutterite population, lissencephaly with cerebellar hypoplasia, and other subtypes of pontocerebellar hypoplasia.

Bibliography is available at Expert Consult.

591.10 Microcephaly

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Microcephaly is defined as a head circumference that measures more than 3 SD below the mean for age and sex. This condition is relatively common, particularly among developmentally delayed children. Although there are many causes of microcephaly, abnormalities in neuronal migration during fetal development, including heterotopias of neuronal cells and cytoarchitectural derangements, are often found. Microcephaly may be subdivided into 2 main groups: primary (genetic) microcephaly and secondary (nongenetic) microcephaly. A precise diagnosis is important for genetic counseling and for prediction for future pregnancies.

ETIOLOGY

Primary microcephaly refers to a group of conditions that usually have no associated malformations and follow a mendelian pattern of inheritance or are associated with a specific genetic syndrome. Affected infants are usually identified at birth because of a small head circumference. The more common types include familial and autosomal dominant microcephaly and a series of chromosomal syndromes that are summarized in Table 591-3. Primary microcephaly is also associated with at least 7 gene loci, and 7 single etiologic genes have been identified. It is known as autosomal recessive primary microcephaly and has autosomal inheritance. Many X-linked causes of microcephaly are caused by gene mutations that lead to severe structural brain

Table 591-3 Causes of Microcephaly

CAUSES	CHARACTERISTIC FINDINGS
PRIMARY (GENETIC)	
Familial (autosomal recessive)	Incidence 1 in 40,000 live births Typical appearance with slanted forehead, prominent nose and ears; severe mental retardation and prominent seizures; surface convolutional markings of the brain, poorly differentiated and disorganized cytoarchitecture
Autosomal dominant	Nondistinctive facies, upslanting palpebral fissures, mild forehead slanting, and prominent ears Normal linear growth, seizures readily controlled, and mild or borderline mental retardation
Syndromes	
Down (trisomy 21)	Incidence 1 in 800 live births Abnormal rounding of occipital and frontal lobes and a small cerebellum; narrow superior temporal gyrus, propensity for Alzheimer neurofibrillary alterations, ultrastructure abnormalities of cerebral cortex
Edward (trisomy 18)	Incidence 1 in 6,500 live births Low birthweight, microstomia, micrognathia, low-set malformed ears, prominent occiput, rocker-bottom feet, flexion deformities of fingers, congenital heart disease, increased gyri, heterotopias of neurons
Cri-du-chat (5 p-)	Incidence 1 in 50,000 live births Round facies, prominent epicanthic folds, low-set ears, hypertelorism, characteristic cry No specific neuropathology
Cornelia de Lange	Prenatal and postnatal growth delay; synophrys; thin, downturning upper lip Proximally placed thumb
Rubinstein-Taybi	Beaked nose, downward slanting of palpebral fissures, epicanthic folds, short stature, broad thumbs and toes
Smith-Lemli-Opitz	Ptosis, scaphocephaly, inner epicanthic folds, anteverted nostrils Low birthweight, marked feeding problems
SECONDARY (NONGENETIC)	
Congenital Infections	
Cytomegalovirus	Small for dates, petechial rash, hepatosplenomegaly, chorioretinitis, deafness, mental retardation, seizures Central nervous system calcification and microgyria
Rubella	Growth retardation, purpura, thrombocytopenia, hepatosplenomegaly, congenital heart disease, chorioretinitis, cataracts, deafness Perivascular necrotic areas, polymicrogyria, heterotopias, subependymal cavitations
Toxoplasmosis	Purpura, hepatosplenomegaly, jaundice, convulsions, hydrocephalus, chorioretinitis, cerebral calcification
Drugs	
Fetal alcohol	Growth retardation, ptosis, absent philtrum and hypoplastic upper lip, congenital heart disease, feeding problems, neuroglial heterotopia, disorganization of neurons
Fetal hydantoin	Growth delay, hypoplasia of distal phalanges, inner epicanthic folds, broad nasal ridge, anteverted nostrils
Other Causes	
Radiation	Microcephaly and mental retardation most severe with exposure before 15th wk of gestation
Meningitis/encephalitis	Cerebral infarcts, cystic cavitation, diffuse loss of neurons
Malnutrition	Controversial cause of microcephaly
Metabolic	Maternal diabetes mellitus and maternal hyperphenylalaninemia
Hyperthermia	Significant fever during 1st 4-6 wk has been reported to cause microcephaly, seizures, and facial anomalies Pathologic studies show neuronal heterotopias Further studies show no abnormalities with maternal fever
Hypoxic–ischemic encephalopathy	Initially diffuse cerebral edema; late stages characterized by cerebral atrophy and abnormal signals on MRI

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malformations such as lissencephaly, holoprosencephaly, polymicrogyria, cobblestone dysplasia, neuronal heterotopia, pontocerebellar hypoplasia; these should be sought on MRI. Secondary microcephaly results from a large number of noxious agents that can affect a fetus in utero or an infant during periods of rapid brain growth, particularly the 1st 2 yr of life.

Acquired microcephaly can be seen in conditions such as Rett, Seckel, and Angelman syndromes and in encephalopathy syndromes associated with severe seizure disorders.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

A thorough family history should be taken, seeking additional cases of microcephaly or disorders affecting the nervous system. It is important to measure a patient's head circumference at birth to diagnose microcephaly as early as possible. A very small head circumference implies a process that began early in embryonic or fetal development. An insult to the brain that occurs later in life, particularly beyond the age of 2 yr, is less likely to produce severe microcephaly. Serial head circumference measurements are more meaningful than a single determination, particularly when the abnormality is minimal. The head circumference of each parent and sibling should be recorded.

Laboratory investigation of a microcephalic child is determined by the history and physical examination. If the cause of the microcephaly is unknown, the mother's serum phenylalanine level should be determined. High phenylalanine serum levels in an asymptomatic mother can produce marked brain damage in an otherwise normal nonphenylketonuric infant. A karyotype and/or array comparative genomic hybridization study is obtained if a chromosomal syndrome is suspected or if the child has abnormal facies, short stature, and additional congenital anomalies. MRI is useful in identifying structural abnormalities of the brain such as lissencephaly, pachygyria, and polymicrogyria, and CT scanning is useful to detect intracerebral calcification. Additional studies include a fasting plasma and urine amino acid analysis; serum ammonia determination; *to*xoplasmosis, *r*ubella, *c*ytomegalovirus, and *h*erpes simplex (TORCH) titers as well as HIV testing of the mother and child; and a urine sample for the culture of cytomegalovirus. Single-gene mutations as a cause of both primary microcephaly and syndromic microcephaly are being increasingly identified.

TREATMENT

Once the cause of microcephaly has been established, the physician must provide accurate and supportive genetic and family counseling. Because many children with microcephaly are also intellectually challenged, the physician must assist with placement in an appropriate program that will provide for maximal development of the child (see Chapter 36).

Bibliography is available at Expert Consult.

591.11 Hydrocephalus

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Hydrocephalus is not a specific disease; it represents a diverse group of conditions that result from impaired circulation and/or absorption of CSF or, in rare circumstances, from increased production of CSF by a choroid plexus papilloma (Table 591-4). Because megalencephaly is often discovered as part of an evaluation for hydrocephalus in children with macrocephaly, it is included in this section.

PHYSIOLOGY

The CSF is formed primarily in the ventricular system by the choroid plexus, which is situated in the lateral, third, and fourth ventricles. Although most CSF is produced in the lateral ventricles, approximately 25% originates from extrachoroidal sources, including the capillary endothelium within the brain parenchyma. There is active neurogenic control of CSF formation because adrenergic and cholinergic nerves innervate the choroid plexus. Stimulation of the adrenergic system diminishes CSF production, whereas excitation of the cholinergic nerves may double the normal CSF production rate. In a normal child, approximately 20 mL/hr of CSF is produced. The total volume of CSF approximates 50 mL in an infant and 150 mL in an adult. Most of the CSF is extraventricular. The choroid plexus forms CSF in several stages; through a series of intricate steps, a plasma ultrafiltrate is ultimately processed into a secretion, the CSF.

Table 591-4 Causes of Hydrocephalus

COMMUNICATING
Achondroplasia
Basilar impression
Benign enlargement of subarachnoid space
Choroid plexus papilloma
Meningeal malignancy
Meningitis
Posthemorrhagic
NONCOMMUNICATING
Aqueductal stenosis
Infectious*
X-linked
Mitochondrial
Autosomal recessive
Autosomal dominant
L1CAM mutations
Chiari malformation
Dandy-Walker malformation
Klippel-Feil syndrome
Mass lesions
Abscess
Hematoma
Tumors and neurocutaneous disorders
Vein of Galen malformation
Walker-Warburg syndrome
HYDRANENCEPHALY
Holoprosencephaly
Massive hydrocephalus
Porencephaly

*Toxoplasmosis, neurocysticercosis mumps.

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CSF flow results from the pressure gradient that exists between the ventricular system and venous channels. Intraventricular pressure may be as high as 180 mm H_2O in the normal state, whereas the pressure in the superior sagittal sinus is in the range of 90 mm H_2O. Normally, CSF flows from the lateral ventricles through the foramina of Monro into the 3rd ventricle. It then traverses the narrow aqueduct of Sylvius, which is approximately 3 mm long and 2 mm in diameter in a child, to enter the fourth ventricle. The CSF exits the fourth ventricle through the paired lateral foramina of Luschka and the midline foramen of Magendie into the cisterns at the base of the brain. Hydrocephalus resulting from obstruction within the ventricular system is called obstructive or noncommunicating hydrocephalus. The CSF then circulates from the basal cisterns posteriorly through the cistern system and over the convexities of the cerebral hemispheres. CSF is absorbed primarily by the arachnoid villi through tight junctions of their endothelium by the pressure forces that were noted earlier. CSF is absorbed to a much lesser extent by the lymphatic channels directed to the paranasal sinuses, along nerve root sleeves, and by the choroid plexus itself. Hydrocephalus resulting from obliteration of the subarachnoid cisterns or malfunction of the arachnoid villi is called nonobstructive or communicating hydrocephalus.

PATHOPHYSIOLOGY AND ETIOLOGY

Obstructive or noncommunicating hydrocephalus develops most commonly in children because of an abnormality of the aqueduct of Sylvius or a lesion in the fourth ventricle. Aqueductal stenosis results from an abnormally narrow aqueduct of Sylvius that is often associated with

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branching or forking. In a small percentage of cases, aqueductal stenosis is inherited as a sex-linked recessive trait. These patients occasionally have minor neural tube closure defects, including spina bifida occulta. Rarely, aqueductal stenosis is associated with neurofibromatosis. Aqueductal gliosis can also give rise to hydrocephalus. As a result of neonatal meningitis or a subarachnoid hemorrhage in a premature infant, the ependymal lining of the aqueduct is interrupted and a brisk glial response results in complete obstruction. Intrauterine viral infections can also produce aqueductal stenosis followed by hydrocephalus, and mumps meningoencephalitis has been reported as a cause in a child. A vein of Galen malformation can expand to become large and, because of its midline position, obstruct the flow of CSF. Lesions or malformations of the posterior fossa are prominent causes of hydrocephalus, including posterior fossa brain tumors, Chiari malformation, and the Dandy-Walker syndrome.

Nonobstructive or communicating hydrocephalus most commonly follows a subarachnoid hemorrhage, which is usually a result of intraventricular hemorrhage in a premature infant. Blood in the subarachnoid spaces can cause obliteration of the cisterns or arachnoid villi and obstruction of CSF flow. Pneumococcal and tuberculous meningitis have a propensity to produce a thick, tenacious exudate that obstructs the basal cisterns, and intrauterine infections can also destroy the CSF pathways. Leukemic infiltrates can seed the subarachnoid space and produce communicating hydrocephalus.

CLINICAL MANIFESTATIONS

The clinical presentation of hydrocephalus is variable and depends on many factors, including the age at onset, the nature of the lesion causing obstruction, and the duration and rate of increase of the intracranial pressure (ICP). In an infant, an accelerated rate of enlargement of the head is the most prominent sign. In addition, the anterior fontanel is wide open and bulging, and the scalp veins are dilated. The forehead is broad, and the eyes might deviate downward because of impingement of the dilated suprapineal recess on the brainstem tectum, producing the setting-sun eye sign. Long-tract signs, including brisk tendon reflexes, spasticity, clonus (particularly in the lower extremities), and Babinski sign, are common owing to stretching and disruption of the corticospinal fibers originating from the leg region of the motor cortex. In an older child, the cranial sutures are less accommodating so that the signs of hydrocephalus may be subtler. Irritability, lethargy, poor appetite, and vomiting are common to both age groups, and headache is a prominent symptom in older patients. A gradual change in personality and deterioration in academic productivity suggest a slowly progressive form of hydrocephalus. With regard to other clinical signs, serial measurements of the head circumference often indicate an increased velocity of growth. Percussion of the skull might produce a cracked pot sound or Macewen sign, indicating separation of the sutures. A foreshortened occiput suggests Chiari malformation, and a prominent occiput suggests the Dandy-Walker malformation. Papilledema, abducens nerve palsies, and pyramidal tract signs, which are most evident in the lower extremities, are apparent in many cases.

Chiari malformation consists of 2 major subgroups. Type I typically produces symptoms during adolescence or adult life and is usually not associated with hydrocephalus. Patients complain of recurrent headache, neck pain, urinary frequency, and progressive lower-extremity spasticity. The deformity consists of displacement of the cerebellar tonsils into the cervical canal (Fig. 591-12). Syrinx of the spinal cord, especially the cervical region should be looked for on MRI imaging. Although the pathogenesis is unknown, a prevailing theory suggests that obstruction of the caudal portion of the fourth ventricle during fetal development is responsible. Other theories include tethering of the cord or additional anomalies (syrinx).

The type II Chiari malformation is characterized by progressive hydrocephalus with a myelomeningocele. This lesion represents an anomaly of the hindbrain, probably owing to a failure of pontine flexure development during embryogenesis, and results in elongation of the fourth ventricle and kinking of the brainstem, with displacement of the inferior vermis, pons, and medulla into the cervical canal

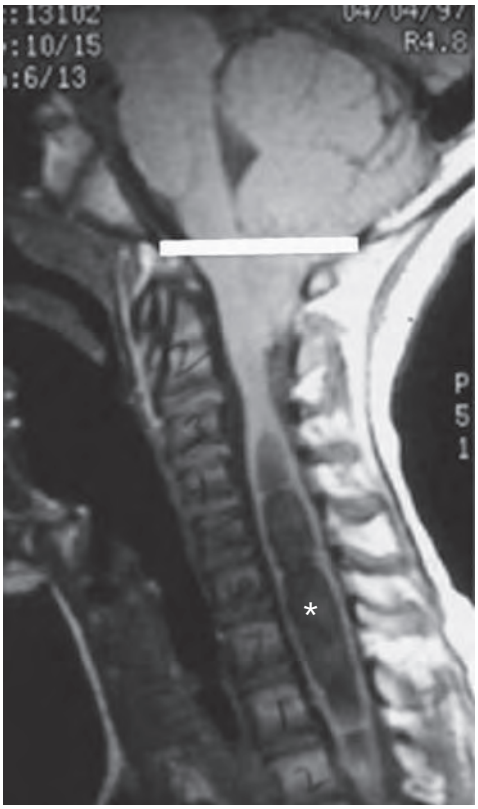


Figure 591-12 Sagittal MR scan of a patient with Chiari malformation type I. Cerebellar tonsils are displaced through the foramen magnum *(white bar)* to the lower aspect of C2 with clear crowding at the foramen. A syrinx *(white asterisk)* is visible extending from C3 to T2. *(From Yassari R, Frim D: Evaluation and management of the Chiari malformation type 1 for the primary care pediatrician,* Pediatr Clin North Am *51:477–490, 2004.)*

(Fig. 591-13). Approximately 10% of type II malformations produce symptoms during infancy, consisting of stridor, weak cry, and apnea, which may be relieved by shunting or by decompression of the posterior fossa. A more indolent form consists of abnormalities of gait, spasticity, and increasing incoordination (including the arms and hands) during childhood.

Plain skull radiographs show a small posterior fossa and a widened cervical canal. CT scanning with contrast and MRI display the cerebellar tonsils protruding downward into the cervical canal and the hindbrain abnormalities. The anomaly is treated by surgical decompression, but asymptomatic or mildly symptomatic patients may be managed conservatively.

The Dandy-Walker malformation consists of a cystic expansion of the fourth ventricle in the posterior fossa and midline cerebellar hypoplasia, which results from a developmental failure of the roof of the fourth ventricle during embryogenesis (Fig. 591-14). Approximately 90% of patients have hydrocephalus, and a significant number of children have associated anomalies, including agenesis of the posterior cerebellar vermis and corpus callosum. Infants present with a rapid increase in head size and a prominent occiput. Transillumination of the skull may be positive. Most children have evidence of long-tract signs, cerebellar ataxia, and delayed motor and cognitive milestones, probably due to the associated structural anomalies. The Dandy-Walker malformation is managed by shunting the cystic cavity (and on occasion the ventricles as well) in the presence of hydrocephalus.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

Investigation of a child with hydrocephalus begins with the history. Familial cases suggest X-linked or autosomal hydrocephalus secondary to aqueductal stenosis. A past history of prematurity with intracranial

hemorrhage, meningitis, or mumps encephalitis is important to ascertain. Multiple café-au-lait spots and other clinical features of neurofibromatosis point to aqueductal stenosis as the cause of hydrocephalus.

Examination includes careful inspection, palpation, and auscultation of the skull and spine. The occipitofrontal head circumference is recorded and compared with previous measurements. The size and configuration of the anterior fontanel are noted, and the back is inspected for abnormal midline skin lesions, including tufts of hair, lipoma, or angioma that might suggest spinal dysraphism. The presence of a prominent forehead or abnormalities in the shape of the occiput can suggest the pathogenesis of the hydrocephalus. A cranial bruit is audible in association with many cases of vein of Galen arteriovenous malformation. Transillumination of the skull is positive with massive dilation of the ventricular system or in the Dandy-Walker syndrome. Inspection of the eyegrounds is mandatory because the finding of chorioretinitis suggests an intrauterine infection, such as toxoplasmosis, as a cause of the hydrocephalus. Papilledema is observed in older children but is rarely present in infants because the cranial sutures separate as a result of the increased pressure.

Plain skull films typically show separation of the sutures, erosion of the posterior clinoids in an older child, and an increase in convolutional markings (beaten-silver appearance) on the inside of the skull with long-standing increased ICP. The CT scan and/or MRI along with ultrasonography in an infant are the most important studies to identify the specific cause and severity of hydrocephalus.

The head might appear enlarged (and can be confused with hydrocephalus) secondary to a thickened cranium resulting from chronic anemia, rickets, osteogenesis imperfecta, and epiphyseal dysplasia. Chronic subdural collections can produce bilateral parietal bone prominence. MRI has revealed the common occurrence of benign external hydrocephalus, a growth-limited condition where intervention is rarely required. Various metabolic and degenerative disorders of the CNS produce megalencephaly as a result of abnormal storage of substances within the brain parenchyma. These disorders include lysosomal diseases (Tay-Sachs disease, gangliosidosis, and the mucopolysaccharidoses), the aminoacidurias (maple syrup urine disease), and the leukodystrophies (metachromatic leukodystrophy, Alexander disease, Canavan disease). In addition, cerebral gigantism (Sotos syndrome), other overgrowth syndromes and neurofibromatosis are characterized by increased brain mass. Familial megalencephaly is inherited as an autosomal dominant trait and is characterized by delayed motor milestones and hypotonia but normal or near-normal intelligence. Measurement of parents' head circumferences is necessary to establish the diagnosis.

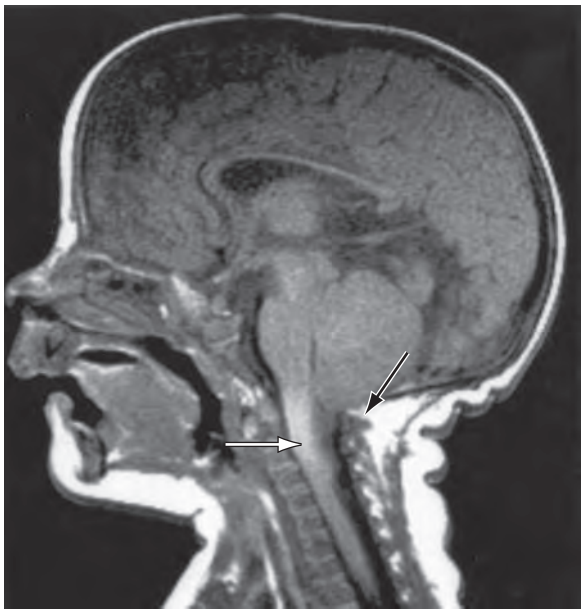


Figure 591-13 A midsagittal T1-weighted MRI of a patient with type II Chiari malformation. The cerebellar tonsils *(white arrow)* have descended below the foramen magnum *(black arrow)*. Note the small, slitlike fourth ventricle, which has been pulled into a vertical position.

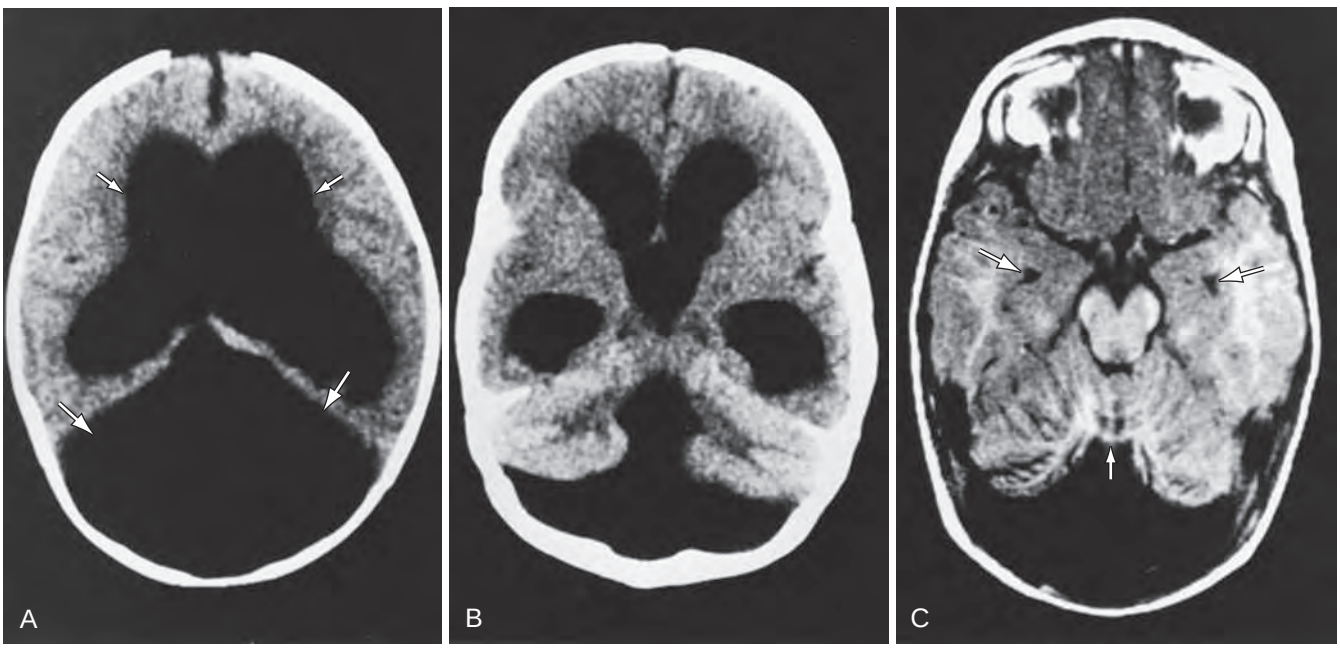


Figure 591-14 Dandy-Walker cyst. **A,** Axial CT scan (preoperative) showing large posterior fossa cyst (Dandy-Walker cyst; *large arrows*) and dilated lateral ventricles *(small arrows)*, a complication secondary to cerebrospinal fluid (CSF) pathway obstruction at the fourth ventricular outlet. **B,** Same patient, with a lower axial CT scan showing splaying of the cerebellar hemispheres by the dilated fourth ventricle (Dandy-Walker cyst). The dilated ventricles proximal to the fourth ventricle again show CSF obstruction caused by the Dandy-Walker cyst. **C,** MRI of the same patient showing decreased size of the Dandy-Walker cyst and temporal horns *(arrows)* after shunting. The incomplete vermis *(small arrow)* now becomes recognizable.

MEGALENCEPHALY

Megalencephaly is an anatomic disorder of brain growth defined as a brain weight:volume ratio >98th percentile for age (or ≥2 SD above the mean) that is usually accompanied by macrocephaly (an occipitofrontal circumference >98th percentile). Various storage and degenerative diseases are associated with megalencephaly, but anatomic and genetic causes exist as well. The most common cause of anatomic megalencephaly is benign familial megalencephaly. This condition is easily diagnosed by careful family history and measurement of the parents' head circumferences (occipitofrontal circumferences). On the other hand, macrocephaly is a known feature of more than 100 syndromes.

Anatomic megalencephaly is usually apparent at birth, and head growth continues to run parallel to the upper percentiles. Sometimes, in some syndromes, increased occipitofrontal circumference is the presenting sign. Neuroimaging is critical in identifying the various structural and gyral abnormalities seen in syndromic macrocephaly and determining whether anatomic megalencephaly exists.

Common megalencephaly-associated macrocephaly syndromes include syndromes with prenatal and/or postnatal somatic overgrowth such as Sotos, Simpson-Golabi-Behmel, fragile X, Weaver, macrocephaly-cutis marmorata telangiectatica congenita, and Bannayan-Ruvalcaba-Riley syndromes, and syndromes without somatic overgrowth such as FG, Greig cephalopolysyndactyly, acrocallosal, and Gorlin.

Sotos syndrome (cerebral gigantism) is the most common megalencephalic syndrome, with 50% of patients having prenatal macrocephaly and 100% of patients having macrocephaly by age 1 yr. Early postnatal overgrowth normalizes by adulthood. Facial features include high forehead with frontal bossing, sparse hair in the frontoparietal region, downslanting palpebral fissures, apparent hypertelorism, long narrow face, prominent mandible, and malar flushing. Hypotonia, poor coordination, and speech delay are common. Most children show cognitive impairment, ranging from mild to severe.

HYDRANENCEPHALY

Hydranencephaly may be confused with hydrocephalus. The cerebral hemispheres are absent or represented by membranous sacs with remnants of frontal, temporal, or occipital cortex dispersed over the membrane. The midbrain and brainstem are relatively intact (Fig. 591-15).



Figure 591-15 Hydranencephaly. MRI scan showing the brainstem and spinal cord with remnants of the cerebellum and the cerebral cortex. The remainder of the cranium is filled with cerebrospinal fluid.

The cause of hydranencephaly is unknown, but bilateral occlusion of the internal carotid arteries during early fetal development would explain most of the pathologic abnormalities. Affected infants can have a normal or enlarged head circumference at birth that grows at an excessive rate postnatally. Transillumination shows an absence of the cerebral hemispheres. The child is irritable, feeds poorly, develops seizures and spastic quadriparesis, and has little or no cognitive development. A ventriculoperitoneal shunt prevents massive enlargement of the cranium.

TREATMENT

Therapy for hydrocephalus depends on the cause. Medical management, including the use of acetazolamide and furosemide, can provide temporary relief by reducing the rate of CSF production, but long-term results have been disappointing. Most cases of hydrocephalus require extracranial shunts, particularly a ventriculoperitoneal shunt. Endoscopic third ventriculostomy has evolved as a viable approach and criteria have been developed for its use, but the procedure might need to be repeated to be effective. Ventricular shunting may be avoided with this approach. The major complications of shunting are occlusion (characterized by headache, papilledema, emesis, mental status changes) and bacterial infection (fever, headache, meningismus), usually caused by *Staphylococcus epidermidis*. With meticulous preparation, the shunt infection rate can be reduced to <5%. The results of intrauterine surgical management of fetal hydrocephalus have been poor (possibly because of the high rate of associated cerebral malformations in addition to the hydrocephalus) except for some promise in cases of hydrocephalus associated with fetal meningomyelocele.

PROGNOSIS

Prognosis depends on the cause of the dilated ventricles and not on the size of the cortical mantle at the time of operative intervention, except in cases in which the cortical mantle has been severely compressed and stretched. Hydrocephalic children are at increased risk for various developmental disabilities. The mean intelligence quotient is reduced compared with the general population, particularly for performance tasks as compared with verbal abilities. Many children have abnormalities in memory function. Vision problems are common, including strabismus, visuospatial abnormalities, visual field defects, and optic atrophy with decreased acuity secondary to increased ICP. The visual evoked potential latencies are delayed and take some time to recover after correction of the hydrocephalus. Although most hydrocephalic children are pleasant and mild mannered, some children show aggressive and delinquent behavior. Accelerated pubertal development in patients with shunted hydrocephalus or myelomeningocele is relatively common, possibly because of increased gonadotropin secretion in response to increased ICP. It is imperative that hydrocephalic children receive long-term follow-up in a multidisciplinary setting.

Bibliography is available at Expert Consult.

591.12 Craniosynostosis

Stephen L. Kinsman and Michael V. Johnston

Craniosynostosis is defined as premature closure of the cranial sutures and is classified as primary or secondary. It is associated with varying types of abnormal skull shape. Primary craniosynostosis refers to closure of 1 or more sutures owing to abnormalities of skull development, whereas secondary craniosynostosis results from failure of brain growth and expansion and is not discussed here. The incidence of primary craniosynostosis approximates 1 in 2,000 live births. The cause is unknown in the majority of children; however, genetic syndromes account for 10-20% of cases. Deformational forces appear important in occipital and frontal plagiocephaly in many cases. Early detection of posterior skull shape is critical and allows successful intervention to be offered in the form of physical therapy for torticollis and other positional asymmetries that lead to plagiocephaly.

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DEVELOPMENT AND ETIOLOGY

The bones of the cranium are well developed by the 5th mo of gestation (frontal, parietal, temporal, and occipital) and are separated by sutures and fontanels. The brain grows rapidly in the 1st several yr of life and is normally not impeded because of equivalent growth along the suture lines. The cause of craniosynostosis is unknown, but the prevailing hypothesis suggests that abnormal development of the base of the skull creates exaggerated forces on the dura that act to disrupt normal cranial suture development. Genetic factors have been identified for some isolated and for many syndromic causes of craniosynostosis (Table 591-5).

Table 591-5 Commonly Used Clinical Genetic Classifications of Craniosynostoses

DISORDER	CAUSE
ISOLATED CRANIOSYNOSTOSIS	
Morphologically described	Unknown, uterine constraint, or *FGFR3* mutation
SYNDROMIC CRANIOSYNOSTOSIS	
Antler-Bixler syndrome	Unknown
Apert syndrome	Usually 1 of 2 mutations in *FGFR2*
Beare-Stevenson syndrome	Mutation in *GFGR2* or *FGFR3*
Baller-Gerold syndrome	Mutation in *TWIST* heterogenous
Carpenter syndrome	Unknown
Craniofrontonasal dysplasia	Unknown gene at *Xp22*
Crouzon syndrome	Numerous different mutations at *FGFR2*
Crouzonomesodermoskeletal syndrome	Mutation in *FGFR3*
Jackson-Weiss syndrome	Mutation in *FGFR2*
Muenke syndrome	Mutation in *FGFR3*
Pfeiffer syndrome	Mutation in *FGFR1* or numerous mutation in *FGFR2*
Saethre-Chotzen syndrome	Mutation in *TWIST*
Shprintzen-Goldberg syndrome	Mutation in *FBEN1*

From Ridgway EB, Weiner HL: Skull deformities, Pediatr Clin North Am *51:359–387, 2004.*

CLINICAL MANIFESTATIONS AND TREATMENT

Most cases of craniosynostosis are evident at birth and are characterized by a skull deformity that is a direct result of premature suture fusion. Palpation of the suture reveals a prominent bony ridge, and fusion of the suture may be confirmed by plain skull roentgenograms, CT scan, or bone scan in ambiguous cases (Table 591-6).

Premature closure of the sagittal suture produces a long and narrow skull, or **scaphocephaly,** the most common form of craniosynostosis. Scaphocephaly is associated with a prominent occiput, a broad forehead, and a small or absent anterior fontanel. The condition is sporadic, is more common in males, and often causes difficulties during labor because of cephalopelvic disproportion. Scaphocephaly does not produce increased ICP or hydrocephalus, and results of neurologic examination of affected patients are normal.

Frontal plagiocephaly is the next most common form of craniosynostosis and is characterized by unilateral flattening of the forehead, elevation of the ipsilateral orbit and eyebrow, and a prominent ear on the corresponding side. The condition is more common in females and is the result of premature fusion of a coronal and sphenofrontal suture. Surgical intervention produces a cosmetically pleasing result. When imaging does not reveal a closed suture, positional factors are of primary importance.

Occipital plagiocephaly is most often a result of positioning during infancy and is more common in an immobile child or a child with a disability, but fusion or sclerosis of the lambdoid suture can cause unilateral occipital flattening and bulging of the ipsilateral frontal bone. **Trigonocephaly** is a rare form of craniosynostosis caused by premature fusion of the metopic suture. These children have a keel-shaped forehead and hypotelorism and are at risk for associated developmental abnormalities of the forebrain. Milder forms of metopic ridging are more common. **Turricephaly** refers to a cone-shaped head from premature fusion of the coronal, and often sphenofrontal and frontoethmoidal, sutures. The **kleeblattschädel deformity** is a peculiarly shaped skull that resembles a cloverleaf. Affected children have very prominent temporal bones, and the remainder of the cranium is constricted. Hydrocephalus is a common complication.

Premature fusion of only 1 suture rarely causes a neurologic deficit. In this situation, the sole indication for surgery is to enhance the child's cosmetic appearance, and the prognosis depends on the suture involved

Table 591-6 Epidemiology and Clinical Characteristics of the Common Craniosynostoses

TYPE	EPIDEMIOLOGY	SKULL DEFORMITY	CLINICAL PRESENTATION
Sagittal	Most common CSO affecting a single suture, 80% male	Dolicocephaly or scaphocephaly (boat-shaped)	Frontal bossing, prominent occiput, palpable keel ridge. OFC normal and reduced biparietal diameter
Coronal	18% of CSO, more common in girls Associated with Apert syndrome (with syndactyly) and Crouzon disease, which includes abnormal sphenoid, orbital, and facial bones (hypoplasia of the midface)	Unilateral: plagiocephaly Bilateral: brachycephaly, acrocephaly	Unilateral: flattened forehead on affected side, flat checks, nose deviation on normal side; higher supraorbital margin leading to harlequin sign on radiograph and outward rotation of orbit can result in amblyopia Bilateral: broad, flattened forehead. In Apert syndrome accompanied by syndactyly and in Crouzon disease by hypoplasia of the midface and progressive proptosis
Lambdoid	10-20% of CSO, M:F ratio 4:1	Lambdoid/occipital plagiocephaly; right side affected in 70% of cases	Unilateral: flattening of occiput, indentation along synostotic suture, bulging of ipsilateral forehead leading to rhomboid skull, ipsilateral ear is anterior and inferior Bilateral: brachycephaly with bilateral anteriorly and inferiorly displaced ears
Metopic	Association with 19p chromosome abnormality	Trigonocephaly	Pointed forehead and midline ridge, hypotelorism
Multiple		Oxycephaly	Tower skull with undeveloped sinuses and shallow orbits, and elevated intercranial pressure

CSO, craniosynostosis; OFC, occipital-frontal circumference.
From Ridgway EB, Weiner HL: Skull deformities, Pediatr Clin North Am *51:359–387, 2004.*

and on the degree of disfigurement. Neurologic complications, including hydrocephalus and increased ICP, are more likely to occur when 2 or more sutures are prematurely fused, in which case operative intervention is essential. The role of early repositioning efforts and therapy for torticollis and the use of cranial molding devices are beyond the scope of this review.

The most prevalent genetic disorders associated with craniosynostosis include Crouzon, Apert, Carpenter, Chotzen, and Pfeiffer syndromes. Crouzon syndrome is characterized by premature craniosynostosis and is inherited as an autosomal dominant trait. The shape of the head depends on the timing and order of suture fusion but most often is a compressed back-to-front diameter or brachycephaly resulting from bilateral closure of the coronal sutures. The orbits are underdeveloped, and ocular proptosis is prominent. Hypoplasia of the maxilla and orbital hypertelorism are typical facial features.

Apert syndrome has many features in common with Crouzon syndrome. Apert syndrome is usually a sporadic condition, although autosomal dominant inheritance can occur. It is associated with premature fusion of multiple sutures, including the coronal, sagittal, squamosal, and lambdoid sutures. The facies tend to be asymmetric, and the eyes are less proptotic than in Crouzon syndrome. Apert syndrome is characterized by syndactyly of the 2nd, 3rd, and 4th fingers, which may be joined to the thumb and the 5th finger. Similar abnormalities often occur in the feet. All patients have progressive calcification and fusion of the bones of the hands, feet, and cervical spine.

Carpenter syndrome is inherited as an autosomal recessive condition, and the many fusions of sutures tend to produce the kleeblattschädel skull deformity. Soft tissue syndactyly of the hands and feet is always present, and intellectual disability is common. Additional but less common abnormalities include congenital heart disease, corneal opacities, coxa valga, and genu valgum.

Chotzen syndrome is characterized by asymmetric craniosynostosis and plagiocephaly. The condition is the most prevalent of the genetic syndromes and is inherited as an autosomal dominant trait. It is associated with facial asymmetry, ptosis of the eyelids, shortened fingers, and soft tissue syndactyly of the 2nd and 3rd fingers.

Pfeiffer syndrome is most often associated with turricephaly. The eyes are prominent and widely spaced, and the thumbs and great toes are short and broad. Partial soft-tissue syndactyly may be evident. Most cases appear to be sporadic, but autosomal dominant inheritance has been reported.

Mutations of the fibroblast growth factor receptor (FGFR) gene family have been shown to be associated with phenotypically specific types of craniosynostosis. Mutations of the *FGFR1* gene located on chromosome 8 result in Pfeiffer syndrome; a similar mutation of the *FGFR2* gene causes Apert syndrome. Identical mutations of the *FGFR2* gene can result in both Pfeiffer and Crouzon phenotypes.

Each of the genetic syndromes poses a risk of additional anomalies, including hydrocephalus, increased ICP, papilledema, optic atrophy resulting from abnormalities of the optic foramina, respiratory problems secondary to a deviated nasal septum or choanal atresia, and disorders of speech and deafness. Craniectomy is mandatory for management of increased ICP, and a multidisciplinary craniofacial team is essential for the long-term follow-up of affected children. Craniosynostosis may be surgically corrected with good outcomes and relatively low morbidity and mortality, especially for nonsyndromic infants.

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Chapter 592

Deformational Plagiocephaly

René P. Myers, Aubrey N. Duncan, and John A. Girotto

Deformational plagiocephaly (DP), also known as positional plagiocephaly, is the development of cranial flattening and asymmetry in the infant *as a result of extrinsic molding forces placed on the skull, such as consistently sleeping on the same area of the head*. Since the suggestion to place sleeping infants on their backs to sleep for the prevention of the **sudden infant death syndrome**, the incidence of DP has risen dramatically, and this has caused concern for parents and clinicians in the primary care setting.

EPIDEMIOLOGY AND ETIOLOGY

Incidence

The incidence is frequent at 6 wk of age (16%), greatest at 4 mo of age (up to 20%), and then decreases over the next 3 yr (7% at 12 mo and 3.3% at 24 mo). It generally resolves completely by 2-3 yr of age. The American Academy of Pediatrics started a campaign in the 1990s that resulted in the recommendation to place infants on their backs or sides while sleeping, which resulted in a 40% decrease in sudden infant death syndrome cases. Within 4 yr, craniofacial centers and primary care offices reported a 600% increase in referrals for plagiocephaly, which was previously reported to be approximately 1 in 300 infants. This may be a result of increasing awareness or early referral, as point prevalence has not changed in the past 40 yr.

Infants cannot reposition their heads in the 1st few wk of life and are not able to hold their own heads up until about 4 mo of age. It is for this reason that DP is most severe around 4 mo of age. It is also during this time that an infant's head circumference is rapidly increasing: about 2 cm/month in the 1st 3 mo, 1 cm/month from 4-6 mo of age, and 0.5 cm/month after 6 mo of age. Around 6 mo of age, an infant has developed head control, and this ability to actively reposition their own head allows for the gradual improvement of the cranial shape because of pressure offloading and continued brain growth.

Risk Factors

Congenital torticollis, positional preference when sleeping, and lower levels of activity are especially prominent in patients with DP. Table 592-1 delineates other risk factors. Many of these risk factors cannot be prevented, but sleeping supine with the head always turned to the same side has been found to predict DP independent of the other factors, and this *can* be prevented. There may be an association between developmental delay and DP. Although not causal, studies have found significant differences in gross motor development such as sitting up, crawling, and rolling back to side, between babies with and without DP.

Table 592-1 Factors That Increase Risk for Deformational Plagiocephaly

Male
Firstborn child
Limited passive neck rotation at birth (e.g., congenital torticollis)
Developmental delay
Sleep position is supine at birth and at 6 weeks
Bottle feeding only
Tummy time <3 times/day
Lower activity level, slower milestone achievement
Sleeping with head to same side, positional preference

Causes

Prenatal causes of DP include uterine compression and intrauterine constraint, such as occurs with oligohydramnios or multifetus gestation. Postnatal causes of DP include infant sleeping position and congenital muscular torticollis.

Muscular torticollis is a condition that is present in as many as 1 in 6 newborns and causes continuous tightening of muscles in the neck preventing passive rotation. It is thought that this condition typically precedes the development of cranial deformity. However, head position preference may result from cervical asymmetry that leads to torticollis and later flattening of a side of the skull from acquired positional preference (see Chapter 680.1).

Sleeping position plays a major role in the incidence of DP. When an infant continuously sleeps with the same part of the skull resting on a flat surface, a continuous force is placed in this area. During this time of rapid skull development, the growth is inhibited at the area where it rests on a hard surface, causing a "flat spot." Because of this inhibition, growth is increased in opposite directions causing a deformation that can be distinguished from other types of plagiocephaly.

EXAMINATION AND DIFFERENTIATING BETWEEN DEFORMATIONAL PLAGIOCEPHALY AND CRANIOSYNOSTOSIS

Abnormal head shape in an infant is distressing for parents. DP is a clinical diagnosis. Management also requires accurate counseling about its cause and treatment. It is especially important to be able to rule out **craniosynostosis** as a primary cause for cranial asymmetry in infants, as management of this condition is very different from that of DP and requires immediate referral to a craniofacial surgeon for evaluation (see Chapter 591.12). Craniosynostosis occurs in approximately 1 in 2,000 live births and results in plagiocephaly as a consequence of the early closure of skull sutures. Craniosynostosis must be distinguished from DP because the management is different. Lambdoidal craniosynostosis, although extremely rare (1 in 300,000 live births), presents with features most similar to those of DP. It can be distinguished from DP by a variety of historical and physical findings. Bilateral coronal synostosis also presents very similarly to posterior DP.

History and Physical Exam

Tables 592-2 and 592-3 outline the key components of history and physical examination.

Observation of the cranial shape as well as ear displacement are the first steps. It is critical to observe the child anteriorly, laterally, and from a vertex view. When cranial shape is viewed from above, DP typically looks like a **parallelogram**, and the ear on the same side of the flat or bald spot is **displaced anteriorly**. In lambdoidal craniosynostosis, the head has a trapezoid shape and the ear on the same side as the flat spot is posteriorly displaced (Fig. 592-1).

Palpation will help to differentiate these 2 conditions. Craniosynostosis presents with palpable ridges along the suture, whereas DP does not. Additionally, patients with craniosynostosis will not have mobile calvarial bones. This can be tested by applying gentle pressure on 2

Table 592-2 Important Historical and Physical Factors in the Evaluation of a Patient with Plagiocephaly

	DEFORMATIONAL	SYNOSTOTIC
Birth history	• Intrauterine compression • Firstborn child	• Typically no complications
Head shape at birth	• Typically normal	• Can be irregular
Age first noticed shape irregularity	• Usually in 1st few mo of life	• Can be at birth
How patient prefers to sleep	• Same side, same position • Same even during naps	• Variable
Bald spot	• Yes	• No
Motor development for age	• If age atypical for deformational plagiocephaly, typically slow motor development for age • Torticollis present • History of limited activity or mobility	• Varies depending on presence of concomitant syndrome
Tummy time	• Decreased	• Suggested time
Signs/symptoms of increasing intracranial pressure	• No	• Possible

Table 592-3 Key Differences Between Synostotic (Craniosynostosis) and Deformational Plagiocephaly

	DEFORMATIONAL PLAGIOCEPHALY	CRANIOSYNOSTOSIS
Causes	External forces applied to the skull • Prenatal: uterine compression, intrauterine constrained • Postnatal: congenital torticollis, sleeping position	Premature fusion of 1 or more cranial sutures
Common types	• Lateral • Posterior	• Bilateral coronal • Sagittal • Metopic
Common distinguishing features	• Normal round head shape at birth • Parallelogram shape to head • Ipsilateral ear anteriorly displaced • No palpable bony ridges	• Can have abnormal head shape at birth • Trapezoid shape to head • Ipsilateral ear posteriorly displaced • Palpable bony ridges
Management	• Repositioning • Physical therapy • Helmet in some cases	• Surgery • Helmet in some cases

Adapted from Nield LS, Brunner MD, Kamat D: The infant with a misshapen head. Clin Pediatr (Phila) *46:292–298, 2007, Tables 1 and 2.*

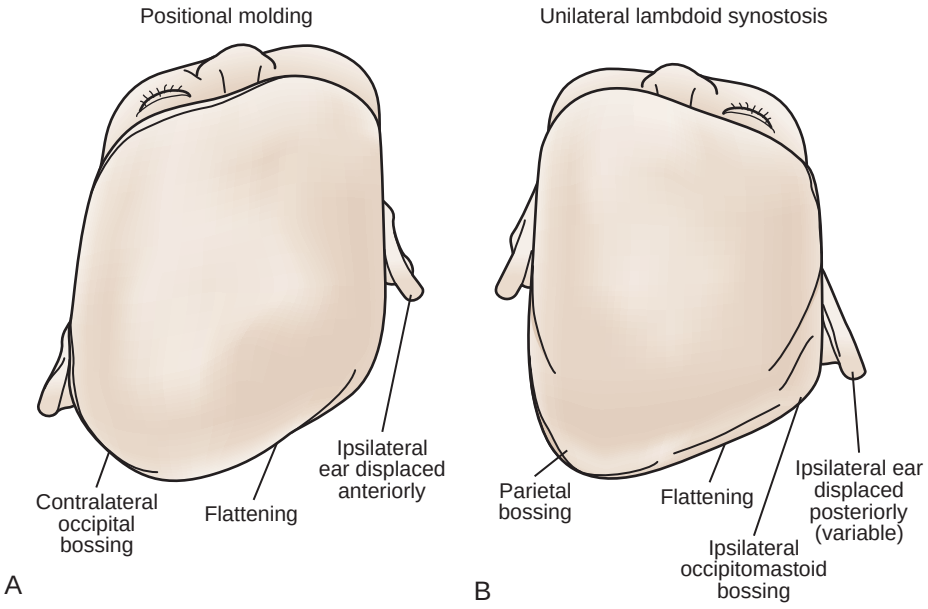


Figure 592-1 Differentiating physical findings between deformational plagiocephaly and craniosynostosis. Vertex views. **A,** Right-sided deformational plagiocephaly exhibiting a parallelogram head shape. **B,** Right-sided lambdoid craniosynostosis exhibiting a trapezoid-like head shape. *(From Lin AY, Losee JE: Pediatric plastic surgery. In Zitelli BJ, McIntire SC, Norwalk AJ, editors:* Zitelli and Davis' atlas of pediatric physical diagnosis, *ed 6, Philadelphia, 2012, Elsevier,* Fig. 22-5.*)*

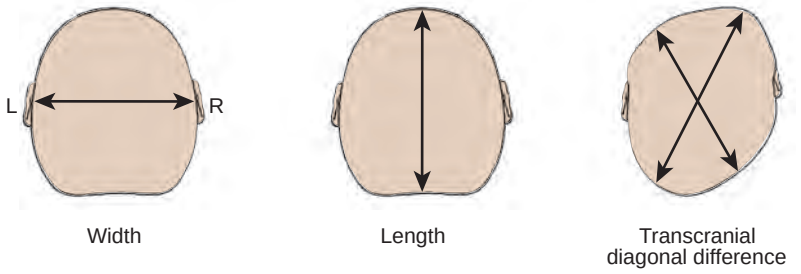


Figure 592-2 Cranial measurements. *(Modified from Looman WS, Flannery AB: Evidence-based care of the child with deformational plagiocephaly, part I: assessment and diagnosis.* J Pediatr Health Care *26:242–250, 2012, Table 1.)*

adjacent skull bones separated by a suspected synostotic suture. If the plates do not move relative to each other, then the suspicion for craniosynostosis is raised.

Verifying neck muscle tone and range of motion is a key part of the exam because it helps in evaluating motor development and in diagnosing congenital torticollis. Resistance to passive motion raises the concern for torticollis. Decreased tone should prompt further evaluation of motor development. Infants do not gain the muscle control to turn or lift their heads until approximately 4 mo of age, and delays in motor development could increase the infant's risk of DP at later ages than those at which it usually occurs. Decreased range of motion can also be seen in cervical spine abnormalities, although this is rare. Early recognition of these conditions is critical in treatment, management, and outcome.

Accurate and consistent measurements will help to distinguish etiologies and manage infants presenting with an abnormal-shape skull. Along with the usual head circumference measurements, the clinician should also measure cranial width, length, and transcranial diameter (as shown in Figure 592-2), which is best performed with calipers. These measurements allow the clinician to diagnose, determine severity, and monitor the plagiocephaly.

- *Cranial length:* Distance from the most prominent point between the eyebrows to the most prominent point of the occiput
- *Width:* Maximum transverse diameter, horizontal
- *Cephalic index* (cranial index): Ratio of the cranial width to the cranial length
- *Occipital-frontal transcranial diameter*: Find the points on either side of the head where the deformation is the worst (2 on the right, 2 on the left), then measure the **diagonal distances** between these points
- *Transdiagonal difference* (transcranial diagonal difference): The difference between 2 transcranial diameters
- *Cranial vault asymmetry:* Ratio of oblique measurements. This is difficult to implement because different physicians and authors propose varying points to use for these measurements

One technology for the evaluation of the severity and improvement over time of DP is the 3-dimensional photographic system. Advantages of this system include an easy and comfortable ability to image in an unbiased manner. Similarly, the use of laser scanners for the prefabrication scans for helmets is frequently employed by orthotists.

After observations and measurements the clinician can determine the type and severity of the DP (Table 592-4 and Fig. 592-3). For *lateral DP*, bossing of the occiput occurs opposite the flattened deformity and the ear on the same side as the flat area can be anteriorly displaced. This type of DP is typically associated with infants who have torticollis or a head position preference to 1 side. Transdiagonal diameter is typically abnormal in this type of plagiocephaly, and this measurement is the gold standard for determining severity.

In *posterior DP*, the occiput is uniformly flattened, temporal bossing can occur, and the ears are normal. It is usually associated with large head size and a history of limited activity or mobility. Cephalic index is increased with posterior DP.

Time and accurate exam records can help in management. If deformation is worsening when DP typically begins to demonstrate improving head shape, craniosynostosis should be suspected.

TREATMENT

Prevention

Sleep position should be monitored and varied. Alternating the infant's head to face the head and foot of the crib on alternate nights will allow the infant to sleep facing into the room without always lying on the same side of the head. Consistently alternating sleeping position early on allows the infant to have equal time on both sides of the occiput, and this will become a pattern the infant is used to. Infants who have

Table 592-4 Diagnostic Guide for Determining Type and Severity of Lateral and Posterior Deformational Plagiocephaly

TYPE CLINICAL FINDINGS	LATERAL DEFORMATIONAL PLAGIOCEPHALY	POSTERIOR DEFORMATIONAL PLAGIOCEPHALY (BRACHYCEPHALY)
Occiput (vertex view)	Ipsilateral occipital flattening; contralateral occipital bossing	Uniform occipital flattening
Ear position (vertex view)	Ipsilateral ear may be anteriorly displaced	Normal
Face, forehead (anterior, lateral, and vertex views)	May be normal; more-severe cases may present with the following: mandibular asymmetry, ipsilateral frontal bossing, contralateral forehead flattening, ipsilateral cheek anteriorly displaced	Temporal bossing, increase in vertical height in severe cases
Other	Torticollis, head position preference	Large size, history of limited activity or limited mobility

SEVERITY	LATERAL DEFORMATIONAL PLAGIOCEPHALY			POSTERIOR DEFORMATIONAL PLAGIOCEPHALY (BRACHYCEPHALY)	
Mild	TDD 3-10 mm	Type I	Flattening restricted to the back of the skull	CI: 0.82-0.9	Central posterior deformity ("ping-pong ball depression")
Moderate	TDD 10-12 mm	Type II Type III	Malposition of ear Forehead deformity	CI: 0.9-1.0	Central posterior deformity and widening of posterior skull
Severe	TDD >12 mm	Type IV Type V	Malar deformity Vertical or temporal skull growth	CI: >1.0	Vertical head, head growth, or temporal bossing

CI, cephalic index (cranial index); TDD, transcranial diameter difference.

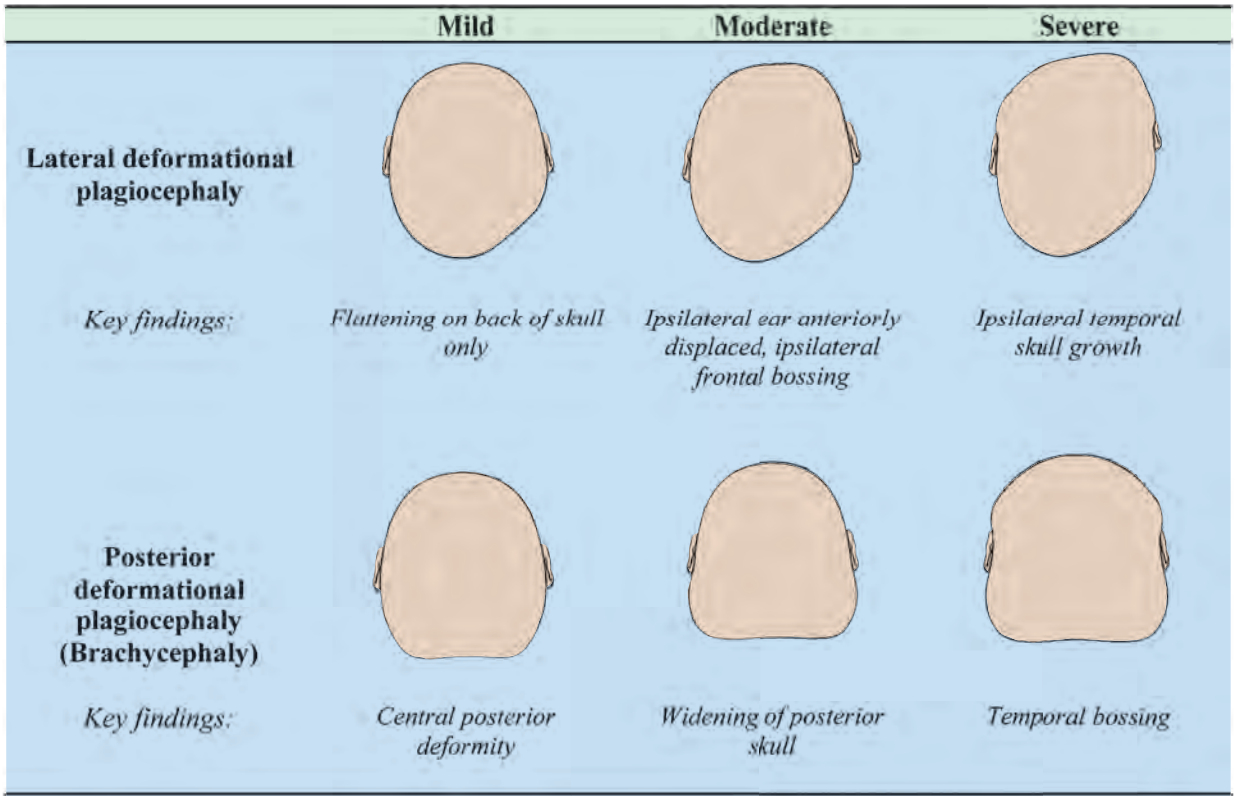


Figure 592-3 Types of deformational plagiocephaly. *(From Looman WS, Flannery AB: Evidence-based care of the child with deformational plagiocephaly, part I: assessment and diagnosis.* J Pediatr Health Care *26:242–250, 2012, Fig. 1.)*

an obvious positional preference to a particular side will take more time and effort in purposefully repositioning them counter to their preference. Parents must be counseled in the benefit of this strategy in preventing bald spots or flat spots that can progress to cranial deformity.

"Tummy time" is the term used to describe the infant's awake time spent lying on their stomach. The suggested amount of tummy time is **10-15 minutes at least 3 times a day**. Reassure parents that sleep is the only time during which the prone position should be avoided, and educate the parents as to the benefits for the infant of awake prone positioning to help progression of motor development.

Treatment Options

Cranial asymmetry from DP does not usually spontaneously improve, nor do the more-severe manifestations of facial and ear asymmetry disappear. Once a flat spot develops, it is unlikely that the infant will be able to overcome the pull to lie on the same spot in time to allow for reversal of the asymmetry.

"Watch-and-wait" management is not recommended in infants with DP. Evidence suggests that, at a minimum, repositioning and physiotherapy should be initiated as soon as asymmetry is observed.

Repositioning and physiotherapy (RPPT) include the counseling and teaching for parents as to positional changes and tummy time in their child as well as **referral to physical therapy in the case of congenital torticollis.** RPPT is the optimal treatment choice for patients younger than 4 mo of age who have mild or moderately severe DP. The earliest types of behavioral modifications can be as simple as increasing tummy time, or repositioning the infant's crib such that everything interesting in the room is on the side opposite the DP.

Molding therapy (helmet therapy) is the use of an orthotic helmet to promote the resolution of cranial asymmetry while the infant's head is still rapidly growing. Orthotic helmets do not actively mold the skull; rather, they protect the areas that are flat and allow the child to "grow into" the flat spot. Studies have shown helmet therapy to achieve correction 3 times faster and better than repositioning alone. This therapy is still debated because of its expense, time requirements, coverage and side effects (irritation, rashes, and pressure sores). The most recent studies suggest that **combined treatment with helmet therapy and RPPT is the most beneficial management of infants older than 4 mo with severe DP or with worsening of mild/moderate DP trialed on RPPT.** Infants with severe DP should be considered for helmet therapy at any age.

Studies suggest helmet therapy should be started for significant DP between 4 and 8 mo and continued for 7-8 mo. Parents should be counseled on the commitment involved in this treatment as helmets need to be worn more than 20 hr a day.

Patients with craniosynostosis require surgery. Sometimes, a molding helmet can be used as an adjunctive therapy after surgery but never as monotherapy.

OUTCOMES

Outcomes may be better when helmet therapy is started before 6 mo of age, and infants starting therapy later than that do not achieve the same degree of normal head measurements as those whose helmet therapy is started before 6 mo of age do. Significant improvements in asymmetry are usually obvious at 4-11 wk after initiation of helmet therapy.

Studies in patients with a median follow-up age of 9 yr old found that 75% of cases had a what both parents and patients considered to be a normal head appearance. Nine percent of patients and 4% of parents noted residual asymmetry that they considered significant.

Cognitive and academic outcomes may be different depending on the side of deformity. Poorer academic performance and greater speech abnormalities were found in patients with left-sided deformities compared to those with right-sided deformities. This manifested as double the number of patients with expressive speech abnormalities and triple the number of special education needs. It is unclear what the underlying mechanism is; treatment differences were apparently not a factor. In general, children with DP and without comorbid conditions are usually developmentally normal, healthy children. This is in contrast to craniosynostosis, in which increases in intracranial pressure may have deleterious effects on central nervous system function.

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Chapter 593

Seizures in Childhood

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A seizure is a transient occurrence of signs and/or symptoms resulting from abnormal excessive or synchronous neuronal activity in the brain. The International Classification of Epileptic Seizures divides epileptic seizures into 2 large categories: In **focal (formerly known as partial) seizures,** the first clinical and electroencephalographic (EEG) changes suggest initial activation of a system of neurons limited to part of 1 cerebral hemisphere. The term *simple partial seizures* is an outdated classification that refers to focal seizures with no alteration in consciousness whereas complex partial seizures, currently also referred to as focal dyscognitive, denote focal seizures with altered awareness of the surroundings. In **generalized seizures,** the first clinical and EEG changes indicate synchronous involvement of all of both hemispheres (Table 593-1). Approximately 30% of patients who have a first afebrile seizure have later epilepsy; the risk is approximately 20% if neurologic exam, EEG, and neuroimaging are normal. **Febrile seizures** are a separate category. **Acute symptomatic seizures** occur secondary to an acute problem affecting brain excitability such as electrolyte imbalance. Most children with these types of seizures do well. However, sometimes these seizures signify major structural, inflammatory, or metabolic disorders of the brain, such as meningitis, encephalitis, acute stroke, or brain tumor. Consequently, the prognosis depends on the underlying disorder, including its reversibility or treatability and the likelihood of developing epilepsy from it. An **unprovoked seizure** is one that is not an acute symptomatic seizure. **Remote symptomatic seizure** is one that is considered to be secondary to a distant brain injury, such as an old stroke. **Reflex seizures** are usually precipitated by a sensory stimulus such as flashing lights (see Chapter 593.9).

Epilepsy is a disorder of the brain characterized by an enduring predisposition to generate seizures and by the neurobiologic, cognitive, psychologic, and social consequences of this condition. The clinical diagnosis of epilepsy usually requires the occurrence of at least 1 unprovoked epileptic seizure with either a second such seizure or enough EEG and clinical information to convincingly demonstrate an enduring predisposition to develop recurrences. For epidemiologic and commonly for clinical purposes, epilepsy is considered to be present when 2 or more unprovoked seizures occur in a time frame of longer than 24 hr. Approximately 4-10% of children experience at least 1 seizure (febrile or afebrile) in the 1st 16 yr of life. The cumulative lifetime incidence of epilepsy is 3%, and more than half of the cases start in childhood. The annual prevalence is 0.5-1.0%. Thus, the occurrence of a single seizure or of febrile seizures does not necessarily imply the diagnosis of epilepsy. **Seizure disorder** is a general term that is usually used to include any 1 of several disorders, including epilepsy, febrile seizures, and possibly single seizures and symptomatic seizures secondary to metabolic, infectious, or other etiologies (e.g., hypocalcemia, meningitis).

An **epileptic syndrome** is a disorder that manifests 1 or more specific seizure types and has a specific age of onset and a specific prognosis. Several types of epileptic syndromes can be distinguished

Table 593-1 Types of Epileptic Seizures

SELF-LIMITED SEIZURE TYPES	CONTINUOUS SEIZURE TYPES
Focal Seizures	***Generalized Status Epilepticus***
Focal sensory seizures	Generalized tonic-clonic status epilepticus
• With elementary sensory symptoms (e.g., occipital and parietal lobe seizures)	Clonic status epilepticus
• With experiential sensory symptoms (e.g., temporoparietooccipital junction seizures)	Absence status epilepticus
Focal motor seizures	Tonic status epilepticus
• With elementary clonic motor signs	Myoclonic status epilepticus
• With asymmetrical tonic motor seizures (e.g., supplementary motor seizures)	***Focal Status Epilepticus***
• With typical (temporal lobe) automatisms (e.g., mesial temporal lobe seizures)	Epilepsia partialis continua of Kojevnikov
• With hyperkinetic automatisms	Aura continua
• With focal negative myoclonus	Limbic status epilepticus (psychomotor status)
• With inhibitory motor seizures	Hemiconvulsive status with hemiparesis
Gelastic seizures	
Hemiclonic seizures	**PRECIPITATING STIMULI FOR REFLEX SEIZURES**
Secondarily generalized seizures	Visual stimuli
Reflex seizures in focal epilepsy syndromes	• Flickering light—color to be specified when possible
Generalized Seizures	• Patterns
Tonic-clonic seizures (includes variations beginning with a clonic or myoclonic phase)	• Other visual stimuli
Clonic seizures	Thinking
• Without tonic features	Music
• With tonic features	Eating
Typical absence seizures	Praxis
Atypical absence seizures	Somatosensory
Absence with special features:	Proprioceptive
• Eyelid myoclonia	Reading
• Myoclonic absence	Hot water
Tonic seizures	Startle
Myoclonic seizures	
Myoclonic atonic seizures	
Negative myoclonus	
Atonic seizures	
Reflex seizures in generalized epilepsy syndromes	
Unknown	
Epileptic Spasms	

Modified from Berg AT, Berkovic SF, Brodie MJ et al: Revised terminology and concepts for organization of seizures and epilepsies: report of the ILAE Commission on Classification and Terminology, 2005–2009. Epilepsia *51(4):676–685, 2010.*

(Tables 593-2 to 593-5). This classification has to be distinguished from the classification of epileptic seizures that refers to single events rather than to clinical syndromes. In general, seizure type is the primary determinant of the type of medications the patient is likely to respond to, and the epilepsy syndrome determines the type of prognosis one could expect. An **epileptic encephalopathy** is an epilepsy syndrome in which there is a severe EEG abnormality which is thought to result in cognitive and other impairments in the patient. **Idiopathic epilepsy** is an older term that refers to an epilepsy syndrome that is genetic or presumed genetic and in which there is no underlying disorder affecting development or other neurologic function (e.g., petit mal epilepsy). In the International League Against Epilepsy (ILAE) classification of etiology of epilepsy, idiopathic epilepsy was replaced by the term **genetic epilepsy**, which implies that the epilepsy syndrome is the direct result of a known or presumed genetic defect(s) in which the genetic defect is not causative of a brain structural or metabolic disorder other than the epilepsy. **Symptomatic epilepsy** is also an older term referring to an epilepsy syndrome caused by an underlying brain disorder that may or may not be genetic (e.g., epilepsy secondary to tuberous sclerosis or to an old stroke); this is referred to as **structural/metabolic epilepsy**, which would be caused by a distinct structural or metabolic entity that increases the risk for seizures and causes the epilepsy. The older terms of **cryptogenic epilepsy** or of presumed **symptomatic epilepsy** refer to an epilepsy syndrome in which there is a presumed underlying brain disorder causing the epilepsy and affecting neurologic function, but the underlying disorder is not known; this is referred to as the **unknown epilepsy**, designating that the underlying cause of the epilepsy is as yet unknown.

EVALUATION OF THE FIRST SEIZURE

Initial evaluation of an infant or child during or shortly after a suspected seizure should include an assessment of the adequacy of the airway, ventilation, and cardiac function, as well as measurement of temperature, blood pressure, and glucose concentration. For acute evaluation of the first seizure, the physician should search for potentially life-threatening causes of seizures such as meningitis, systemic sepsis, unintentional or nonaccidental intentional head trauma, and ingestion of drugs of abuse or accidental ingestion of drugs or of other toxins. The history should attempt to define factors that might have promoted the convulsion and to provide a detailed description of the seizure and the child's postictal state (see Chapter 593.9). Most parents vividly recall their child's initial convulsion and can describe it in detail.

The subsequent step in an evaluation is to determine whether the seizure has a focal onset or is generalized. **Focal seizures** may be characterized by motor or sensory symptoms, which could include forceful turning of the head and eyes to 1 side, unilateral clonic movements beginning in the face or extremities, or a sensory disturbance, such as paresthesias or pain localized to a specific area. Focal seizures in an adolescent or adult usually indicate a localized lesion, whereas these seizures during childhood are often, but not always, secondary to a

Text continued on p. 2829

Table 593-2 Classification for Epilepsy Syndromes with an Indication of Age of Onset, Duration of Active Epilepsy, Prognosis, and Therapeutic Options

SPECIFIC SYNDROMES	AGE AT ONSET	AGE AT REMISSION	PROGNOSIS	MONOTHERAPY OR ADD-ON*	POSSIBLE ADD-ON†	SURGERY†
EPILEPSIES OF UNKNOWN CAUSE OF INFANCY AND CHILDHOOD						
Benign infantile seizures (nonfamilial)	Infant	Infant	Good	PB	—	No
Benign childhood epilepsy with centrotemporal spikes	3-13 yr	16 yr	Good	CBZ, LEV, OXC, VPA	—	No
Early and late-onset idiopathic occipital epilepsy	2-8 yr; 6-17 yr	12 yr or younger; 18 yr	Good	CBZ, LEV, OXC, VPA	—	No
FAMILIAL (AUTOSOMAL DOMINANT) EPILEPSIES						
Benign familial neonatal convulsions	Newborn to young infant	Newborn to young infant	Good	PB	—	No
Benign familial infantile convulsions	Infant	Infant	Good	CBZ, PB	—	No
Autosomal dominant nocturnal frontal lobe epilepsy	Childhood		Variable	CBZ, GBP, OXC, PHT, TPM	CLB, LEV, PB, PHT	No
Familial lateral temporal lobe epilepsy	Childhood to adolescence		Variable	CBZ, GBP, OXC, PHT, TPM, VPA	CLB, LEV, PB, PHT	No
Generalized epilepsies with febrile seizures plus	Childhood to adolescence		Variable	ESM, LTG, TPM, VPA	CLB, LEV	No
STRUCTURAL–METABOLIC FOCAL EPILEPSIES						
Limbic Epilepsy						
Mesial temporal lobe epilepsy with hippocampal sclerosis	School-age or earlier	Long lasting	Variable	CBZ, LEV, OXC, TPM, VPA	CLB, GBP, LAC, PB, PHT, ZON	Temporal resection
Mesial temporal lobe epilepsy defined by specific causes	Variable	Long lasting	Variable	CBZ, LEV, OXC, TPM, VPA	CLB, GBP, LAC, PB, PHT, ZON	Temporal resection
Other types defined by location and causes	Variable	Long lasting	Variable	CBZ, LEV, OXC, TPM, VPA	CLB, FBM, GBP, LAC, PB, PHT, ZON	Lesionectomy ± temporal resection
Neocortical Epilepsies						
Rasmussen syndrome	6-12 yr	Progressive	Ominous	Plasmapheresis, immunoglobulins	CBZ, LAC, PB, PHT, TPM	Functional hemispherectomy
Hemiconvulsion-hemiplegia syndrome	1-5 yr	Chronic	Severe	CBZ, LEV, OXC, TPM, VPA	CLB, GBP, LAC, PB, PHT, ZON	Functional hemispherectomy
Other types defined by location and cause	Variable	Long lasting	Variable	CBZ, LEV, OXC, TPM, VPA	PHT, PB, CLB, GBP, LAC, ZON	Lesionectomy ± cortical resection
Migrating partial seizures of early infancy	Infant	No remission	Ominous	Bromides, CBZ, LEV, PB, PHT, TPM, VPA	BDZ, LAC, ZON	No
GENERALIZED EPILEPSIES OF UNKNOWN CAUSE						
Benign myoclonic epilepsy in infancy	3 mo-3 yr	3-5 yr	Variable	LEV, TPM, VPA	BDZ, ZON	No
Epilepsy with myoclonic astatic seizures	3-5 yr	Variable	Variable	ESM, TPM, VPA	BDZ, ketogenic diet, LEV, LTG, steroids, ZON	No
Childhood absence epilepsy	5-6 yr	10-12 yr	Good	ESM, LTG, VPA	Acetazolamide, ketogenic diet, ZON	No
Epilepsy with myoclonic absences	1-12 yr	Variable	Guarded	ESM, VPA	BDZ, ZON	No

*Reflects current trends in practice, which may be off-label and may not be FDA approved for that indication. See Table 593-10 for FDA indications.

†May apply to selected cases only. Vagus nerve stimulation has been used for all types of refractory seizures and epilepsy types.

ACTH, adrenocorticotropic hormone; BDZ, benzodiazepine; CBZ, carbamazepine; CLB, clobazam; DZP: diazepam; ESM, ethosuximide; FBM: felbamate; GBP, gabapentin; IVIG, intravenous immunoglobulin; LAC, lacosamide; LEV, levetiracetam; LTG, lamotrigine; n/a, not applicable; OXC: oxcarbazepine; PB, phenobarbital; PHT, phenytoin; PRM, primidone; RFD, rufinamide; TPM, topiramate; VGB: vigabatrin; VPA, valproic acid; ZON, zonisamide.

Continued

Table 593-2 Classification for Epilepsy Syndromes with an Indication of Age of Onset, Duration of Active Epilepsy, Prognosis, and Therapeutic Options—cont'd

SPECIFIC SYNDROMES	AGE AT ONSET	AGE AT REMISSION	PROGNOSIS	MONOTHERAPY OR ADD-ON*	POSSIBLE ADD-ON†	SURGERY†
GENERALIZED EPILEPSIES OF UNKNOWN CAUSE WITH VARIABLE PHENOTYPES						
Juvenile absence epilepsy	10-12 yr	Usually lifelong	Good	ESM, LTG, VPA	BDZ	No
Juvenile myoclonic epilepsy	12-18 yr	Usually lifelong	Good	LEV, TPM, VPA	BDZ, LTG, PB, PRM, ZON	No
Epilepsy with generalized tonic-clonic seizures only	12-18 yr	Usually lifelong	Good	LEV, LTG, TPM, VPA	BDZ, CBZ, ZON	No
REFLEX EPILEPSIES						
Idiopathic photosensitive occipital lobe epilepsy	10-12 yr	Unclear	Variable	VPA	BDZ, LEV, LTG, ZON	No
Other visual sensitive epilepsies	2-5 yr	Unclear	Variable	VPA	BDZ, LEV, LTG, ZON	No
Startle epilepsy	Variable	Long lasting	Guarded	CBZ, GBP, OXC, PHT, TPM, VPA	CLB, LEV, PB, PHT, ZON	Lesionectomy ± cortical resection in some
EPILEPTIC ENCEPHALOPATHIES						
Early myoclonic encephalopathy and Ohtahara syndrome	Newborn-infant	Poor, Ohtahara syndrome evolves into West syndrome	Ominous	PB, steroids, VGB	BDZ, ZON	No
West syndrome	Infant	Variable	Variable	ACTH, steroids, VGB	BDZ, FBM, IVIG, TPM, ZON	Lesionectomy ± cortical resection
Dravet syndrome (severe myoclonic epilepsy in infancy)	Infant	No remission	Severe	CLB, stiripentol, TPM, VPA	BDZ, ZON	No
Lennox-Gastaut syndrome	3-10 yr	No remission	Severe	CLB, LTG, RFD, TPM, VPA	BDZ, FBM, IVIG, steroids, ZON	Callosotomy
Landau-Kleffner syndrome	3-6 yr	8-12 yr	Guarded	LEV, nocturnal DZP, steroids, VPA	BDZ, ESM, IVIG, LTG	Multiple subpial transections, rarely lesionectomy
Epilepsy with continuous spike waves during slow-wave sleep	4-7 yr	8-12 yr	Guarded	LEV, nocturnal DZP, steroids, VPA	BDZ, ESM, IVIG, LTG	No
PROGRESSIVE MYOCLONUS EPILEPSIES						
Unverricht-Lundborg, Lafora, ceroid lipofuscinoses, etc.	Late infant to adolescent	Progressive	Ominous	TPM, VPA, ZON	BDZ, PB	No
OTHER EPILEPSIES AND SEIZURE DISORDERS OF UNKNOWN OR OTHER CAUSES						
Benign neonatal seizures	Newborn	Newborn	Good	LEV, PB	—	No
Febrile seizures	3-5 yr	3-6 yr	Good	PB or VPA if repeated and prolonged	—	No
Reflex seizures	Variable	n/a		LEV, VPA	LTG, ZON	No
Drug or other chemically induced seizures	Variable	n/a		Withdraw offending agent	—	No
Immediate and early posttraumatic seizures	Variable	n/a		LEV, PHT	—	No

Modified from Guerrini R: Epilepsy in children, Lancet *367:499–524, 2006; and Parisi P, Verrotti A, Paolino MC, et al. "Electro-clinical syndromes" with onset in the pediatric age group: the highlights of the clinical-EEG, genetic and therapeutic advances.* Ital J Pediatr *37:58, 2011.*

Table 593-3 Identified Genes for Epilepsy Syndromes*†

EPILEPSY TYPE	GENE	PROTEIN
INFANTILE ONSET		
Benign familial neonatal seizures	*KCNQ2*	Potassium voltage-gated channel
	KCNQ3	Potassium voltage-gated channel
Benign familial neonatal infantile seizures	*SCN2A*	Sodium channel protein type 2α
Early familial neonatal infantile seizures	*SCN2A*	Sodium channel protein type 2α
Early infantile epileptic encephalopathy (EIEE)	*CDKL5 (EIEE2)*	Cyclin-dependent kinase-like 5
	ARX (EIEE1)	Aristaless-related homeobox
	TSC1	Hamartin
	TSC2	Tuberin
	SCN1A (EIEE6)	Sodium channel protein type 1α
	PCDH19(EIEE9)	Protocadherin-19
	KCNQ2 (EIEE7)	Potassium voltage-gated channel
	STXBP1 (EIEE4)	Syntaxin binding protein 1
	SLC2A1	Solute carrier family 2, facilitated glucose transporter member 1
	ALDH7A1	α-Aminoadipic semialdehyde dehydrogenase (antiquitin)
	POLG	DNA polymerase subunit gamma-1
	SCN2A (EIEE11)	Sodium channel protein type 2α
	PLCβ1 (EIEE12)	Phospholipase C β1
	ATP6AP2	Renin receptor
	SPTAN1 (EIEE5)	α_2-Spectrin
	SLC25A22 (EIEE3)	Mitochondrial glutamate carrier 1
	PNPO	Pyridoxine-5′-phosphate oxidase
Generalized epilepsy with febrile seizures plus (early onset)	*SCN1A*	Sodium channel protein type 1α
	SCN1B	Sodium channel protein type 1β
	GABRG2	γ-Aminobutyric acid receptor subunit γ2
	SCN2A	Sodium channel protein type 1α
CHILDHOOD ONSET		
Childhood onset epileptic encephalopathies	*SCN1A*	Sodium channel protein type 1α
	PCDH19	Protocadherin-19
	SLC2A1	Solute carrier family 2, facilitated GTM1
	POLG	DNA polymerase subunit γ1
	SCN2A	Sodium channel protein type 2α
Early onset absence seizures, refractory epilepsy of multiple types at times with movement disorder	*GLUT-1* deficiency syndrome, *SLC2A1*gene	Solute carrier family 2, facilitated GTM1
Generalized epilepsy with febrile seizure plus	*SCN1A*	Sodium channel protein type 1α
	SCN1B	Sodium channel protein type 1β
	GABRG2	γ-Aminobutyric acid receptor subunit γ2
	SCN2A	Sodium channel protein type 1α
Juvenile myoclonic epilepsy (more commonly presents in adolescence)	*EFHC1*	EF-hand domain-containing protein 1
	CACNB4	Voltage-dependent L-type calcium channel
	GABRA1	γ-Aminobutyric acid receptor subunit α1
Progressive myoclonic epilepsy (different forms present from infancy through adulthood)	*EPM2A*	Laforin
	NHLRC1	NHL repeat-containing protein 1 (Malin)
	CSTB	Cystatin-B
	PRICKLE1	Prickle-like protein 1
	PPT1, TPP1,CLN3, CLN5, CLN6, CLN8, CTSD, DNAJC5, MFSD8	Multiple proteins causing neuronal ceroid lipofuscinosis
Autosomal dominant nocturnal frontal lobe epilepsies (presents in childhood through adulthood)	*CHRNA4*	Neuronal acetylcholine receptor α4
	CHRNB2	Neuronal acetylcholine receptor β2
	CHRNA2	Neuronal acetylcholine receptor α2
ADOLESCENT ONSET		
Juvenile myoclonic epilepsy (JME)	See Childhood Onset JME	
Progressive myoclonic epilepsy (PME)	See Childhood Onset PME	
Autosomal dominant nocturnal frontal lobe epilepsies (AD-NFLE)	See Childhood Onset AD-NFLE	
Autosomal dominant lateral temporal lobe epilepsy (AD-LTLE)	See Childhood Onset AD-LTLE	
Autosomal dominant lateral temporal lobe epilepsy (usually presents in adulthood)	*LGI1*	Leucine-rich glioma-inactivated protein 1

*Note that the same gene (different mutations) often appears as causing different epilepsy syndromes.

†Most of these genes can be tested for through commercially available targeted single-gene sequencing or through commercially available gene panels or though exome sequencing (http://www.ncbi.nlm.nih.gov/sites/GeneTests/review?db=genetests).

Table 593-4 Identified Genes for Syndromic Epilepsy Syndromes*

SYNDROME	GENE	PROTEIN
Rett/atypical Rett syndromes	*MECP2* *CDKL5* *FOXG1* *MBD5* *MEF2C*	Methyl CpG binding protein 2 Cyclin-dependent kinase-like 5 Forkhead box protein G1 Methyl-CpG-binding domain protein 5 Myocyte-specific enhancer factor 2C
Angelman/Angelman-like/Pitt-Hopkins syndromes	*UBE3A* *SLC9A6* *MBD5* *TCF4* *NRXN1* *CNTNAP2*	Ubiquitin protein ligase E3A Sodium/hydrogen exchanger 6 Methyl-CpG-binding domain protein 5 Transcription factor 4 Neurexin-1 Contactin-associated protein-like 2
Mowat-Wilson syndrome	*ZEB2*	Zinc finger E-box-binding homeobox 2
Creatine deficiency syndromes	*GAMT* *GATM*	Guanidinoacetate *N*-methyltransferase Glycine amidinotransferase, mitochondrial
Neuronal ceroid lipofuscinosis (NCL)	*PPT1 (CLN1)* *TPP1 (CLN2)* *CLN3* *CLN5* *CLN6* *MFSD8 (CLN7)* *CLN8* *CTSD (CLN10)* *KCTD7 (CLN14)*	Palmitoyl-protein thioesterase 1 Tripeptidyl-peptidase 1 Battenin Ceroid-lipofuscinosis neuronal protein 5 Ceroid-lipofuscinosis neuronal protein 6 Major facilitator superfamily domain-containing protein 8 Ceroid-lipofuscinosis neuronal protein 8 Cathepsin D BTB/POZ domain-containing protein KCTD7
Adenosuccinate lyase deficiency	*ADSL*	Adenylosuccinate lyase
Cerebral folate deficiency	*FOLR1*	Folate receptor alpha
Epilepsy with variable learning and behavioral disorders	*GRIN2A* *SYN1*	Glutamate receptor ionotropic, *N*-methyl-D-aspartate (NMDA) 2A Synapsin-1
17q21.31 microdeletion syndrome	*KANSL1*	KAT8 regulatory nonspecific lethal (NSL) complex subunit 1
Microcephaly with early-onset intractable seizures and developmental delay (MCSZ)	*PNKP*	Bifunctional polynucleotide phosphatase/kinase

*Most of these genes can be tested for through commercially available targeted single-gene sequencing or through commercially available gene panels or though exome sequencing.

Table 593-5 Childhood Epileptic Syndromes with Generally Good Prognosis

SYNDROME	COMMENT
Benign neonatal familial convulsions	Dominant, may be severe and resistant for a few days Febrile or afebrile seizures (benign) occur later in a minority
Infantile familial convulsions	Dominant; seizures often in clusters
Febrile convulsions plus syndromes (see Table 593-2)	Febrile and afebrile generalized convulsions, absence and myoclonic seizures occur in different members. Seizures usually generalized (GEFS+) but in some families may be focal
Benign myoclonic epilepsy of infancy	Often seizures during sleep; 1 rare variety with reflex myoclonic seizures (touch, noise)
Partial idiopathic epilepsy with rolandic spikes (benign epilepsy with centrotemporal spikes)	Seizures with falling asleep or on awakening; focal sharp waves with centrotemporal location on EEG
Idiopathic occipital partial epilepsy	Early childhood form with seizures during sleep and ictal vomiting; can occur as status epilepticus Later form with occipital spikes that block on eye opening; migrainous symptoms and seizures; not always benign
Petit mal absence epilepsy	Cases with absences only; some have generalized seizures In most cases, absences disappear on therapy but there are resistant cases (unpredictable); 60-80% full remission
Juvenile myoclonic epilepsy	Adolescence onset, with early morning myoclonic seizures and generalized seizures during sleep or upon awakening; often history of absences in childhood

EEG, electroencephalogram; GEFS+, generalized epilepsy with febrile seizures plus.

Modified from Deonna T: Management of epilepsy, Arch Dis Child *90:5–9, 2005; and Seneviratne U: The prognosis of idiopathic generalized epilepsy,* Epilepsia *53(12):2079–2090, 2012.*

lesion or the result of a genetic, idiopathic, epilepsy. Focal seizures in a neonate may be seen because of focal lesions like perinatal stroke or because of a metabolic abnormality like hypocalcemia caused by immaturity of the brain connections. Focal and generalized motor seizures may be tonic–clonic, tonic, clonic, myoclonic, or atonic. **Tonic seizures** are characterized by increased tone or rigidity, and **atonic seizures** are characterized by flaccidity or lack of movement during a convulsion. **Clonic seizures** consist of rhythmic fast muscle contractions and slightly longer relaxations; **myoclonus** is a "shock-like" contraction of a muscle of <50 msec that is often repeated. The duration of the seizure and state of consciousness (retained or impaired) should be documented. The history should determine whether an **aura** preceded the convulsion and the behavior of the child immediately preceding the seizure. The most common aura experienced by children consists of epigastric discomfort or pain and a feeling of fear. The posture of the patient, presence or absence and distribution of cyanosis, vocalizations, loss of sphincter control (particularly of the urinary bladder), and postictal state (including sleep, headache, and hemiparesis) should be noted.

In addition to the assessment of cardiorespiratory and metabolic status, examination of a child with a seizure disorder should be geared toward the search for an organic cause. The child's head circumference, length, and weight are plotted on a growth chart and compared with previous measurements. A careful general and neurologic examination should be performed. The **eyegrounds** must be examined for the presence of papilledema, optic neuritis, retinal hemorrhages, uveitis, chorioretinitis, coloboma, or macular changes, as well as retinal phakoma. The finding of unusual facial features or of associated physical findings such as hepatosplenomegaly point to an underlying metabolic or storage disease as the cause of the neurologic disorder. The presence of a **neurocutaneous disorder** may be indicated by the presence of vitiliginous ash leaf–type lesions using an ultraviolet light (Wood lamp), of adenoma sebaceum, shagreen patches, or of retinal phakomas (tuberous sclerosis), of multiple café-au-lait spots (neurofibromatosis), or of V1 or V2 distribution nevus flammeus (Sturge-Weber syndrome).

Localizing neurologic signs, such as a subtle **hemiparesis** with hyperreflexia, an equivocal Babinski sign, and a downward-drifting of an extended arm with eyes closed, might suggest a contralateral hemispheric structural lesion, such as a slow-growing glioma, as the cause of the seizure disorder. Unilateral growth arrest of the thumbnail, hand, or extremity in a child with a focal seizure disorder suggests a chronic condition, such as a porencephalic cyst, arteriovenous malformation, or cortical atrophy of the opposite hemisphere.

After the initial acute investigation, which often includes metabolic and CT scanning, depending on the clinical presentation in emergency room, in a child with a first nonfebrile seizure, it is recommended to obtain an EEG to help predict the risk of seizure recurrence. Subsequent imaging studies with MRI should be seriously considered in any child with a significant cognitive or motor impairment of unknown etiology, unexplained abnormalities on neurologic or psychiatric examination, a seizure of focal onset with or without secondary generalization, an EEG that does not represent a benign partial epilepsy of childhood or primary generalized epilepsy, or in children younger than 1 year of age. Other laboratory tests or lumbar punctures may be pursued depending on the specific clinical settings. Further details regarding the approach to a first seizure are included in Chapter 593.2.

593.1 Febrile Seizures

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Febrile seizures are seizures that occur between the age of 6 and 60 mo with a temperature of 38°C (100.4°F) or higher, that are not the result of central nervous system infection or any metabolic imbalance, and that occur in the absence of a history of prior afebrile seizures. A **simple febrile seizure** is a primary generalized, usually tonic–clonic, attack associated with fever, lasting for a maximum of 15 min, and not recurrent within a 24-hr period. A **complex febrile seizure** is more prolonged (>15 min), is focal, and/or reoccurs within 24 hr. **Febrile status epilepticus** is a febrile seizure lasting longer than 30 min. Some use the term **simple febrile seizure plus** for those with recurrent febrile seizures within 24 hr. Most patients with simple febrile seizures have a very short postictal state and usually return to their baseline normal behavior and consciousness within minutes of the seizure.

Between 2% and 5% of neurologically healthy infants and children experience at least 1, usually simple, febrile seizure. Simple febrile seizures do not have an increased risk of mortality even though they are, understandably, concerning to the parents when they first witness them. Complex febrile seizures may have an approximately 2-fold long-term increase in mortality, as compared to the general population, over the subsequent 2 yr, probably secondary to coexisting pathology. There are no long-term adverse effects of having 1 or more simple febrile seizures. Compared with age-matched controls, patients with febrile seizures do not have any increase in the incidence of abnormalities of behavior, scholastic performance, neurocognitive function, or attention. Children who develop later epilepsy, however, might experience such difficulties. Febrile seizures recur in approximately 30% of those experiencing a first episode, in 50% after 2 or more episodes, and in 50% of infants younger than 1 yr old at febrile seizure onset. Several factors affect recurrence risk (Table 593-6). Although approximately 15% of children with epilepsy have had febrile seizures, only 2-7% of children who experience febrile seizures proceed to develop epilepsy later in life. There are several predictors of epilepsy after febrile seizures (Table 593-7).

GENETIC FACTORS

The genetic contribution to the incidence of febrile seizures is manifested by a positive family history for febrile seizures in many patients. In some families, the disorder is inherited as an autosomal dominant

Table 593-6 Risk Factors for Recurrence of Febrile Seizures

MAJOR
Age <1 yr
Duration of fever <24 hr
Fever 38-39°C (100.4-102.2°F)
MINOR
Family history of febrile seizures
Family history of epilepsy
Complex febrile seizure
Daycare
Male gender
Lower serum sodium at time of presentation

Having no risk factors carries a recurrence risk of approximately 12%; 1 risk factor, 25-50%; 2 risk factors, 50-59%; 3 or more risk factors, 73-100%.

Table 593-7 Risk Factors for Occurrence of Subsequent Epilepsy After a Febrile Seizure

RISK FACTOR	RISK FOR SUBSEQUENT EPILEPSY
Simple febrile seizure	1%
Recurrent febrile seizures	4%
Complex febrile seizures (more than 15 min duration or recurrent within 24 hr)	6%
Fever <1 hr before febrile seizure	11%
Family history of epilepsy	18%
Complex febrile seizures (focal)	29%
Neurodevelopmental abnormalities	33%

trait, and multiple single genes that cause the disorder have been identified in such families. However, in most cases the disorder appears to be polygenic, and the genes predisposing to it remain to be identified. Identified single genes include *FEB 1, 2, 3, 4, 5, 6, 7, 8, 9,* and *10* genes on chromosomes 8q13-q21, 19p13.3, 2q24, 5q14-q15, 6q22-24, 18p11.2, 21q22, 5q34, 3p24.2-p23, and 3q26.2-q26.33. Only the function of *FEB 2* is known: it is a sodium channel gene, *SCN1A*.

Almost any type of epilepsy can be preceded by febrile seizures, and a few epilepsy syndromes typically start with febrile seizures. These are **generalized epilepsy with febrile seizures plus** (GEFS+), **severe myoclonic epilepsy of infancy** (also called **Dravet syndrome**), and, in many patients, temporal lobe epilepsy secondary to mesial temporal sclerosis.

GEFS+ is an autosomal dominant syndrome with a highly variable phenotype. Onset is usually in early childhood and remission is usually in mid-childhood. It is characterized by multiple febrile seizures and by several subsequent types of afebrile generalized seizures, including generalized tonic–clonic, absence, myoclonic, atonic, or myoclonic astatic seizures with variable degrees of severity. A focal febrile seizures plus epilepsy variant, in which the seizures are focal rather than generalized, has also been described.

Dravet syndrome is the most severe of the phenotypic spectrum of febrile seizure-associated epilepsies. It constitutes a distinct entity in the onset of which is in infancy. Its onset is characterized by febrile and afebrile unilateral clonic seizures recurring every 1 or 2 mo. These early seizures are typically induced by fever, but they differ from the usual febrile convulsions in that they are more prolonged, are more frequent, are focal and come in clusters. Seizures subsequently start to occur with lower fevers and then without fever. During the 2nd yr of life, myoclonus, atypical absences, and partial seizures occur frequently and developmental delay usually follows. This syndrome is usually caused by a de novo mutation, although rarely it is inherited in an autosomal dominant manner. The mutated gene is located on 2q24-31 and encodes for *SCN1A*, the same gene mutated in GEFS+ spectrum. However, in Dravet syndrome the mutations lead to loss of function and thus to a more severe phenotype. There are several milder variants of Dravet syndrome that manifest some but not all of the above features and that are referred to as Dravet syndrome spectrum or Borderland. Mutations in other genes may also cause Dravet syndrome or GEFS+ phenotypes.

The majority of patients who had prolonged febrile seizures and encephalopathy after vaccination and who had been presumed to have suffered from **vaccine encephalopathy** (seizures and psychomotor regression occurring after vaccination and presumed to be caused by it) turn out to have Dravet syndrome mutations, indicating that their disease is caused by the mutation and not secondary to the vaccine. This has raised doubts about the very existence of the entity termed vaccine encephalopathy.

EVALUATION

Figure 593-1 delineates the general approach to the patient with febrile seizures. Each child who presents with a febrile seizure requires a detailed history and a thorough general and neurologic examination. Febrile seizures often occur in the context of otitis media, roseola and human herpesvirus (HHV) 6 infection, shigella, or similar infections, making the evaluation more demanding. In patients with febrile status, HHV-6B (more frequently) and HHV-7 infections were found to account for one-third of the cases. Several laboratory studies need to be considered in evaluating the patient with febrile seizures.

Lumbar Puncture

Meningitis should be considered in the differential diagnosis, and lumbar puncture should be performed for all infants younger than 6 mo of age who present with fever and seizure, or if the child is ill-appearing or at any age if there are clinical signs or symptoms of concern. A lumbar puncture is an option in a child 6-12 mo of age who is deficient in *Haemophilus influenzae* type b and *Streptococcus pneumoniae* immunizations or for whom immunization status is unknown. A lumbar puncture is an option in children who have been pretreated with antibiotics. *In patients presenting with febrile status epilepticus in the absence of a central nervous system infection, a nontraumatic lumbar puncture rarely shows cerebrospinal fluid (CSF) pleocytosis (96% have <3 nucleated cells in the CSF) and the CSF protein and glucose are usually normal.*

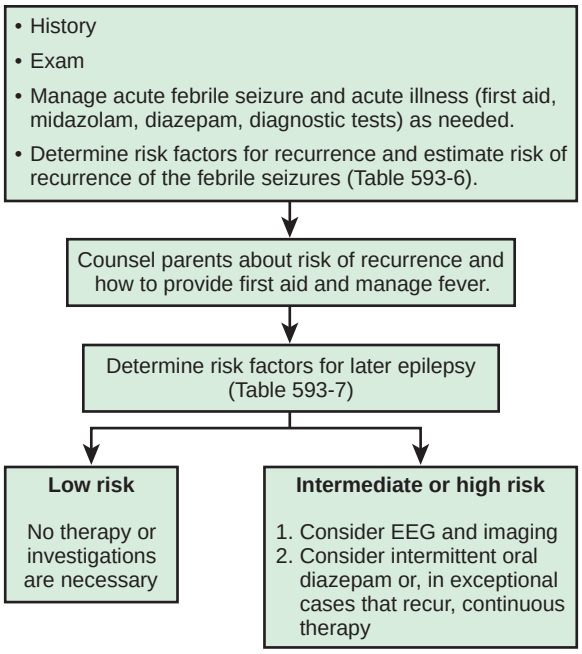


Figure 593-1 Management of febrile seizures. *(Modified from Mikati MA, Rahi A: Febrile seizures: from molecular biology to clinical practice,* Neurosciences (Riyadh) *10:14–22, 2004.)*

Electroencephalogram

If the child is presenting with the first simple febrile seizure and is otherwise neurologically healthy, an EEG need not normally be performed as part of the evaluation. An EEG would not predict the future recurrence of febrile seizures or epilepsy even if the result is abnormal. Spikes during drowsiness are often seen in children with febrile seizures, particularly those older than age 4 yr, and these do not predict later epilepsy. EEGs performed within 2 wk of a febrile seizure often have nonspecific slowing, usually posteriorly. Thus, in many cases, if an EEG is indicated, it is delayed until or repeated after more than 2 wk have passed. An EEG should, therefore, generally be restricted to special cases in which epilepsy is highly suspected, and, generally, it should be used to delineate the type of epilepsy rather than to predict its occurrence. If an EEG is done, it should be performed for at least 20 min in wakefulness and in sleep according to international guidelines to avoid misinterpretation and drawing of erroneous conclusions. At times, if the patient does not recover immediately from a seizure, then an EEG can help distinguish between ongoing seizure activity and a prolonged postictal period, sometimes termed a **nonepileptic twilight state.** EEG can also be helpful in patients who present with febrile status epilepticus because the presence of focal slowing present on the EEG obtained within 72 hr of the status has been shown to be highly associated with MRI evidence of acute hippocampal injury.

Blood Studies

Blood studies (serum electrolytes, calcium, phosphorus, magnesium, and complete blood count) are not routinely recommended in the work-up of a child with a first simple febrile seizure. Blood glucose should be determined in children with prolonged postictal obtundation or with poor oral intake (prolonged fasting). Serum electrolyte values may be abnormal in children after a febrile seizure, but this should be suggested by precipitating or predisposing conditions elicited in the history and reflected in abnormalities of the physical examination. If clinically indicated (e.g., in a history or physical examination

suggesting dehydration), these tests should be performed. A low sodium level is associated with higher risk of recurrence of the febrile seizure within the following 24 hr.

Neuroimaging

A CT or MRI is not recommended in evaluating the child after a first simple febrile seizure. The work-up of children with complex febrile seizures needs to be individualized. This can include an EEG and neuroimaging, particularly if the child is neurologically abnormal. Approximately 11% of children with febrile status epilepticus are reported to have (usually) unilateral swelling of their hippocampus acutely, which is followed by subsequent long-term hippocampal atrophy. Whether these patients will ultimately develop temporal lobe epilepsy remains to be determined.

TREATMENT

In general, antiepileptic therapy, continuous or intermittent, is not recommended for children with 1 or more simple febrile seizures. Parents should be counseled about the relative risks of recurrence of febrile seizures and recurrence of epilepsy, educated on how to handle a seizure acutely, and given emotional support. If the seizure lasts for longer than 5 min, acute treatment with diazepam, lorazepam, or midazolam is needed (see Chapter 593.8 for acute management of seizures and status epilepticus). Rectal diazepam is often prescribed to be given at the time of reoccurrence of a febrile seizure lasting longer than 5 min (see Table 593-12 for dosing). Alternatively, buccal or intranasal midazolam may be used and is often preferred by parents. Intravenous benzodiazepines, phenobarbital, phenytoin, or valproate may be needed in the case of febrile status epilepticus. If the parents are very anxious concerning their child's seizures, intermittent oral diazepam (0.33 mg/kg every 8 hr during fever) or intermittent rectal diazepam (0.5 mg/kg administered as a rectal suppository every 8 hr), can be given during febrile illnesses. Intermittent oral nitrazepam, clobazam, and clonazepam (0.1 mg/kg/day) have also been used. Such therapies help reduce, but do not eliminate, the risks of recurrence of febrile seizures. Other therapies have included continuous phenobarbital (4-5 mg/kg/day in 1 or 2 divided doses), and continuous valproate (20-30 mg/kg/day in 2 or 3 divided doses). *In the vast majority of cases, it is not justified to use continuous therapy owing to the risk of side effects and lack of demonstrated long-term benefits, even if the recurrence rate of febrile seizures is expected to be decreased by these drugs.*

Antipyretics can decrease the discomfort of the child but do not reduce the risk of having a recurrent febrile seizure, probably because the seizure often occurs as the temperature is rising or falling. Chronic antiepileptic therapy may be considered for children with a high risk for later epilepsy. Currently available data indicate that the possibility of future epilepsy does not change with or without antiepileptic therapy. Iron deficiency is associated with an increased risk of febrile seizures, and thus screening for that problem and treating it appears appropriate.

Bibliography is available at Expert Consult.

593.2 Unprovoked Seizures

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HISTORY AND EXAMINATION

Acute evaluation of a first seizure includes assessment of vital signs and respiratory and cardiac function, and institution of measures to normalize and stabilize them as needed. Signs of head trauma, abuse, drug intoxication, poisoning, meningitis, sepsis, focal abnormalities, increased intracranial pressure, herniation, neurocutaneous stigmata, brainstem dysfunction, and/or focal weakness should all be sought because they could suggest an underlying etiology for the seizure.

The **history** should also include details of the seizure manifestations, particularly those that occurred at its initial onset. These could give clues to the type and brain localization of the seizure. One should also probe for previous signs or symptoms of other seizures in the preceding weeks, or longer, that the parents may have overlooked and did not report. In some instances, if the events have been going on for a time and there is a question about their nature (e.g., sleep myoclonus vs seizures), then the family could video record the patient and make the video available to the healthcare provider. Having the parents imitate the seizure can also be helpful. Seizure patterns (e.g., clustering), precipitating conditions (e.g., sleep or sleep deprivation, television, visual patterns, mental activity, stress), exacerbating conditions (e.g., menstrual cycle, medications), frequency, duration, time of occurrence, and other characteristics need to be carefully documented (see Chapter 593.9). Parents often overlook, do not report, or underreport absence, complex partial, or myoclonic seizures. A history of personality change or symptoms of increased intracranial pressure can suggest an intracranial tumor. Similarly, a history of cognitive regression can suggest a degenerative or metabolic disease. Certain medications such as stimulants or antihistamines, particularly sedating ones, can precipitate seizures. A history of prenatal or perinatal distress or of developmental delay can suggest etiologic congenital or perinatal brain dysfunction. Details of the spells can suggest nonepileptic paroxysmal disorders that mimic seizures (see Chapter 594).

DIFFERENTIAL DIAGNOSIS

This involves consideration of nonepileptic paroxysmal events (see Chapter 594), determination of the seizure type, as classified by the new ILAE system (see Table 593-1) and consideration of potential underlying etiologies. Some seizures might begin with **auras**, which are sensory experiences reported by the patient and not observed externally. These can take the form of visual (e.g., flashing lights or seeing colors or complex visual hallucinations), somatosensory (tingling), olfactory, auditory, vestibular, or experiential (e.g., déjà vu, déjà vécu feelings) sensations, depending upon the precise localization of the origin of the seizures.

Motor seizures can be **tonic** (sustained contraction), **clonic** (rhythmic contractions), **myoclonic** (rapid shock-like contractions, usually <50 msec in duration, that may be isolated or may repeat but usually are not rhythmic), **atonic**, or **astatic**. **Astatic** seizures often follow myoclonic seizures and cause a very momentary loss of tone with a sudden fall. **Atonic** seizures, on the other hand, are usually longer and the loss of tone often develops more slowly. Sometimes it is difficult to distinguish among tonic, myoclonic, atonic, or astatic seizures based on the history alone when the family reports only that the patient "falls"; in such cases, the seizure may be described as a **drop attack**. Loss of tone or myoclonus in only the neck muscles results in a milder seizure referred to as a **head drop**. Tonic, clonic, myoclonic, and atonic seizures can be focal (including 1 limb or 1 side only), focal with secondary generalization, or primary generalized. Epileptic **spasms** (axial spasms, these terms being preferred over infantile spasms because they can occur beyond infancy) consist of flexion or extension of truncal and extremity musculature that is sustained for 1-2 sec, shorter than what is seen in tonic seizures, which last longer than 2 sec. Focal motor clonic and/or myoclonic seizures that persist for days, months, or even longer are termed **epilepsia partialis continua**.

Absence seizures are generalized seizures consisting of staring, unresponsiveness, and eye flutter lasting usually for few seconds. **Typical absences** are associated with 3 Hz spike–and–slow-wave discharges and with petit mal epilepsy, which has a good prognosis. **Atypical absences** are associated with 1-2 Hz spike–and–slow-wave discharges, and with head atonia and myoclonus during the seizures. They occur in Lennox-Gastaut syndrome, which has a poor prognosis. **Juvenile absences** are similar to typical absences but are associated with 4-5 Hz spike-and-slow waves and occur in juvenile myoclonic epilepsy. Seizure type and other EEG and clinical manifestations determine the type of **epilepsy syndrome** with which a particular patient is afflicted (Table 593-8; see Chapter 593.3 and 593.4).

Family history of certain forms of epilepsy, like benign neonatal seizures, can suggest the specific epilepsy syndrome. More often, however, different members of a family with a positive history of epilepsy have different types of epilepsy. Head circumference can indicate

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Table 593-8 Selected Epilepsy Syndromes by Age of Onset

NEONATAL PERIOD
Benign familial neonatal seizures (BFNS)
Early myoclonic encephalopathy (EME)
Ohtahara syndrome
INFANCY
Epilepsy of infancy with migrating focal seizures
West syndrome
Myoclonic epilepsy in infancy (MEI)
Benign infantile seizures
Benign familial infantile epilepsy
Dravet syndrome
Myoclonic encephalopathy in nonprogressive disorders
CHILDHOOD
Febrile seizures plus (FS+) (can start in infancy; this can be with generalized [GEFS+] or with focal seizures)
Early-onset benign childhood occipital epilepsy (Panayiotopoulos type)
Epilepsy with myoclonic atonic (previously astatic) seizures
Benign epilepsy with centrotemporal spikes (BCECTS)
Late-onset childhood occipital epilepsy (Gastaut type)
Autosomal dominant nocturnal frontal lobe epilepsy (AD-NFLE)
Epilepsy with myoclonic absences
Lennox-Gastaut syndrome
Epileptic encephalopathy with continuous spike-and-wave during sleep (CSWS)
Landau-Kleffner syndrome
Childhood absence epilepsy (CAE)
ADOLESCENCE–ADULT
Juvenile absence epilepsy (JAE)
Juvenile myoclonic epilepsy (JME)
Epilepsy with generalized tonic–clonic seizures alone
Progressive myoclonus epilepsies (PME)
Autosomal dominant epilepsy with auditory features (ADEAF)
Other familial temporal lobe epilepsies
AGE-RELATED (AGE OF ONSET LESS SPECIFIC)
Familial focal epilepsy with variable foci (childhood to adult)
Reflex epilepsies
SEIZURE DISORDERS THAT ARE NOT TRADITIONALLY GIVEN THE DIAGNOSIS OF EPILEPSY
Benign neonatal seizures (BNS)
Febrile seizures (FS)
EPILEPTIC ENCEPHALOPATHIES
EME
Ohtahara syndrome
Migrating partial seizures of infancy
West syndrome
Dravet syndrome
Myoclonic encephalopathy in nonprogressive disorders
Epilepsy with myoclonic astatic seizures
Lennox-Gastaut syndrome
Epileptic encephalopathy with CSWS
Landau-Kleffner syndrome
OTHER SECONDARY GENERALIZED EPILEPSIES
Generalized epilepsy secondary to neurodegenerative disease
Progressive myoclonus epilepsies

Modified from Berg AT, Berkovic SF, Bordie MJ, et al. Revised terminology and concepts for organization of seizures and epilepsies: report of the ILAE Commission on Classification and Terminology, 2005-2009. Epilepsia *51:676–685, 2010.*

Table 593-9 Proposed Diagnostic Scheme for People with Epileptic Seizures and with Epilepsy

Epileptic seizures and epilepsy syndromes are to be described and categorized according to a system that uses standardized terminology and that is sufficiently flexible to take into account the practical and dynamic aspects of epilepsy diagnosis:

- Axis 1: Ictal phenomenology, used to describe ictal events with any degree of detail needed.
- Axis 2: Seizure type, from the List of types of Epileptic Seizures. Localization within the brain and precipitating stimuli for reflex seizures should be specified when appropriate.
- Axis 3: Syndrome, from the List of Epilepsy Syndromes, with the understanding that a syndromic diagnosis may not always be possible.
- Axis 4: Etiology, from a Classification of Diseases Frequently Associated with Epileptic Seizures or Epilepsy Syndromes when possible, genetic defects, or specific pathologic substrates for symptomatic focal epilepsies.
- Axis 5: Impairment; this is often useful to make sure one does not overlook the consequences of epilepsy, such as medication side effects, and learning and socialization difficulties.

Modified from Engel J. A proposed diagnostic scheme for people with epileptic seizures and with epilepsy: report of the ILAE task force on classification and terminology. Epilepsia. 2001;42:796–803.

the presence of microcephaly or of macrocephaly. Eye exam may show optic disc edema, retinal hemorrhages, chorioretinitis, colobomata (associated with brain malformations), a cherry-red spot, optic atrophy, macular changes (associated with genetic neurodegenerative and storage diseases), or phakomas (associated with tuberous sclerosis). Skin exam could show a trigeminal V_1 distribution capillary hemangioma (associated with Sturge-Weber syndrome), hypopigmented lesions (sometimes associated with tuberous sclerosis and detected more reliably by viewing the skin under UV light), or other neurocutaneous manifestations such as Shagreen patches and adenoma sebaceum (associated with tuberous sclerosis), or whorl-like hypopigmented areas (hypomelanosis of Ito, associated with hemimegalencephaly). Subtle asymmetries on the exam such as drift of 1 of the extended arms, posturing of an arm on stress gait, slowness in rapid alternating movements, small hand or thumb and thumb nail on 1 side, or difficulty in hopping on 1 leg relative to the other can signify a subtle hemiparesis associated with a lesion on the contralateral side of the brain.

Guidelines on the evaluation of a **first unprovoked nonfebrile** seizure include a careful history and physical examination and brain imaging by head CT or MRI. Emergency head CT in the child presenting with a first unprovoked nonfebrile seizure is often useful for acute management of the patient. Laboratory studies are recommended in specific clinical situations: Spinal tap is considered in patients with suspected meningitis or encephalitis, in children without brain swelling or papilledema, and in children in whom a history of intracranial bleeding is suspected without evidence of such on head CT. In the second of these, examination of the CSF for xanthochromia is essential. Electrocardiography (ECG) to rule out long QT or other cardiac dysrhythmias and other tests directed at disorders that could mimic seizures may be needed (see Chapter 594). EEG is highly recommended to assess for focal abnormalities and predict seizure recurrence.

LONG-TERM APPROACH TO THE PATIENT AND ADDITIONAL TESTING

The approach to the patient with epilepsy is based on the diagnostic scheme proposed by the ILAE Task Force on Classification and Terminology and presented in Table 593-9. This emphasizes the total approach to the patient, including identification, if possible, of the underlying etiology of the epilepsy and the impairments that result from it. The impairments are very often just as important as, if not more important than, the seizures themselves. Most epilepsy syndromes are potentially caused by any 1 of multiple underlying or still undetermined etiologies. However, in addition, there are many epilepsy syndromes that are associated with specific gene mutations (see Table 593-2). Different mutations of the same gene can result in different epilepsy syndromes, and mutations of different genes can cause the same epilepsy syndrome phenotype. The clinical use of gene testing in the diagnosis and management of childhood epilepsy has been limited to patients manifesting specific underlying malformational, metabolic, or degenerative disorders, patients with severe named epilepsy syndromes (such as West and Dravet syndromes and progressive

myoclonic epilepsies), and to patients with syndromes of mendelian inheritance (see Table 593-2).

Patients with **recurrent seizures**, specifically with 2 seizures spaced apart by longer than 24 hr, warrant further work-up directed at the underlying etiology. In patients with drug-resistant epilepsy, or in infants with new-onset epilepsy in whom the initial testing did not reveal an underlying etiology, a full metabolic work-up, including amino acids, organic acids, biotinidase, and CSF studies, is needed. Additional testing can include, depending on the case, some or most of the following:

1. Measurement of serum lactate, pyruvate, acyl carnitine profile, creatine, very-long-chain fatty acids, and guanidino-acetic acid.
2. Blood and serum sometimes need to be tested for white blood cell lysosomal enzymes, serum coenzyme Q levels, and serum copper and ceruloplasmin levels (for Menkes syndrome).
3. Serum immune isoelectric focusing is performed for carbohydrate-deficient transferrin.
4. CSF glucose testing looks for glucose transporter deficiency, and CSF can be examined for cells and proteins (for parainfectious and postinfectious syndromes, and for Aicardi-Goutières syndrome, which also shows cerebral calcifications and has a specific gene defect test available).
5. Other laboratory studies include immunoglobulin (Ig) G index, NMDA (*N*-methyl-D-aspartate) receptor antibodies, and measles titers.
6. CSF tests can also confirm with, the appropriate clinical setup, the diagnosis of cerebral folate deficiency, pyridoxine dependency, pyridoxal dependency, mitochondrial disorders, nonketotic hyperglycinemia, neopterin/biopterin metabolism disorders, adenylosuccinate lyase deficiency, and neurotransmitter deficiencies. In infants who do not respond immediately to antiepileptic therapy, vitamin B_6 (100 mg intravenously) is given as a therapeutic trial to help diagnose pyridoxine-responsive seizures, with precautions to guard against possible apnea. The trial is best done with continuous EEG monitoring, including a preadministration baseline recording period. Prior to the vitamin B_6 trial, a pipecolic acid level and urine and CSF α-aminoadipic acid semialdehyde levels should be drawn, because they often elevated in this rare syndrome and the therapeutic trial result may not be definitive. Some patients are pyridoxal phosphate, rather than pyridoxine, dependent. Also patients with cerebral folate deficiency can have intractable seizures. Thus trials of pyridoxal phosphate given orally (up to 50 mg/kg) and folinic acid (up to 3 mg/kg) over several weeks can help diagnose these rare disorders while waiting for the definitive diagnosis from CSF or genetic testing for these disorders. Certain EEG changes such as continuous spike–and–slow-wave seizure activity and burst-suppression patterns may also suggest these vitamin-responsive syndromes.
7. Urine may also need to be tested for urinary sulfites indicating molybdenum cofactor deficiency and for oligosaccharides and mucopolysaccharides. MR spectroscopy is performed for lactate and creatine peaks to rule out mitochondrial disease and creatine transporter deficiency.
8. Gene testing looks for specific disorders that can manifest with seizures, including *SCN1A* mutations in Dravet syndrome; *ARX* gene for West syndrome in boys; *MECP2, CDKL5,* and protocadherin 19 for Rett syndrome and similar presentations; syntaxin binding protein for Ohtahara syndrome; and polymerase G for West syndrome and other seizures in infants. Gene testing can also be performed for other dysmorphic or metabolic syndromes.
9. Muscle biopsy can be performed for mitochondrial enzymes and coenzyme Q10 levels, and skin biopsy for inclusion bodies seen in neuronal ceroid lipofuscinosis and Lafora body disease is sometimes needed.
10. Genetic panels are available that include multiple genes that can cause epilepsy at specific ages; whole-exome sequencing is also available. These can be helpful in selected patients.

Most patients do not require a work-up anywhere near the above described extensive testing. The pace and extent of the work-up must depend critically upon the clinical epileptic and nonepileptic features, the family and antecedent personal history of the patient, the medication responsiveness of the seizures, the likelihood of identifying a treatable condition, and the wishes and need of the family to assign a specific diagnosis to the child's illness.

Bibliography is available at Expert Consult.

593.3 Partial Seizures and Related Epilepsy Syndromes

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Partial (now referred to as focal) seizures account for approximately 40% of seizures in children and can be divided into **simple partial seizures** (currently referred to in the most recent ILAE classification as **focal seizures without impairment of consciousness**), in which consciousness is not impaired, and **complex partial seizures** (currently referred to as **focal seizures with impairment of consciousness**, also called **focal dyscognitive seizures**), in which consciousness is affected. Simple and complex partial seizures can each occur in isolation, one can temporally lead to the other (usually simple to complex), and/or each can progress into **secondary generalized seizures** (tonic, clonic, atonic, or most often tonic–clonic).

FOCAL SEIZURES WITHOUT IMPAIRMENT OF CONSCIOUSNESS

These can take the form of sensory seizures (auras) or brief motor seizures, the specific nature of which gives clues as to the location of the seizure focus. Brief motor seizures are the most common and include focal tonic, clonic, or atonic seizures. Often there is a motor (jacksonian) march from face to arm to leg, adversive head and eye movements to the contralateral side, or postictal (Todd) paralysis that can last minutes or hours, and sometimes longer. Unlike tics, motor seizures are not under partial voluntary control; seizures are more often stereotyped and less likely than tics to manifest different types in a given patient.

FOCAL SEIZURES WITH IMPAIRMENT OF CONSCIOUSNESS

These seizures usually last 1-2 min and are often preceded by an **aura**, such as a rising abdominal feeling, déjà vu or déjà vécu, a sense of fear, complex visual hallucinations, micropsia or macropsia (temporal lobe), generalized difficult-to-characterize sensations (frontal lobe), focal sensations (parietal lobe), or simple visual experiences (occipital lobe). Children younger than 7 yr old are less likely than older children to report auras, but parents might observe unusual preictal behaviors that suggest the experiencing of auras. Subsequent manifestations consist of decreased responsiveness, staring, looking around seemingly purposelessly, and automatisms. **Automatisms** are automatic semipurposeful movements of the mouth (oral, alimentary such as chewing) or of the extremities (manual, such as manipulating the sheets; leg automatisms such as shuffling, walking). Often there is salivation, dilation of the pupils, and flushing or color change. The patient might appear to react to some of the stimulation around him or her but does not later recall the epileptic event. At times, walking and/or marked limb flailing and agitation occur, particularly in patients with frontal lobe seizures. Frontal lobe seizures often occur at night and can be very numerous and brief, but other complex partial seizures from other areas in the brain can also occur at night, too. There is often contralateral dystonic posturing of the arm and, in some cases, unilateral or bilateral tonic arm stiffening. Some seizures have these manifestations with minimal or no automatisms. Others consist of altered consciousness with contralateral motor, usually clonic, manifestations. After the seizure, the patient can have postictal automatisms, sleepiness, and/or other transient focal deficits such as weakness (Todd paralysis) or aphasia.

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SECONDARY GENERALIZED SEIZURES

Seizures of this type were previously known as focal seizures with impairment of consciousness evolving to bilateral convulsive seizures. Secondary generalized seizures can start with generalized clinical phenomena (from rapid spread of the discharge from the initial focus), or as simple or complex partial seizures with subsequent clinical generalization. There is often adversive eye and head deviation to the side contralateral to the side of the seizure focus followed by generalized tonic, clonic, or tonic–clonic activity. Tongue biting, urinary and stool incontinence, vomiting with risk of aspiration, and cyanosis are common. Fractures of the vertebrae or humerus are rare complications. Most such seizures last 1-2 min. Tonic focal or secondary generalized seizures often manifest adversive head deviation to the contralateral side, or fencing, hemi- or full figure-of-four arm, or Statue of Liberty postures. These postures often suggest frontal origin, particularly when consciousness is preserved during them, indicating that the seizure originated from the medial frontal supplementary motor area.

EEG in patients with focal/partial seizures usually shows focal spikes or sharp waves in the lobe where the seizure originates. A sleep-deprived EEG with recording during sleep increases the diagnostic yield and is advisable in all patients whenever possible (Fig. 593-2). Despite that, approximately 15% of children with epilepsy initially have normal EEGs because the discharges are relatively infrequent or the focus is deep. If repeating the test does not detect paroxysmal findings, then longer recordings in the laboratory or using ambulatory EEG or even inpatient 24-hr video EEG monitoring may be helpful. The latter is particularly helpful if the seizures are frequent enough, because it then can allow visualization of the clinical events and the corresponding EEG tracing.

Brain imaging is critical in patients with focal seizures. In general, MRI is preferable to CT, which misses subtle but occasionally potentially clinically significant lesions. MRI can show pathologies such as changes as a result of previous strokes or hypoxic injury, malformations, medial temporal sclerosis, arteriovenous malformations, inflammatory pathologies, or tumors (Fig. 593-3).

BENIGN EPILEPSY SYNDROMES WITH FOCAL SEIZURES

The most common such syndrome is **benign childhood epilepsy with centrotemporal spikes** which typically starts during childhood (ages 3-10 yr) and is outgrown in adolescence. The child typically wakes up at night owing to a focal (simple partial) seizure causing buccal and throat tingling and tonic or clonic contractions of 1 side of the face, with drooling and inability to speak but with preserved consciousness and comprehension. Dyscognitive focal (complex partial) and secondary generalized seizures can also occur. EEG shows typical broad-based centrotemporal spikes that are markedly increased in frequency during drowsiness and sleep. MRI is normal. Patients respond very well to antiepileptic drugs (AEDs) such as carbamazepine. In some patients who only have rare and mild seizures treatment might not be needed.

Benign epilepsy with occipital spikes can occur in early childhood (**Panayiotopoulos type**) and manifests with complex partial seizures with ictal vomiting, or they appear in later childhood (**Gastaut type**) with complex partial seizures, visual auras, and migraine headaches. Both are typically outgrown in a few years. Manifestations may include visual hallucinations and postictal headache (epilepsy–migraine sequence).

In infants, several less-common **benign infantile familial convulsion syndromes** have been reported. For some of these, the corresponding gene mutation and its function are known (see Tables 593-2 and 593-5), but for others, the genetic underpinnings are yet to be determined. Specific syndromes include benign infantile familial convulsions with parietooccipital foci linked to chromosomal loci 19q and 2q, benign familial infantile convulsions with associated choreoathetosis linked to chromosomal locus 16p12-q12, and benign

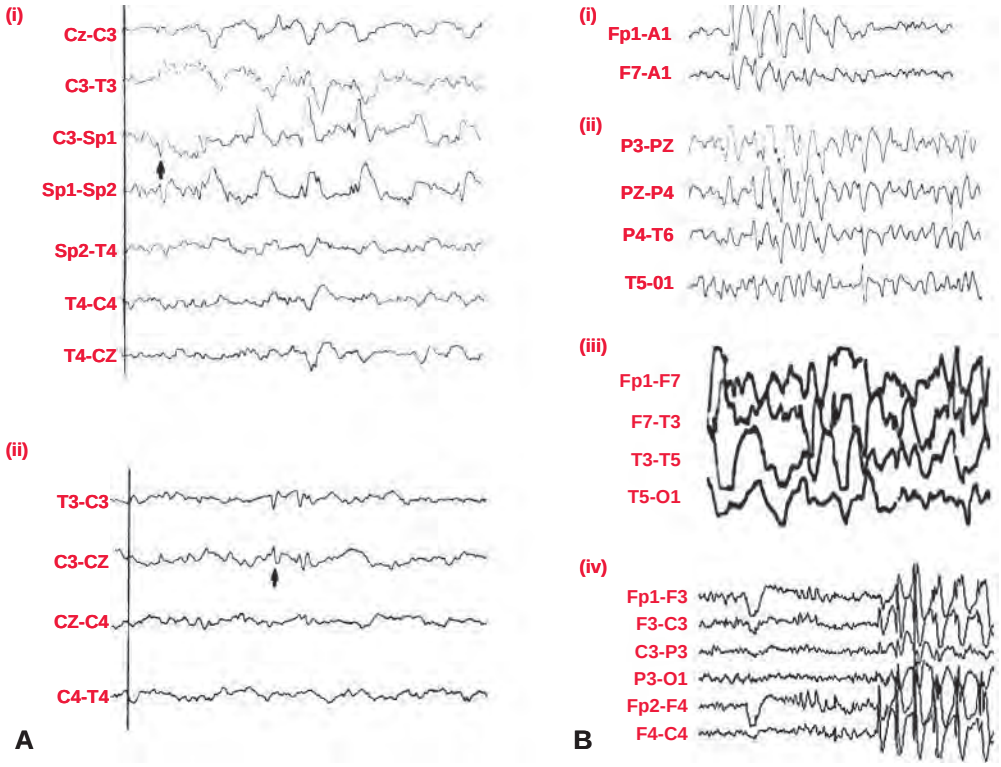


Figure 593-2 **A,** Representative EEG associated with partial seizures: (i) Spike discharges from the left temporal lobe *(arrow)* in a patient with complex partial seizures caused by mesial temporal sclerosis; (ii) left central-parietal spikes *(arrow)* characteristic of benign partial epilepsy with centrotemporal spikes. **B,** Representative EEGs associated with generalized seizures: (i) 3/sec spike-and-wave discharge of absence seizures with normal background activity; (ii) 1-2/sec interictal slow spike waves in a patient with Lennox-Gastaut syndrome; (iii) hypsarrhythmia with an irregular multifocal high-voltage spike and wave activity with chaotic high-voltage slow background; (iv) juvenile myoclonic epilepsy EEG showing 4-6/sec spike and waves enhanced by photic stimulation.

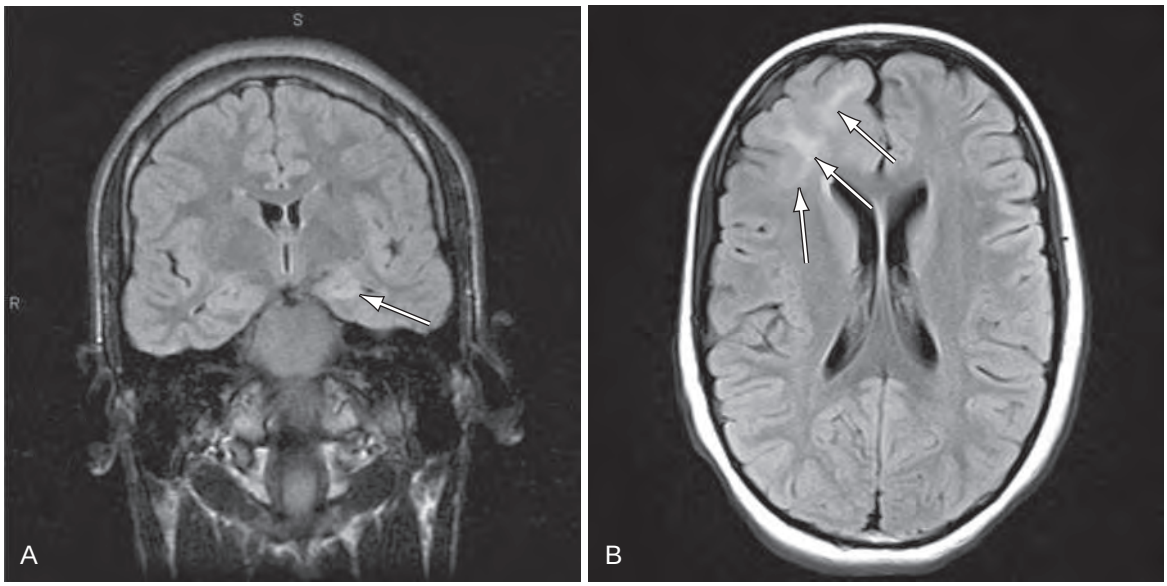


Figure 593-3 **A,** Coronal fluid-attenuated inversion-recovery (FLAIR) MRI scan of a 13 yr old with intractable seizures and mesial temporal sclerosis (MTS). The *arrow* points at the hippocampus with the high-intensity signal characteristic of MTS. **B,** Axial FLAIR MRI of a 7 yr old with intractable seizures and right frontal cortical dysplasia. The *arrows* point at the high-intensity signal corresponding to the dysplasia. *(**A** from Lee JYK, Adelson PD: Neurosurgical management of pediatric epilepsy,* Pediatr Clin North Am *51:441–456, 2004.)*

infantile familial convulsions with hemiplegic migraine linked to chromosome 1. A number of **benign infantile nonfamilial syndromes** have been reported, including dyscognitive focal (complex partial) seizures with temporal foci, secondary generalized tonic–clonic seizures with variable foci, tonic seizures with midline foci, and partial seizures in association with mild gastroenteritis. All of these have a good prognosis and respond to treatment promptly, often necessitating only short-term (e.g., 6 mo), if any, therapy. **Nocturnal autosomal dominant frontal lobe epilepsy** has been linked to acetylcholine-receptor gene mutations and manifests with nocturnal seizures with dystonic posturing and agitation, screaming, kicking that respond promptly to carbamazepine. Several other less-frequent familial benign epilepsy syndromes with different localizations have also been described, some of which occur exclusively or predominantly in adults (see Table 593-2).

SEVERE EPILEPSY SYNDROMES WITH FOCAL SEIZURES

Symptomatic structural/metabolic epilepsy secondary to focal brain lesions has a higher chance of being severe and refractory to therapy than idiopathic genetic epilepsy. It is important to note that many patients with focal lesions, for example, old strokes or brain tumors, either never have seizures or have well-controlled epilepsy. In infants, drug-resistant epilepsy with focal seizures is often caused by severe metabolic problems, hypoxic–ischemic injury, or congenital malformations. In addition, in this age group, a syndrome of multifocal severe partial seizures with progressive mental regression and cerebral atrophy called **migrating partial seizures of infancy** has been described. In infants and older children, several types of lesions, which can occur in any lobe, can cause intractable epilepsy and seizures and some cases may be secondary to mutations in the calcium sensitive potassium channel KCNT1. Brain malformations causing focal epilepsy include focal cortical dysplasia, hemimegalencephaly, Sturge-Weber hemangioma, tuberous sclerosis, and congenital tumors such as ganglioglioma, and dysembryoplastic neuroepithelial tumors, as well as others. The intractable seizures can be simple partial, complex partial, secondary generalized, or combinations thereof. If secondary generalized seizures predominate and take the form of absence-like seizures and drop attacks, the clinical picture can mimic the generalized epilepsy syndrome of Lennox-Gastaut syndrome and has been termed by some **pseudo–Lennox-Gastaut syndrome**.

Temporal lobe epilepsy can be caused by any temporal lobe lesion. A common cause is **mesial** (also termed **medial**) **temporal sclerosis**, a condition often preceded by febrile seizures and, rarely, genetic in origin. Pathologically, these patients have atrophy and gliosis of the hippocampus and, in some, of the amygdala. It is the most common cause of surgically remediable partial epilepsy in adolescents and adults. Occasionally, in patients with other symptomatic or cryptogenic partial or generalized epilepsies, the focal discharges are so continuous that they cause an epileptic encephalopathy. Activation of temporal discharges in sleep can lead to loss of speech and verbal auditory agnosia (**Landau-Kleffner epileptic aphasia syndrome**). Activation of frontal and secondary generalized discharges in sleep leads to more global delay secondary to the **syndrome of continuous spike waves in slow-wave sleep** (>85% of slow-wave sleep recording dominated by discharges).

The syndrome of **Rasmussen encephalitis** is a form of chronic encephalitis that manifests with unilateral intractable partial seizures, epilepsia partialis continua, and progressive hemiparesis of the affected side, with progressive atrophy of the contralateral hemisphere. The etiology is usually unknown. Some cases have been attributed to cytomegalovirus and others to anti-NMDA receptor autoantibodies.

593.4 Generalized Seizures and Related Epilepsy Syndromes

Mohamad A. Mikati and Abeer J. Hani

ABSENCE SEIZURES

Typical absence seizures usually start at 5-8 yr of age and are often, owing to their brevity, overlooked by parents for many months even though they can occur up to hundreds of times per day. Unlike complex partial seizures they do not have an aura, usually last for only a few seconds, and are accompanied by eye lid flutter or upward rolling of the eyes but typically not by the usually more florid automatisms of complex partial seizures (absence seizures can have simple automatisms like lip-smacking or picking at clothing and the head can minimally fall forward). Absence seizures do not have a postictal period and are characterized by immediate resumption of what the patient was doing before the seizure. Hyperventilation for 3-5 min can precipitate the seizures and the accompanying 3 Hz spike–and–slow-wave

discharges. The presence of periorbital, lid, perioral or limb myoclonic jerks with the typical absence seizures usually predicts difficulty in controlling the seizures with medications. Early onset absence seizures (before the age of 4 yr) should trigger evaluation for glucose transporter defect that is often associated with low CSF glucose levels and an abnormal sequencing test of the transporter gene.

Atypical absence seizures have associated myoclonic components and tone changes of the head (head drop) and body and are also usually more difficult to treat. They are precipitated by drowsiness and are usually accompanied by 1-2 Hz spike–and–slow-wave discharges.

Juvenile absence seizures are similar to typical absences but occur at a later age and are accompanied by 4-6 Hz spike–and–slow-wave and polyspike–and–slow-wave discharges. These are usually associated with juvenile myoclonic epilepsy (see "Benign Generalized Epilepsies").

GENERALIZED MOTOR SEIZURE

The most common generalized motor seizures are generalized tonic–clonic seizures that can be either primarily generalized (bilateral) or secondarily generalized (as described in Chapter 593.3) from a unilateral focus. If there is no partial component, then the seizure usually starts with loss of consciousness and, at times, with a sudden cry, upward rolling of the eyes, and a generalized tonic contraction with falling, apnea, and cyanosis. In some, a clonic or myoclonic component precedes the tonic stiffening. The tonic phase is followed by a clonic phase that, as the seizure progresses, shows slowing of the rhythmic contractions until the seizure stops usually 1-2 min later. Incontinence and a postictal period often follow. The latter usually lasts for 30 min to several hours with semicoma or obtundation and postictal sleepiness, weakness, ataxia, hyper- or hyporeflexia, and headaches. There is a risk of aspiration and injury. First aid measures include positioning the patient on his or her side, clearing the mouth if it is open, loosening tight clothes or jewelry, and gently extending the head and, if possible, insertion of an airway by a trained professional. The mouth should not be forced open with a foreign object (this could dislodge teeth, causing aspiration) or with a finger in the mouth (this could result in serious injury to the examiner's finger). Many patients have single **idiopathic generalized tonic–clonic seizures** that may be associated with intercurrent illness or with a cause that cannot be ascertained (see Chapter 593.2). Generalized tonic, atonic, and astatic seizures often occur in severe generalized pediatric epilepsies. Generalized myoclonic seizures can occur in either benign or difficult-to-control generalized epilepsies (see "Benign Generalized Epilepsies" and "Severe Generalized Epilepsies").

BENIGN GENERALIZED EPILEPSIES

Petit mal epilepsy typically starts in mid-childhood, and most patients outgrow it before adulthood. Approximately 25% of patients also develop generalized tonic–clonic seizures, half before and half after the onset of absences. **Benign myoclonic epilepsy of infancy** consists of the onset of myoclonic and other seizures during the 1st yr of life, with generalized 3 Hz spike–and–slow-wave discharges. Often, it is initially difficult to distinguish this type from more-severe syndromes, but follow-up clarifies the diagnosis. **Febrile seizures plus syndrome** manifests febrile seizures and multiple types of generalized seizures in multiple family members, and at times different individuals within the same family manifest different generalized and febrile seizure types (see Chapter 593.1).

Juvenile myoclonic epilepsy (Janz syndrome) is the most common generalized epilepsy in young adults, accounting for 5% of all epilepsies. It has been linked to mutations in many genes including *CACNB4; CLNC2; EJM2, 3, 4, 5, 6, 7, 9; GABRA1; GABRD;* and *Myoclonin1/EFHC1* (see Table 593-2). Typically, it starts in early adolescence with 1 or more of the following manifestations: myoclonic jerks in the morning, often causing the patient to drop things; generalized tonic–clonic or clonic–tonic–clonic seizures upon awakening; and juvenile absences. Sleep deprivation, alcohol (in older patients), and photic stimulation, or, rarely, certain cognitive activities can act as precipitants. The EEG usually shows generalized 4-5 Hz polyspike–and–slow-wave discharges. There are other forms of generalized epilepsies such as **photoparoxysmal epilepsy**, in which generalized tonic–clonic, absence or myoclonic generalized seizures are precipitated by photic stimuli such as strobe lights, flipping through TV channels and viewing video games. Other forms of **reflex** (i.e., **stimulus-provoked**) **epilepsy** can occur; associated seizures are usually generalized, although some may be focal (see Table 593-1 and Chapter 593.9).

SEVERE GENERALIZED EPILEPSIES

Severe generalized epilepsies are associated with intractable seizures and developmental delay. **Early myoclonic infantile encephalopathy** starts during the 1st 2 mo of life with severe myoclonic seizures and burst suppression pattern on EEG. It is usually caused by inborn errors of metabolism such as non-ketotic hyperglycinemia. **Early infantile epileptic encephalopathy (Ohtahara syndrome)** has similar age of onset and EEG but manifests tonic seizures and is usually caused by brain malformations or syntaxin binding protein 1 mutations. Severe **myoclonic epilepsy of infancy (Dravet syndrome)** starts as focal febrile status epilepticus or focal febrile seizures and later manifests myoclonic and other seizure types (see Chapter 593.1).

West syndrome starts between the ages of 2 and 12 mo and consists of a triad of infantile epileptic spasms that usually occur in clusters (particularly in drowsiness or upon arousal), developmental regression, and a typical EEG picture called **hypsarrhythmia** (see Fig. 593-2). Hypsarrhythmia is a high-voltage, slow, chaotic background with multifocal spikes. Patients with cryptogenic (sometimes called idiopathic, now referred to as unknown etiology) West syndrome have normal development before onset, while patients with symptomatic West syndrome have preceding developmental delay owing to perinatal encephalopathies, malformations, underlying metabolic disorders, or other etiologies (see Chapter 593.2). In boys, West syndrome can also be caused by *ARX* gene mutations (often associated with ambiguous genitalia and cortical migration abnormalities). West syndrome, especially in cases of unknown etiology (cryptogenic cases, i.e., cases that are not symptomatic of metabolic or structural brain disorder), is a medical emergency because diagnosis delayed for 3 wk or longer can affect long-term prognosis. The spasms are often overlooked by parents and by physicians, being mistaken for startles caused by colic or for other benign paroxysmal syndromes (see Chapter 594).

Lennox-Gastaut syndrome typically starts between the ages of 2 and 10 yr and consists of a triad of developmental delay, multiple seizure types that as a rule include atypical absences, myoclonic, astatic, and tonic seizures. The tonic seizures occur either in wakefulness (causing falls and injuries) or also, typically, in sleep. The third component is the EEG findings (see Fig. 593-2): 1-2 Hz spike–and–slow waves, polyspike bursts in sleep, and a slow background in wakefulness. Patients commonly have myoclonic, atonic, and other seizure types that are difficult to control, and most are left with long-term cognitive impairment and intractable seizures despite multiple therapies. Some, but not all, patients start with Ohtahara syndrome, develop West syndrome, and then progress to Lennox-Gastaut syndrome. **Myoclonic astatic epilepsy** is a syndrome similar to, but milder than, Lennox-Gastaut syndrome that usually does not have tonic seizures or polyspike bursts in sleep. The prognosis is more favorable than that for Lennox-Gastaut syndrome. Another syndrome characterized by atonic seizures causing head nodding as well as tonic, clonic and stimulus sensitive seizures is the **nodding syndrome**, which is a recently described epidemic type of epilepsy seen in some African countries and often associated with encephalopathy, stunted growth, and variable degrees of cognitive deficits. The underlying etiology is unknown.

Progressive myoclonic epilepsies are a group of epilepsies characterized by progressive dementia and worsening myoclonic and other seizures. **Type I** or **Unverricht-Lundborg disease** (secondary to a cystatin B mutation) is more slowly progressive than the other types and usually starts in adolescence. **Type II** or **Lafora body disease** can have an early childhood onset but usually starts in adolescence, is more quickly progressive, and is usually fatal within the 2nd or 3rd decade. It can be associated with photosensitivity, manifests periodic acid–Schiff-positive Lafora inclusions on muscle or skin biopsy (in eccrine

sweat gland cells), and has been shown to be caused by laforin *(EPM2A)* or malin *(EPM2B)* gene mutations. Other causes of progressive myoclonic epilepsy include myoclonic epilepsy with ragged red fibers, sialidosis type I, neuronal ceroid lipofuscinosis, juvenile neuropathic Gaucher disease, dentatorubral-pallidoluysian atrophy, and juvenile neuroaxonal dystrophy.

Myoclonic encephalopathy in nonprogressive disorders is an epileptic encephalopathy that occurs in some congenital disorders affecting the brain, such as Angelman syndrome, and consists of almost continuous and difficult-to-treat myoclonic and, at times, other seizures.

Landau-Kleffner syndrome is a rare condition of unknown cause characterized by loss of language skills attributed to auditory agnosia in a previously normal child. At least 70% have associated clinical seizures, but some do not. The seizures when they occur are of several types, including focal, generalized tonic–clonic, atypical absence, partial complex, and, occasionally, myoclonic seizures. High-amplitude spike-and-wave discharges predominate and tend to be bitemporal. In the later evolutionary stages of the condition, the EEG findings may be normal. The spike discharges are always more apparent during non–rapid eye movement sleep; thus, a child in whom Landau-Kleffner syndrome is suspected should have an EEG during sleep, particularly if the awake record is normal. CT and MRI studies typically yield normal results. In the related but clinically distinct epilepsy syndrome with **continuous spike waves in slow-wave sleep**, the discharges are more likely to be frontal or generalized and the delays more likely to be global. The approach and therapy to the 2 syndromes are similar. Valproic acid is often the anticonvulsant that is used first to treat the clinical seizures and may help the aphasia. Some children respond to clobazam, to the combination of valproic acid and clobazam, or to levetiracetam. For therapy of the aphasia, nocturnal diazepam therapy (0.2-0.5 mg/kg PO at bedtime for several months) is often used as first- or second-line therapy, as are oral steroids. Oral prednisone is started at 2 mg/kg/24 hr for 1 mo and decreased to 1 mg/kg/24 hr for an additional month. With clinical improvement, the prednisone is reduced further to 0.5 mg/kg/24 hr for up to 6-12 mo. Long-term therapy is often needed irrespective of what the patient responds to. If the seizures and aphasia persist after diazepam and steroids trials, then a course of intravenous immunoglobulins should be considered. It is imperative to initiate speech therapy and maintain it for several years, because improvement in language function occurs over a prolonged period.

Amenably treatable metabolic epilepsies are becoming increasingly recognized. **Pyridoxine-dependent epilepsy** typically presents as neonatal encephalopathy shortly after birth with, at times, report of increased fetal movements (seizure) in utero. There are associated gastrointestinal symptoms with emesis and abdominal distention, neurologic irritability, sleepless and facial grimacing along with recurrent partial motor seizure, generalized tonic seizures, and myoclonus. Seizures are usually refractory and may progress to status epilepticus if no pyridoxine is used. Some cases start in infancy or in childhood. Diagnosis is confirmed by the presence of elevated plasma, urine and CSF α-aminoadipic semialdehyde and elevated plasma and CSF pipecolic acid levels. The presence of either homozygous or compound heterozygous mutations in ALDH7A1 alleles (which encode the protein antiquitin) confirms the diagnosis. The use of pyridoxine 100 mg daily orally (up to 600 mg/day) or intravenously helps stop the seizures. **Pyridoxal phosphate responsive neonatal epileptic encephalopathy** (Pyridox[am]ine 5′-phosphate oxidase [PNPO] deficiency) may present similarly in the absence of gastrointestinal symptoms. Diagnostically, there are reduced pyridoxal phosphate levels in the CSF with increased levels of CSF levodopa and 3-methoxytyrosine along with decreased CSF homovanillic acid and 5-hydroxyindolacetic acid. The EEG may show a burst suppression pattern and treatment is by enteral administration of pyridoxal phosphate (up to 60 mg/kg/day). **Folinic acid–responsive seizures** may also present with neonatal epileptic encephalopathy and intractable seizures. These patients have a similar diagnostic profile as pyridoxine-dependent epilepsy patients and are caused by the same gene mutations but respond to folinic acid supplementation in addition to pyridoxine use. **Cerebral folate deficiency**, which also responds to high doses of folinic acid (2-3 mg/kg/day), may manifest with epilepsy, intellectual disability, developmental regression, dyskinesias, and autism. CSF 5-methyltetrahydrofolate levels are decreased with normal plasma and red blood cell folate levels. There are usually mutations in the folate receptor *(FOLR1)* gene or blocking autoantibodies against membrane-associated folate receptors of the choroid plexus. **Tetrahydrobiopterin deficiencies** with or without hyperphenylalaninemia may present with epilepsies, and symptoms resulting from deficiencies of dopamine (parkinsonism, dystonia), noradrenaline (axial hypotonia), serotonin (depression, insomnia, temperature changes) and folate (myelin formation, basal ganglia calcifications, and seizures). Treatment is by substitution therapy with tetrahydrobiopterin and neurotransmitter precursors started as early as possible. **Creatine deficiency syndromes** present typically with developmental delay, seizures, autistic features, and movement disorders and are diagnosed by abnormal levels of urine creatine and guanidinoacetic acid and/or, depending on the type of underlying genetic etiology, with absent creatine peak on MR spectroscopy of the brain. Use of creatine monohydrate and dietary restrictions are helpful. **Biotinidase deficiency** presenting as developmental delay, seizures, ataxia, alopecia, and skin rash and often associated with intermittent metabolic acidosis and organic profile of lactic and propionic acidemia, responds to the use of biotin. Serine biosynthesis defects with low serine levels in plasma or CSF amino acids often present with congenital microcephaly, intractable seizures, and psychomotor retardation and respond to supplemental serine and glycine use. **Developmental delay, epilepsy, and neonatal diabetes** is caused by activating mutations in the adenosine triphosphate-sensitive potassium channels. Sulfonylurea drugs that block the potassium channel treat the neonatal diabetes and probably also favorably affect the central nervous system (CNS) symptoms and affect seizures. Hyperinsulinism-hyperammonemia syndrome is caused by activating mutations of the glutamate dehydrogenase encoded by the *GLUD1* gene. Patients present with hypoglycemic seizures after a protein-rich meal with hyperammonemia (ammonia levels 80-150 μmol/L). They are managed with a combination of protein restriction, AEDs, and diazoxide (a potassium channel agonist that inhibits insulin release). **GLUT-1 deficiency syndrome** classically presents with infantile-onset epilepsy, developmental delay, acquired microcephaly, and complex movement disorders. It causes impaired glucose transport to the brain typically diagnosed by genetic testing or finding of low CSF lactate and CSF glucose, or low CSF to serum glucose ratios (less than 0.4). The manifestations of the disease are usually responsive to ketogenic diet.

593.5 Mechanisms of Seizures

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One can distinguish in the pathophysiology of epilepsy 4 distinct, often sequential, mechanistic processes. First is the **underlying etiology**, which is any pathology or pathologic process that can disrupt neuronal function and connectivity and that eventually leads to the second process (epileptogenesis) which makes the brain epileptic. The underlying etiologies of epilepsy are diverse and include, among other entities, brain tumors and malformations, strokes, scarring, or mutations of specific genes. These mutations can involve voltage-gated channels (Na^+, K^+, Ca^{2+}, Cl^-, and HCN [hydrogen cyanide]), ligand-gated channels (nicotinic acetylcholine and γ-aminobutyric acid A receptors [$GABA_A$]) or other proteins. In some but not in all such mutations, the molecular and cellular deficits caused by the mutations have been identified. For example, in Dravet syndrome, the loss of function mutation in the *SCN1A* gene causes decreased excitability in inhibitory GABAergic interneurons, leading to increased excitability and epilepsy. In human cortical dysplasia, the expression of the NR2B subunit of the NMDA receptor is increased, leading to excessive depolarizing currents. In many other epileptic conditions, a clear etiology is still lacking and in others the etiology may be known, but it is still not

known how the identified underlying genetic etiology or brain insult results in epileptogenesis.

Second, **epileptogenesis** is the mechanism through which the brain, or part of it, turns epileptic. The presence of this process explains why some patients with the above pathologies develop epilepsy and some do not. **Kindling** is an animal model for human focal epilepsy in which repeated electrical stimulation of selected areas of the brain with a low-intensity current initially causes no apparent changes but with repeated stimulation results in epilepsy. This repetitive stimulation can lead to temporal lobe epilepsy, for example, through activation of metabotropic and ionotropic glutamate receptors (by glutamate), as well as the tropomyosin-related kinase B receptor (by brain-derived neurotrophic factor and neurotrophin-4). This leads to an increase in the intraneuronal calcium, which, in turn, activates calcium calmodulin–dependent protein kinase and calcineurin, a phosphatase, resulting eventually in calcium-dependent epileptogenic gene expression (e.g., c-fos) and promotion of mossy fiber sprouting. **Mossy fibers** are excitatory fibers that connect the granule cells to the CA3 region within the hippocampus, and their pathologic sprouting underlies increased excitability in medial temporal lobe epilepsy associated with mesial temporal sclerosis in humans and in animal models. The cell loss in the CA3 region that is a characteristic of mesial temporal sclerosis (presumably resulting from an original insult such as a prolonged febrile status epilepticus episode or hypoxia) leads to a pathologic attempt at compensation by sprouting of the excitatory mossy fibers. Consequently, mossy fiber sprouting, which has been demonstrated in humans also, leads to increased excitability and to epilepsy. Complex febrile seizures in rats induce hyperactivation of, paradoxically excitatory, $GABA_A$ receptors leading to granule cell ectopia and to subsequent temporal lobe epilepsy. Possibly similar yet to be fully characterized epileptogenesis mechanisms may underlie other focal epilepsies.

Lately, the role of large-scale molecular cell signaling pathways in epileptogenesis, namely the mammalian target of rapamycin (mTOR), the Ras/ERK, and repressor element 1 (RE1)-silencing transcription factor (REST; also known as neuron-restrictive silencer factor) pathways have been implicated in the mechanisms leading to epilepsy. The mTOR pathway in tuberous sclerosis, hemimegalencephaly and cortical dysplasia-related epilepsies, Ras/ERK in a number of syndromes, and REST in epileptogenesis after acute neuronal injury.

The third process is the resultant **epileptic state of increased excitability** that is present in all patients irrespective of the underlying etiology or mechanism of epileptogenesis. In a seizure focus, each neuron has a stereotypic synchronized response called **paroxysmal depolarization shift** that consists of a sudden depolarization phase, resulting from glutamate and calcium channel activation, with a series of action potentials at its peak followed by an after-hyperpolarization phase, resulting from activation of potassium channels and GABA receptors that open chloride channels. When the after-hyperpolarization is disrupted in a sufficient number of neurons, the inhibitory surround is lost and a population of neurons fire at the same rate and time, resulting in a seizure focus. In childhood absence epilepsy, the discharging neurons also develop a paroxysmal depolarization shift similar to the one found in partial epilepsy. However, the mechanism of paroxysmal depolarization shift generation is different because it involves thalamocortical connections bilaterally. T-type calcium channels on thalamic relay neurons are activated during hyperpolarization by GABAergic interneurons in the reticular thalamic nucleus, which results in enhancement of synchronization in the thalamocortical loop and consequently in the typical generalized spike-wave pattern. In tumor-related epilepsy, particularly in that related to oligodendroglioma, the voltage-gated sodium channels are present on the surface of tumor cells at a higher density than on normal cells, and their inactivation is impaired by the alkaline pH present in this condition. In hypothalamic hamartoma causing gelastic seizures, clusters of GABAergic interneurons spontaneously fire, thus synchronizing the output of the hypothalamic hamartoma neurons projecting to the hippocampus.

The fourth process is **seizure-related neuronal injury** as demonstrated by MRI in patients after prolonged febrile and afebrile status epilepticus. Many such patients show acute swelling in the hippocampus and long-term hippocampal atrophy with sclerosis on MRI. Nonetheless in most patients with seizure-related MRI abnormalities, the findings are transient. In experimental models, the mechanisms of such injuries have been shown to involve both apoptosis and necrosis of neurons in the involved regions. There is evidence from surgically resected epileptic tissue that apoptotic pathways are activated in foci of intractable epilepsy.

In infantile spasms, recently developed animal models suggest that increases in stress-related corticotropin-releasing hormone, sodium channel blockade, and NMDA receptor stimulation are contributing mechanisms. Prior positron emission tomography data suggest that an interaction between focal cortical lesions and the brainstem raphe nuclei is important at least in some infantile spasms patients.

Bibliography is available at Expert Consult.

593.6 Treatment of Seizures and Epilepsy

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DECIDING ON LONG-TERM THERAPY

After a *first seizure*, if the risk of recurrence is low, such as when the patient has normal neurodevelopmental status, EEG, and MRI (risk approximately 20%), then treatment is usually not started. If the patient has abnormal EEG, MRI, development, and/or neurologic exam, and/or a positive family history of epilepsy, then the risk is higher and often treatment is started. Other considerations are also important, such as motor vehicle driving status and type of employment in older patients or the parents' ability to deal with recurrences or AED drug therapy in children. The decision is therefore always individualized. All aspects of this decision-making process should be discussed with the family. Figure 593-4 presents an overview of the approach to the treatment of seizures and epilepsy.

COUNSELING

An important part of the management of a patient with epilepsy is educating the family and the child about the disease, its management, and the limitations it might impose and how to deal with them. It is important to establish a successful therapeutic alliance. Restrictions on driving (in adolescents) and on swimming are usually necessary (Table 593-10). In most states, the physician is not required to report the epileptic patient to the motor vehicle registry; this is the responsibility of the patient. The physician then is requested to complete a specific form for patients who are being cleared to drive. Also in most states, a seizure-free period of 6 mo, and in some states longer, is required before driving is allowed. Often swimming in rivers, lakes, or sea, and underwater diving are prohibited, but swimming in swimming pools may be allowable. When swimming, even patients with epilepsy that is under excellent control should be under the continuous supervision of an observer who is aware of their condition and capable of lifeguard-level rescue.

The physician, parents, and child should jointly evaluate the risk of involvement in athletic activities. To participate in athletics, proper medical management, good seizure control, and proper supervision are crucial to avoid significant risks. Any activity where a seizure might cause a dangerous fall should be avoided; these activities include rope climbing, use of the parallel bars, and high diving. Participation in collision or contact sports depends on the patient's condition. Epileptic children should not automatically be banned from participating in hockey, baseball, basketball, football, or wrestling. Rather, individual consideration should be based on the child's specific case (see Table 593-10).

Counseling is helpful to support the family and to educate them about the resources available in the community. Educational and, in some cases, psychologic evaluation may be necessary to evaluate for possible learning disabilities or abnormal behavioral patterns that might coexist with the epilepsy. Epilepsy does carry a risk of increased

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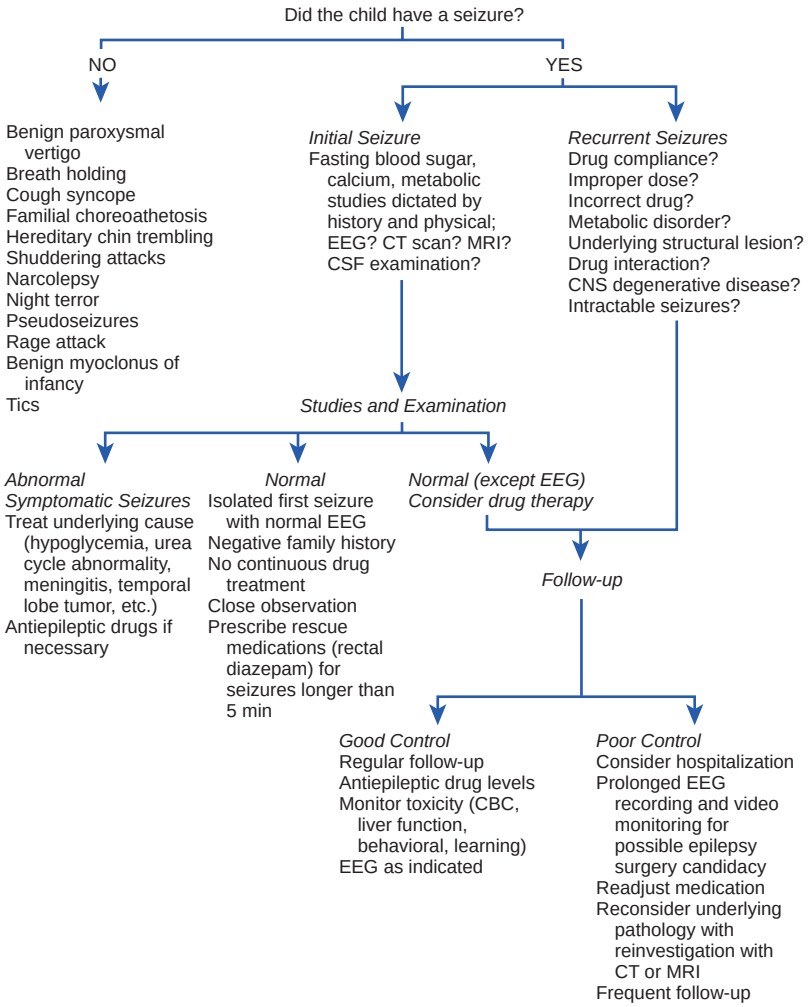


Figure 593-4 Approach to the child with a suspected convulsive disorder.

Table 593-10 Sports and Special Considerations for the Child with Epilepsy*

SPORTS TYPE	SPECIAL CONSIDERATIONS
Body contact sports	If there are more than occasional seizures, physician evaluation of benefits and risks of participation should be made based on the child's condition. No contraindications in general except for boxing.
Noncontact sports	Generally recommended. Anxiety and fatigue can cause a problem in some children. Individualization based on clinical history must be the rule.
Gymnastics	A fall can result if the child experiences a sudden seizure, especially with trampolines, parallel bars, and rope climbing, which should be avoided. Individual consideration remains the basic determinant.
Swimming	The child should always be under supervision, and scuba diving should be discouraged in poorly controlled epileptics.

*Specific advice should be individualized depending on the patient's clinical condition. Many patients actually have fewer seizures when they are active than when they are idle.

Modified from Committee on Children with Handicaps: The epileptic child and competitive school athletics, Pediatrics *42:700–702, 1968; and Knowles BD: Athletes with seizure disorders,* Curr Sports Med Rep *11(1):16–20, 2012, Table 1.*

mortality (2 or more times the standardized mortality rates of the general population) and of sudden unexpected death. This is mostly related to the conditions associated with or underlying the epilepsy (e.g., tumor, metabolic diseases), to poor seizure control (e.g., in patients with severe epileptic encephalopathies, or drug-resistant seizures), and to poor compliance with prescribed therapies. Thus, family members can usually be informed about this increased risk without inappropriately increasing their anxiety. Many family members feel they need to observe the patient continuously in wakefulness and sleep and have the patient sleep in the parents' room to detect seizures. There are currently advertised seizure-detection equipment that use motion sensors placed under the mattress to detect seizures. Some are disappointing and ineffective in detecting seizures, whereas data from other equipment are encouraging in that they were useful in detecting a majority of generalized tonic–clonic seizures during sleep (see bibliography for details). Whether such measures can reduce sudden unexpected death in epilepsy (SUDEP) risk remains to be seen and the parents need to guard against being overprotective to avoid adversely affecting the psychology of the child. Education about what to do in case of seizures, the choices of treatment or no treatment and of medications and their side effects, and potential complications of epilepsy should be provided to the parents and, if the child is old enough, to the child.

MECHANISMS OF ACTION OF ANTIEPILEPTIC DRUGS

AEDs reduce excitability by interfering with the sodium, potassium or calcium ion channels, by reducing excitatory neurotransmitter release

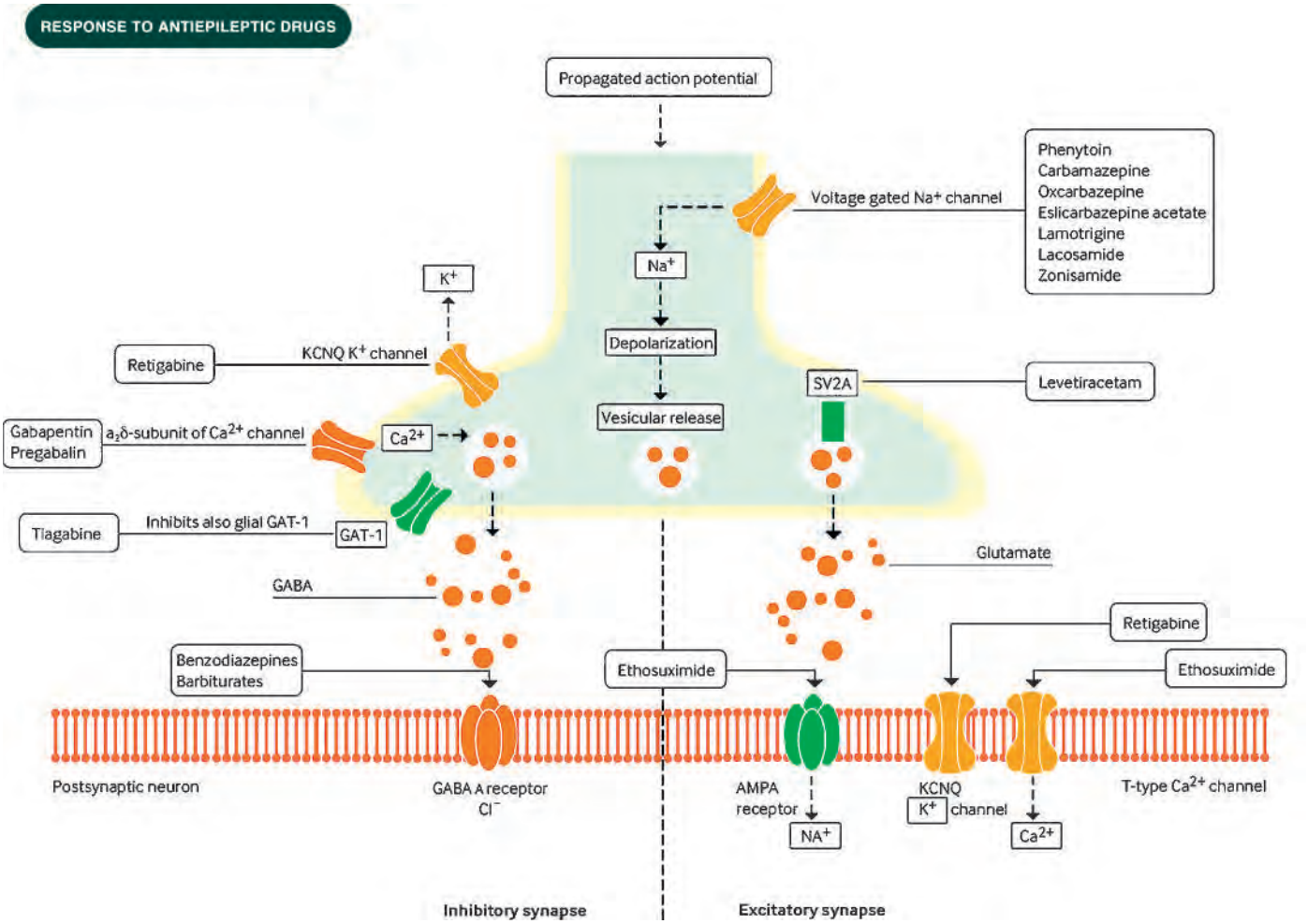


Figure 593-5 Mechanisms of action of antiepileptic drugs, which act by diverse mechanisms, mainly involving modulation of voltage activated ion channels, potentiation of GABA, and inhibition of glutamate. Approved antiepileptic drugs have effects on inhibitory *(left hand side)* and excitatory *(right hand side)* nerve terminals. The antiepileptic efficacy in trials of most of these drugs as initial add-on does not differ greatly, indicating that seemingly similar antiseizure activity can be obtained by mechanisms aimed at diverse targets. However, putative mechanisms of action were determined only after discovering the antiseizure effects; mechanism driven drug discovery has been largely ignored. AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid; GABA, γ-aminobutyric acid; GAT-1, sodium-dependent and chloride-dependent GABA transporter 1; SV2A, synaptic vesicle glycoprotein 2A. *(From Schmidt D, Schachter SC: Drug treatment of epilepsy in adults. BMJ, 348:bmj.g254, 2014.)*

or function, or by enhancing GABAergic inhibition (Fig. 593-5). Most medications have multiple mechanisms of action, and the exact mechanism responsible for their activity in human epilepsy is usually not fully understood. Often, medications acting on sodium channels are effective against partial seizures, and medications acting on T-type calcium channels are effective against absence seizures. Voltage-gated sodium channels are blocked by felbamate, valproate, topiramate, carbamazepine, oxcarbazepine, lamotrigine, phenytoin, rufinamide, lacosamide, and zonisamide. T-type calcium channels, found in the thalamus area, are blocked by valproate, zonisamide, and ethosuximide. Voltage-gated calcium channels are inhibited by gabapentin, pregabalin, lamotrigine, and felbamate. N-type calcium channels are inhibited by levetiracetam. Ezogabine/retigabine opens KCNQ/Kv7 voltage-gated potassium channels.

$GABA_A$ receptors are activated by phenobarbital, benzodiazepines, topiramate, felbamate, and levetiracetam. Tiagabine, by virtue of its binding to GABA transporters 1 (GAT-1) and 3 (GAT-3), is a GABA reuptake inhibitor. GABA levels are increased by vigabatrin via its irreversible inhibition of GABA transaminases. Valproate inhibits GABA transaminases, acts on $GABA_B$ presynaptic receptors (also done by gabapentin), and activates glutamic acid decarboxylase (the enzyme that forms GABA).

Glutaminergic transmission is decreased by felbamate that blocks NMDA and AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid)/kainate receptors. Topiramate also blocks AMPA/kainate receptors. Levetiracetam binds to the presynaptic vesicle protein SV2A found in all neurotransmitter vesicles and possibly results in inhibition of presynaptic neurotransmitter release in a use-dependent manner. Perampanel blocks glutamate AMPA receptors.

CHOICE OF DRUG ACCORDING TO SEIZURE TYPE AND EPILEPSY SYNDROME

Drug therapy should be based on the type of seizure and the epilepsy syndrome as well as on other individual factors. In general, the **drugs of first choice** for focal seizures and epilepsies are oxcarbazepine and carbamazepine; for absence seizures, ethosuximide; for juvenile myoclonic epilepsy, valproate and lamotrigine; for Lennox-Gastaut syndrome, clobazam, valproate, topiramate, lamotrigine, and, most recently, as add on, rufinamide; and for infantile spasms, adrenocorticotropic hormone (ACTH). There is significant controversy about these choices, and therapy should always be individualized (see Choice of Drug: Other Considerations below and Table 593-10).

West syndrome is best treated with ACTH. There are several protocols that range in dose from high to intermediate to low. The recommended regimen of ACTH (80 mg/mL) is a daily dose of 150 units/m^2 (divided into twice-daily intramuscular injections of 75 units/m^2, the lot number is recorded) administered over a 2-wk period with a subsequent gradual taper over a 2-wk period (30 units/m^2 in the morning

for 3 days; 15 units/m^2 in the morning for 3 days; 10 units/m^2 in the morning for 3 days; and 10 units/m^2 every other morning for 6 days, then stop). The increase in price of ACTH gel in the United States has led many physicians to use the lower-dose regimen because it may be just as effective (initial: 20 units/day for 2 wk, if patient responds, taper and discontinue over a 1-wk period; if patient does not respond, increase dose to 30 units/day for 4 wk then taper and discontinue over a 1-wk period). Response is usually observed within the 1st 7 days; however, if no response is observed within 2 wk, the lot is changed. During the tapering period of any regimen, and especially in symptomatic patients, relapse can occur. Remediation entails increasing the dose to the previously effective dose for 2 wk and then beginning the taper again. Synthetic ACTH has also been used: Synacthen Depot intramuscular 0.25 mg/mL or 1 mg/mL is used; 1 mg is considered to have the potency of 100 IU in stimulating the adrenal gland.

Awake and asleep EEGs are often done 1, 2, and 4 wk after the initiation of ACTH to monitor the patient's response, with the aim of clearing the EEG from hypsarrhythmia and of stopping the seizures. Side effects, more common with the higher doses, include hypertension, electrolyte imbalance, infections, hyperglycemia and/or glycosuria, and gastric ulcers. All should be carefully monitored for and prophylactic therapy for ulcers is desirable. ACTH is generally thought to offer an added advantage, particularly in cryptogenic cases, over vigabatrin and possibly over prednisone and other steroids.

Vigabatrin is considered by some as a drug of second choice for infantile spasms and by some even as an alternative to ACTH as a drug of first choice. Its principal side effect is retinal toxicity that is seen in approximately 30% of the patients, with resultant visual field defects that persist despite withdrawal of the drug. The level of evidence for its efficacy is weaker than that for ACTH but stronger than that of other alternative medications, including valproate, benzodiazepines like nitrazepam and clonazepam, topiramate, lamotrigine, zonisamide, pyridoxine, ketogenic diet, and intravenous gamma globulin (IVIG). None of these alternative drugs offers uniformly satisfactory results. However, they are useful for decreasing the frequency and severity of seizures in patients with symptomatic infantile spasms and as adjunctive therapy in patients with cryptogenic infantile spasms who do not respond completely to ACTH or vigabatrin.

Lennox-Gastaut syndrome is another difficult-to-treat epilepsy syndrome. Treatment of seizures in Lennox-Gastaut syndrome varies according to the preponderant seizure type. For drop attacks (tonic, atonic, or myoclonic astatic seizures), valproate, lamotrigine, topiramate, clobazam, felbamate, and rufinamide are considered to be effective. Felbamate is used as a last resort medication because of its potential toxicity. These drugs might control other types of seizures (partial, generalized tonic–clonic, atypical absence, other tonic, myoclonic) as well. For patients who have a preponderance of atypical absence seizures, lamotrigine or ethosuximide are often suitable drugs to try because they are relatively less toxic than many of the alternative drugs. Valproate is helpful against these seizures, too. Clonazepam is often helpful but produces significant sedation, hyperactivity, and drooling, and often tolerance to its antiepileptic effects develops in a few months. Consequently, clonazepam is often used as a rescue medication for clusters of seizures (disintegrating tablet preparation). In resistant cases of Lennox-Gastaut syndrome and related epilepsies, zonisamide, levetiracetam, acetazolamide, methsuximide, corticosteroids, ketogenic diet, or IVIG can be used.

Dravet syndrome is usually treated with valproate and benzodiazepines such as clobazam or clonazepam. The ketogenic diet can also be useful in patients with this syndrome, including cases with refractory status. Stiripentol, which is available in some countries, is useful, particularly if used in combination with valproate and clobazam, but doses need to be adjusted, since stirpentol can increase clobazam levels and valproate can increase stirpentol levels. Other medications include zonisamide and topiramate. Lamotrigine, carbamazepine, and phenytoin are reported to exacerbate seizures. Barbiturate use during status epilepticus in this syndrome is suspected to be associated with adverse outcomes; consequently, alternative acute therapies in such cases need to be considered.

Very rare cases of patients who have neonatal, infantile, or early childhood seizures who have **pyridoxine-dependent epilepsy** (demonstrated to be caused by antiquitin gene mutation) respond to pyridoxine 10-100 mg/day orally (up to 600 mg/day has been used) within 3-7 days of the initiation of oral therapy and almost immediately if given parenterally. Some patients have seizures that are intractable from onset, but others have seizures that show an initial but transient response to traditional AEDs. Some of these patients also require concurrent folinic acid (5-15 mg/day). Other patients require the active form of vitamin B_6, specifically, pyridoxal phosphate (50 mg/day initial dose that can be increased gradually up to 15 mg/kg every 6 hr) owing to their deficiency of **PNPO**. In both the PNPO-deficient/pyridoxal phosphate–dependent and the pyridoxine-dependent forms, hypotonia and hypopnea can occur after initiation of vitamin therapy. Pyridoxine has also been used by some, specifically in Japan, early in the treatment of West syndrome. Patients with **cerebral folate deficiency** can respond to folinic acid supplementation (usually at doses of 2-3 mg/kg/day). Traditionally these entities have been diagnosed by giving the vitamin B_6 or folinic acid in therapeutic trials, but currently laboratory testing is available to confirm the diagnosis (see Chapter 593.4).

Absence seizures are most often initially treated with ethosuximide, which is, as effective as, but less toxic than, valproate and more effective than lamotrigine. Alternative drugs of first choice are lamotrigine and valproate, especially if generalized tonic–clonic seizures coexist with absence seizures, as these 2 medications are effective against the latter seizures whereas ethosuximide is not. Patients resistant to ethosuximide might still respond to valproate or to lamotrigine. In absence seizures, the EEG is usually helpful in monitoring the response to therapy and is often more sensitive than the parents' observations in detecting these seizures. The EEG often normalizes when complete seizure control is achieved. This is usually not true for partial epilepsies. Other medications that could be used for absence seizures include acetazolamide, zonisamide, or clonazepam.

Benign myoclonic epilepsies are often best treated with valproate, particularly when patients have associated generalized tonic–clonic and absence seizures. Benzodiazepines, clonazepam, lamotrigine, and topiramate are alternatives for the treatment of benign myoclonic epilepsy. **Severe myoclonic epilepsies** are treated with medications effective for Lennox-Gastaut syndrome such topiramate, clobazam, and valproate, as well as zonisamide. Levetiracetam may also have efficacy in myoclonic epilepsies.

Partial and secondary generalized tonic and clonic seizures can be treated with oxcarbazepine, levetiracetam, carbamazepine, phenobarbital, topiramate, valproic acid, lamotrigine, clobazam, or clonazepam (see Table 593-8). Oxcarbazepine, levetiracetam, carbamazepine (United States), or valproate (Europe) are often being used first. One study favored lamotrigine as initial monotherapy for partial seizures and valproate for generalized seizures. Almost any of these medications has been used as first or second choice. depending on the individualization of the therapy.

CHOICE OF DRUG: OTHER CONSIDERATIONS

Because there are many options for each patient, the choice of which drug to use is always an individualized decision based on comparative effectiveness data from randomized controlled trials and on several other considerations delineated below.

Comparative effectiveness (Table 593-11) and **potential for paradoxical seizure aggravation** by some AEDs (e.g., precipitation of myoclonic seizures by lamotrigine in Dravet syndrome and exacerbation of absence seizures by carbamazepine and tiagabine) must be considered.

- **Comparative tolerability** (see Table 593-14): Adverse effects can vary according to the profile of the patient. The most prominent example is the increased risk of liver toxicity for valproate therapy in children who are younger than 2 yr of age, on polytherapy, and/or have metabolic disorders. Thus, if metabolic disorders are suspected, other drugs should be considered first and valproate should not be started until the metabolic disorders are ruled out by normal amino acids, organic acids, acylcarnitine profile, lactate,

Table 593-11 Comparison of Recommendations for the Treatment of Pediatric Epilepsy

SEIZURE TYPE OR EPILEPSY SYNDROME	FDA APPROVED	SIGN (2005)	NICE (2012)	AAN (2004)	ILAE (2013)*	PEDIATRIC EXPERT CONSENSUS SURVEY (NORTH AMERICA–2005)	PEDIATRIC EXPERT CONSENSUS SURVEY (EUROPE–2007)
Partial-onset	CBZ, ezogabine, lacosamide, LEV, LTG, OXC, PB, perampanel, PHT, TPM, VGB	CBZ, CLB, LTG, OXC, PHT, TPM, VGB, VPA	CBZ, LEV, LTG, OXC, VPA	CBZ, GBP, LTG, OXC, PB, PHT, TPM	A: OXC B: None C: CBZ, PB, PHT, TPM, VGB, VPA D: CLB, CZP, LTG, ZNS	CBZ, OXC	CBZ, OXC
BCECT	None	Not specifically mentioned	CBZ, LEV, LTG, OXC, VPA	Not surveyed	A, B: None C: CBZ, VPA D: GBP, LEV, OXC, STM	CBZ, OXC	VPA
Childhood absence epilepsy	ESM, VPA	ESM, LTG, VPA	ESM, LTG, VPA	LTG	A: ESM, VPA B: None C: LTG D: None	ESM	VPA
Juvenile myoclonic epilepsy	LEV, LTG, TPM	VPA	LEV, LTG, TPM, VPA	Not surveyed	A, B, C: None D: TPM, VPA	LTG, VPA	VPA
Lennox-Gastaut syndrome	CLB, FLB, LTG, rufinamide (atonic), TPM	CLB, LTG, VPA	VPA	Not surveyed	Not reviewed	LTG, VPA	VPA
Infantile spasms	VGB	Nitrazepam, TPM, VGB, VPA	Corticosteroids, VGB	ACTH, VGB (updated IS guidelines 2012)	Not reviewed	ACTH, VGB	VGB
Primary generalized tonic-clonic seizures	LEV, LTG, TPM	TPM, VPA	LTG, TPM, VPA	No evidence given	A: None B: None C: CBZ, PB, PHT, TPM, VPA D: OXC		

*ILAE recommendations are listed according to levels of evidence supporting the efficacy of the options. Level A: ≥1 class I randomized controlled trial (RCT) or ≥2 class II RCTs; Level B: 1 class II RCT or ≥2 class III RCTs; Level C: ≥2 class III RCTs; Level D: 1 class III double-blind or open-label study *or* 1 class IV clinical study *or* data from expert committee reports, opinions from experienced clinicians.

AAN, American Academy of Neurology; ACTH, adrenocorticotropic hormone; BCECT, benign childhood epilepsy with centrotemporal spikes; CBZ, carbamazepine; CLB, clobazam; CZP, clonazepam; ESM, ethosuximide; FDA, Food and Drug Administration; FLB, felbamate; GBP, gabapentin; ILAE, International League against Epilepsy; LEV, levetiracetam; LTG, lamotrigine; NICE, National Institute for Clinical Excellence; OXC, oxcarbazepine; PB, phenobarbital; PHT, phenytoin; SIGN, Scottish Intercollegiate Guidelines Network; STM, sulthiame; TPM, topiramate; VGB, vigabatrin; VPA, valproic acid; ZNS, zonisamide.

Modified and updated from Wheless JW, Clarke DF, Arzimanoglou A, et al: Treatment of pediatric epilepsy: European expert opinion, Epileptic Disord *9:353–412, 2007; and Perucca E, Tomson T; ILAE Subcommission on AED Guidelines. Updated ILAE evidence review of antiepileptic drug efficacy and effectiveness as initial monotherapy for epileptic seizures and syndromes.* Epilepsia *54(3):551–563, 2013.*

pyruvate, liver function tests, and perhaps other tests. The choice of an AED can also be influenced by the likelihood of occurrence of nuisance side effects such as weight gain (valproate, carbamazepine), gingival hyperplasia (phenytoin), alopecia (valproate), hyperactivity (benzodiazepines, barbiturates, levetiracetam, valproate, gabapentin). Children with behavior problems and/or with attention-deficit disorder can become particularly hyperactive with GABAergic drugs mentioned above. This often affects the choice of medications.

- **Cost and availability:** The cost of the newer AEDs often precludes their use, particularly in developing countries where cost is a major issue. Also, many drugs are not available in many countries either because they are too expensive, because, paradoxically, they are too inexpensive (lower profit margin), or because of regulatory restrictions. AEDs have a narrow therapeutic range and thus switching from brand name to generic formulations, or from one generic to another, can result in changes in levels that could result in breakthrough seizures or side effects. Thus, generic substitution is generally best avoided, particularly in fragile patients, if a brand name drug has already proved efficacious.
- **Ease of initiation** of the AED: Medications that are started very gradually such as lamotrigine and topiramate should not be chosen in situations when there is a need to achieve a therapeutic level quickly. In such situations, medications that have intravenous preparations or that can be started and titrated more quickly, such as valproate, phenytoin, or levetiracetam, should be considered instead.
- **Drug interactions** and presence of background medications: An example is the potential interference of enzyme-inducing drugs with many chemotherapeutic agents. In those cases, medications like gabapentin or levetiracetam are used. Also, valproate inhibits the metabolism and increases the levels of lamotrigine, phenobarbital, and felbamate. It also displaces protein-bound phenytoin from protein-binding sites, increasing the free fraction, and, thus, the free and not the total level needs to be checked when both medications are being used together. Enzyme inducers like phenobarbital, carbamazepine, phenytoin, and primidone reduce levels of lamotrigine, valproate, and, to a lesser extent, topiramate and zonisamide. Medications exclusively excreted by the kidney like levetiracetam and gabapentin are not subject to such interactions.

Table 593-12 Teratogenesis and Perinatal Outcomes of Antiepileptic Drugs

FINDING	RECOMMENDATION	LEVEL OF RECOMMENDATION
VPA as part of polytherapy and possibly monotherapy probably contributes to the development of major congenital malformations and adverse cognitive outcome	If possible, avoidance of valproate polytherapy during the 1st trimester of pregnancy should be considered so as to decrease the risk of major congenital malformations and adverse cognitive outcome	B
AED polytherapy, as compared to monotherapy, regimens probably contribute to the development of major congenital malformations and to adverse cognitive outcomes	If possible, avoidance of AED polytherapy during the 1st trimester of pregnancy should be considered to decrease the risk of major congenital malformations and adverse cognitive outcome	B
Monotherapy exposure to phenytoin or phenobarbital possibly increases the likelihood of adverse cognitive outcomes	If possible, avoidance of phenytoin and phenobarbital during pregnancy may be considered to prevent adverse cognitive outcomes	C
Neonates of women with epilepsy taking AEDs probably have an increased risk of being small for gestational age and possibly have an increased risk of a 1 min Apgar score of <7	Pregnancy risk stratification should reflect that the offspring of women with epilepsy taking AEDs are probably at increased risk for being small for gestational age (level B) and possibly at increased risk of 1 min Apgar scores of <7	C

Levels of recommendation: A: strongest recommendation; based on class 1 evidence; B and C: lower levels of recommendations.

Types of malformations: Prior studies had reported the occurrence of spina bifida with valproate and carbamazepine therapy, and of cardiac malformation and cleft palate after carbamazepine, phenytoin, and phenobarbital exposure. There is variability from study to study. However, in general the relative incidence of major malformations of approximately 10% for valproate monotherapy, higher with valproate polytherapy, and in the range of 5% for monotherapy with the other above 3 AEDs and higher with polytherapy.

FDA categories: Valproate, phenobarbital, carbamazepine, and phenytoin are classified by the FDA as category D. Ethosuximide, felbamate, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, tiagabine, topiramate, and zonisamide are category C. Category C: Animal studies have shown an adverse effect and there are no adequate and well-controlled studies in pregnant women or no animal studies have been conducted and there are no adequate and well-controlled studies in pregnant women. Category D: Studies, adequate, well-controlled, or observational, in pregnant women have demonstrated a risk to the fetus. However, the benefits of therapy might outweigh the potential risk.

AED, antiepileptic drug; VPA, valproate.

Data from Harden CI, Meador KJ, Pennell PB, et al: Practice parameter update: management issues for women with epilepsy—focus on pregnancy (an evidence-based review): teratogenesis and perinatal outcomes. Report of the Quality Standards Subcommittee and Therapeutics and Technology Subcommittee of the American Academy of Neurology and American Epilepsy Society, Neurology *73(2):133–141, 2009.*

- **The presence of comorbid conditions:** For example, the presence of migraine in a patient with epilepsy can lead to the choice of a medication that is effective against both conditions such as valproate or topiramate. In an obese patient, a medication such as valproate might be avoided, and a medication that decreases appetite such as topiramate might be used instead. In adolescent girls of child-bearing potential, enzyme-inducing AEDs are often avoided because they can interfere with birth control pills; other AEDs, particularly valproate, can increase risks for fetal malformations (Table 593-12). Valproic acid may unmask or exacerbate certain underlying metabolic disorders; these include nonketotic hyperglycinemia, DNA polymerase γ mutations *(POLG)* with mitochondrial DNA depletion (also known as Alpers-Huttenlocher syndrome), other mitochondrial disorders (Leigh syndrome; mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes [MELAS]; myoclonic epilepsy with ragged red fibers; myoclonic epilepsy-myopathy-sensory ataxia syndrome), and hyperammonemic encephalopathies. Manifestations may include hepatotoxicity or encephalopathy.
- **Coexisting seizures:** In a patient with both absence and generalized tonic–clonic seizures, a drug that has a broad spectrum of antiseizure effects such as lamotrigine or valproate could be used rather than medications that have a narrow spectrum of efficacy, such as phenytoin and ethosuximide.
- **History of prior response** to specific AEDs: For example, if a patient or a family member with the same problem had previously responded to carbamazepine, carbamazepine could be a desirable choice.
- **Mechanism of drug actions:** At present, the current understanding of the pathophysiology of epilepsy does not allow specific choice of AEDs based on the assumed pathophysiology of the epilepsy. However, in general, it is believed that it is better to avoid combining medications that have similar mechanisms of action, such as phenytoin and carbamazepine (both work on sodium channels). A number of medications, such as lamotrigine and valproate or topiramate and lamotrigine, are reported to have synergistic effects, possibly because they have different mechanisms of action.
- **Ease of use:** Medications that are given once or twice a day are easier to use than medications that are given 3 or 4 times a day. Availability of a pediatric liquid preparation, particularly if palatable, also plays a role.
- **Ability to monitor the medication** and adjust the dose: Some medications are difficult to adjust and to follow, requiring frequent blood levels. The prototype of such medications is phenytoin, but many of the older medications also require blood level monitoring for optimal titration. However, monitoring in itself can represent a practical or patient satisfaction disadvantage for the older drugs as compared to the newer AEDs, which generally do not require blood-level monitoring except to check for compliance.
- **Patient's and family's preferences:** All things being equal, the choice between 2 or more acceptable alternative AEDs might also depend on the patient's or family's preferences. For example, some patients might want to avoid gingival hyperplasia and hirsutism as side effects but might tolerate weight loss, or vice versa.
- **Genetics** and genetic testing: A genetic predisposition to developing AED-induced side effects is another factor that may be a consideration. For example, there is a strong association between the human leukocyte antigen HLA-B*1502 allele and severe cutaneous reactions induced by carbamazepine, phenytoin, or lamotrigine in Chinese Han patients and, to a lesser extent, South East Asian populations; hence these AEDs should be avoided in genetically susceptible persons after testing for the allele. The testing for other alleles that predispose to such allergies in other populations is not yet clinically useful. Mutations of the *SCN1A* sodium channel gene indicating Dravet syndrome could also lead to avoiding lamotrigine, carbamazepine, and phenytoin, and to the use of the more appropriate valproate, clobazam, or stiripentol.

- **Teratogenic profiles:** Some AEDs, including valproate and to a lesser extent carbamazepine, phenobarbital, and phenytoin, are associated with teratogenic effects (see Table 593-12).

Some of these considerations can be addressed by resorting to expert opinion surveys (see Table 593-11) or to guidelines developed by concerned societies such as the ILAE, National Institute for Clinical Excellence (NICE) in England, Scottish Intercollegiate Guidelines Network (SIGN), or the American Academy of Neurology (AAN). Some guidelines are totally evidence based (AAN, ILAE), and others (NICE, SIGN) incorporate other considerations as well. However, no guideline is able to incorporate all the considerations relevant to each patient.

INITIATING AND MONITORING THERAPY

In nonemergency situations, or when loading is not necessary, the **maintenance dose** of the chosen AED is started (Table 593-13). With some medications (e.g., carbamazepine and topiramate), even smaller doses are initially started then **gradually increased** up to the maintenance dose to build tolerance to adverse effects such as sedation. For example, the starting dose of carbamazepine is usually 5-10 mg/kg/day. Increments of 5 mg/kg/day can be added every 3 days until a therapeutic level is achieved and a therapeutic response is established or until unacceptable adverse effects occur. With other medications such as zonisamide, phenobarbital, phenytoin, or valproate, starting at the maintenance dose is usually tolerated. With some, such as levetiracetam and gabapentin, either approach can be used. Patients should be counseled about potential adverse effects, and these should be monitored during follow-up visits (Table 593-14).

Titration

Levels of many AEDs should usually be determined after initiation to ensure compliance and therapeutic concentrations. Monitoring is most helpful for the older AEDs such as phenytoin, carbamazepine, valproate, phenobarbital, and ethosuximide. After starting the maintenance dosage or after any change in the dosage, a steady state is not reached until 5 half-lives have elapsed, which, for most AEDs, is 2-7 days (half-life: 6-24 hr). For phenobarbital, it is 2-4 wk (mean half-life: 69 hr). For zonisamide it is 14 days during monotherapy and less than that during polytherapy with enzyme inducers (half-life: 63 hr in monotherapy and 27-38 hr during combination therapy with enzyme inducers). If a therapeutic level has to be achieved faster, a **loading dose** may be used for some drugs, usually with a single dose that is twice the average maintenance dose per half-life. For valproate it is 25 mg/kg, for phenytoin it is 20 mg/kg, and for phenobarbital it is 10-20 mg/kg. A lower loading dosage of phenobarbital is sometimes given in older children (5 mg/kg, which may be repeated once or more in 24 hr), to avoid excessive sedation.

Only 1 drug should be used initially and the dose increased until complete control is achieved or until side effects prohibit further increases. Then, and only then, may another drug be added and the initial drug subsequently tapered. Control with 1 drug (**monotherapy**) should be the goal, although some patients eventually need to take

Table 593-13 Dosages of Selected Antiepileptic Drugs

MEDICATION	FDA APPROVAL (AGE APPROVED)	MAINTENANCE ORAL DOSAGE (mg/kg/day) UNLESS OTHERWISE SPECIFIED	USUAL DOSING	THERAPEUTIC LEVELS	PREPARATIONS
Acetazolamide	Absence seizures (adults)	1-12 mo; 10 <1 yr: 20-30	bid or tid	10-15 mg/L	125, 250, 500 mg tabs
Bromide		50-100	bid or qd	10-15 mEq/L	Supplied as triple bromide soln (240 mg/mL of bromide salt)
Carbamazepine*	Partial and GTC (all ages)	10-20	tid or qid SR usually bid	3-12 mg/L	150, 300 mg ER caps 100, 200, 400 mg ER tabs 100 mg chewable tabs 200 mg tabs 100 mg/5 mL susp
Clobazam†	LGS (all ages above 2 yr)	10-20 mg/day	bid or tid	60-200 µg/L	5 mg, 10 mg, 20 mg tabs 2.5 mg/mL soln
Clonazepam†	Absence sz, LGS, myoclonic sz (all ages)	0.05-0.2	bid or tid	25-85 µg/L	0.5, 1, 2 mg tabs 0.125, 0.25, 0.5 mg orally disintegrating tabs
Diazepam	Partial sz (all ages >6 mo)	0.25-1.5 0.01-0.25 IV 0.2-0.5 mg/kg rectal (according to age; see Table 593-15)	bid or tid	100-700 µg/L	2, 5, 10 mg tabs 5 mg/mL, 5 mg/5 mL soln Rectal gel that can be dialed to dispense 2.5, 5, 7.5, 10, 12.5, 15, 17.5, 20 mg
Ethosuximide	Absence sz (>3 yr)	20-30	bid or tid	40-100 mg/L	250 mg caps 250 mg/5 mL syrup, soln
Ezogabine	Partial sz (adults)	No pediatric dose approved	tid	—	50, 200, 300, 400 mg tabs
Felbamate	LGS (>2 yr) Partial sz (>14 yr)	15-45	bid or tid	50-110 mg/L	400, 600 mg tabs 600 mg/5 mL susp
Gabapentin‡	Partial sz (>3 yr)	30-60	tid	2-20 mg/L	100, 300, 400 mg caps, 600, 800 mg tabs
Lacosamide	Partial sz (>17 yr)	No FDA approved dose. 4-12	bid	<= 15 µg/L	50, 100, 150, 200 mg tabs 10 mg/mL oral soln

Table 593-13 Dosages of Selected Antiepileptic Drugs—cont'd

MEDICATION	FDA APPROVAL (AGE APPROVED)	MAINTENANCE ORAL DOSAGE (mg/kg/day) UNLESS OTHERWISE SPECIFIED	USUAL DOSING	THERAPEUTIC LEVELS	PREPARATIONS
Lamotrigine	LGS, partial and tonic–clonic sz (age >2 yr)	5-15[§] 1-5[¶]	tid bid	1-15 mg/L	25, 100, 150, 200 mg tabs 5, 25 mg chewable dispersible tabs 25, 50, 100, 200 mg ODTs 25, 50, 100, 200, 250, 300 mg ER tabs
Levetiracetam[†]	Myoclonic, partial and tonic–clonic sz (age >4-6 yr)	20-40	bid or tid	6-20 mg/L	250, 500, 750 mg tabs 100 mg/mL soln 500, 750 mg SR (ER) tabs
Lorazepam	Status epilepticus (all ages)	0.05-0.1	bid or tid	20-30 µg/L	0.5, 1, 2 mg tabs 2 mg/mL soln
Methsuximide (or methsuximide)	Absence sz (children and older)	10-30	bid or tid	10-50 mg/L	150, 300 mg caps
Nitrazepam	–	0.25-1	bid or tid	<200 µg/L	5 mg tabs
Oxcarbazepine[*]	Partial sz (>2 yr)	20-40	bid	13-28 mg/L	150, 300, 600 mg tabs 300 mg/5 mL susp
Perampanel	Partial sz (>12 yr)	2-12 mg per day (older than 12 yr)	qhs	-	2 mg, 4 mg, 6 mg, 8 mg, 10 mg, 12 mg tabs
Phenobarbital	Myoclonic, partial, and tonic–clonic sz and status (all ages)	<5 yr, 3-5 >5 yr, 2-3	bid or qd	10-40 mg/L	15, 30, 60, 90, 100 mg tabs 4 mg/mL soln
Phenytoin	Partial, tonic–clonic sz and status (all ages)	<3 yr, 8-10 >3 yr, 4-7	tabs, susp: tid caps: qd	5-20 mg/L	50 mg tabs 30,100 mg caps 125 mg/5 mL susp
Pregabalin	Partial sz (adults)	2-14	bid	Up to 10 µg/mL	25, 50, 75, 100, 150, 200, 225, 300 mg caps 20 mg/mL soln
Primidone	Partial and tonic–clonic sz (all ages)	10-20	bid or tid	4-13 mg/L	50, 250 mg tabs, susp
Rufinamide[†]	LGS (age >4 yr)	30-45	bid	<60 µg/mL	200, 400 mg tabs
Sulthiame[‖]		5-15	bid or tid	1.5-20 µg/mL	50, 200 mg caps Not available in all countries
Tiagabine	Partial sz (age >2 yr)	0.5-2	bid, tid, qid	80-450 µg/L	2, 4, 12, 16 mg tabs
Topiramate[†]	LGS, partial and tonic–clonic sz (all ages)	3-9, slow titration	bid or tid	2-25 mg/L	25, 100, 200 mg tabs 15, 25 mg sprinkle caps
Valproate	Absence, myoclonic, partial and tonic–clonic sz (age >2 yr)	15-40. Higher doses are used if the patient is on enzyme inducers (up to 60 kg/day)	Sprinkle caps: bid Soln: tid	50-100 mg/L	250 mg caps 125 mg sprinkle caps 125, 250, 500 mg tabs 250 mg/5 mL soln
Vigabatrin	Infantile spasms and partial sz (age >1 mo)	50-150	bid	20-160 µg/mL	500 mg tabs 500 mg powder for soln
Zonisamide	Partial sz (age >16 yr)	4-8	bid or qd	10-40 mg/L	100 mg caps

Unless specified otherwise, as above, one would usually target the lower range of therapeutic dose then adjust as needed depending on response and/or levels. Dosing schedule (e.g., bid or tid) can depend on if a sustained release preparation is available and if the patient is on enzyme inducers (e.g., carbamazepine) or inhibitors (e.g., valproic acid) that could affect that drug (as indicated in the dosing in the table and in the text).

*Usually start by one-fourth maintenance dose and increase by one-fourth every 2-3 days to full dose.

[†]Usually start with one-fourth maintenance dose and increase by one-fourth every 7 days to full dose.

[‡]Usually start with one-fourth maintenance dose and increase by one-fourth every day to full dose.

[§]Child on enzyme inducers.

[‖]Available in some European countries.

[¶]Child on valproate.

cap, capsule; ER, extended release; GTC, generalized tonic–clonic; LGS, Lennox-Gastaut syndrome; ODT, orally disintegrating tablet; soln, solution; SR, sustained release; susp, suspension; sz, seizure(s); tab, tablet.

Table 593-14 Some Common Adverse Effects of Antiepileptic Drugs*

ANTIEPILEPTIC DRUG	SIDE EFFECT(S)
Acetazolamide	Nuisance: dizziness, polyuria, electrolyte imbalance Serious: Stevens-Johnson syndrome
Benzodiazepines	Nuisance: dose-related neurotoxicity (drowsiness, sedation, ataxia), hyperactivity, drooling, increased secretions Serious: apnea
Bromide	Nuisance: irritability, spurious hyperchloremia (falsely high chloride owing to bromide) Serious: psychosis, rash, toxicity developing slowly owing to the very long half-life
Carbamazepine	Nuisance: tics, transient leukopenia; hyponatremia, weight gain, nausea; dizziness Serious: Stevens-Johnson syndrome, agranulocytosis, aplastic anemia, liver toxicity
Ezogabine	Nuisance: dizziness, somnolence tremor, abnormal coordination, disturbance in attention, memory impairment, blurred vision, gait disturbance, and dysarthria Serious: blue discoloration of the skin and retinal pigmentation that requires close ophthalmologic monitoring in follow up, urinary retention
Felbamate	Nuisance: anorexia, vomiting, insomnia, hyperactivity, dizziness Serious: major risks for liver and hematologic toxicity requiring close monitoring (1 in 500 in children >2 yr with complex neurological disorders)
Gabapentin	In children: acute onset of aggression, hyperactivity In adults: euphoria and behavioral disinhibition, weight gain
Lacosamide	Nuisance: diplopia, headache, dizziness, nausea Serious: possibly cardiac arrhythmias (if predisposed)
Lamotrigine	Nuisance: CNS side effects: headache, ataxia, dizziness, tremor, but usually less than other AEDs Serious: Stevens-Johnson syndrome, rarely liver toxicity
Levetiracetam	CNS adverse events: somnolence, asthenia, dizziness, but usually less than other AEDs In children: behavioral symptoms are common In adults: depressive mood
Oxcarbazepine	Somnolence, headache, dizziness, nausea, apathy, rash, hypertrichosis, gingival hypertrophy, hyponatremia
Perampanel	Dizziness, somnolence, fatigue, irritability, falls, nausea, weight gain, vertigo, ataxia, gait disturbance, and balance disorder
Phenobarbital and other barbiturates	Nuisance: neurotoxicity, insomnia, hyperactivity, signs of distractibility, fluctuation of mood, aggressive outbursts Serious: liver toxicity, Stevens-Johnson syndrome
Phenytoin and other hydantoins	Nuisance: gingival hyperplasia, coarsening of the facies, hirsutism, cerebellovestibular symptoms (nystagmus and ataxia) Serious: Stevens-Johnson syndrome, liver toxicity
Pregabalin	Nuisance: dizziness, peripheral edema, blurred vision, weight gain, thrombocytopenia Serious: hypersensitivity reactions, rhabdomyolysis
Primidone	Nuisance: CNS toxicity (dizziness, slurred speech, giddiness, drowsiness, depression) Serious: liver toxicity, Stevens-Johnson syndrome
Rufinamide	Nuisance: somnolence, vomiting Serious: contraindicated in familial short QT interval
Succinimides	Nuisance: nausea, abdominal discomfort, anorexia, hiccups Serious: Stevens-Johnson syndrome, drug-induced lupus
Tiagabine	Nuisance: dizziness, somnolence, asthenia, headache and tremor, precipitation of absence or myoclonic seizures Serious: precipitation of nonconvulsive status epilepticus
Topiramate	Nuisance: cognitive dysfunction, weight loss, renal calculi, hypohidrosis, fever Serious: precipitation of glaucoma
Valproic acid	Nuisance: weight gain; hyperammonemia tremor, alopecia, menstrual irregularities Serious: hepatic and pancreatic toxicity
Vigabatrin	Nuisance: hyperactivity Serious: irreversible visual field deficits, retinopathy that requires frequent ophthalmologic evaluations and follow up
Zonisamide	Fatigue, dizziness, anorexia, psychomotor slowing, ataxia, rarely hallucinations, hypohidrosis and fever

*Essentially all AEDs can cause CNS toxicity and potentially rashes and serious allergic reactions.
AED, antiepileptic drug; CNS, central nervous system.

multiple drugs. When appropriate, levels should also be checked upon addition (or discontinuation) of a second drug because of potential drug interactions. During follow-up, repeating the EEG every few months may be helpful to evaluate changes in the predisposition to seizures. This is especially true in situations where tapering off of medication is contemplated in any seizure type and during follow-up to assess response for absence seizures, as the EEG mirrors response in such patients.

Monitoring

For the older AEDs, before starting treatment, **baseline laboratory studies,** including complete blood count, platelets, liver enzymes, and possibly kidney function tests and urinalysis, are often obtained and repeated periodically. Laboratory monitoring is more relevant early on, because idiosyncratic adverse effects such as allergic hepatitis and agranulocytosis are more likely to occur in the 1st 3-6 mo of therapy. These laboratory studies are usually initially checked once or twice during the 1st mo, then every 3-4 mo thereafter. Serious concerns have been raised about the real usefulness of routine monitoring (in the absence of clinical signs) because the yield of significant adverse effects is low and the costs may be high. There are currently many advocates of less-frequent routine monitoring.

In approximately 10% of patients, a reversible dose-related leukopenia may occur in patients on carbamazepine or on phenytoin. This adverse effect responds to decreasing the dose or to stopping the medication and should be distinguished from the much-less-common idiosyncratic aplastic anemia or agranulocytosis. One exception requiring frequent (even weekly) monitoring of liver function and of blood counts throughout the therapy is felbamate, owing to the high incidence of liver and hematologic toxicity (1 in 500 children under 2 yr of age with complex neurological disorders who are on the drug). The gum hyperplasia that is seen with phenytoin necessitates good oral hygiene (brushing teeth at least twice per day and rinsing the mouth after taking the phenytoin); in a few cases, it may be severe enough to warrant surgical reduction and/or change of medication. Allergic rash can occur with any medication, but is probably most common with lamotrigine, carbamazepine, and phenytoin.

SIDE EFFECTS

During follow-up the patient should be monitored for **side effects**. Occasionally, a Stevens-Johnson–like syndrome develops, probably most commonly with lamotrigine; it also has been found to be particularly common in Chinese patients who have the allele HLA-B*1502 and are taking carbamazepine and lamotrigine.

Other potential side effects are rickets from phenytoin, phenobarbital, primidone, and carbamazepine (enzyme inducers that reduce 25-hyrdroxy-vitamin D level by inducing its metabolism) and hyperammonemia from valproate. Skeletal monitoring is warranted in patients on chronic AED therapy because it is often associated with vitamin D abnormalities (low bone density, rickets, and hypocalcemia) in children and adults, particularly those on enzyme-inducing medications. Thus, counseling the patient about sun exposure and vitamin D intake, monitoring its levels, and, in most cases, vitamin D supplementation are recommended. There is currently no consensus on the dose to be used for supplementation or prophylaxis, but starting doses of 400-2,000 IU/day with follow-up of the levels are reasonable.

Irreversible hepatic injury and death are particularly feared in young children (<2 yr old) who are on valproate in combination with other AEDs, particularly those who might have inborn errors of metabolism such as acidopathies and mitochondrial disease. Virtually all AEDs can produce sleepiness, ataxia, nystagmus, and slurred speech with toxic levels.

The FDA has determined that the use of AEDs may be associated with an increased risk of suicidal ideation and action and has recommended counseling about this side effect before starting these medications. This is obviously more applicable to adolescents and adults.

When adding a new AED, the doses used are often affected by the background medications. For example, if the patient is on enzyme inducers, the doses needed of valproate and lamotrigine are often double the usual maintenance doses. On the other hand, if the patient is on valproate, the doses of phenobarbital or lamotrigine are approximately half of what is usually needed. Thus, changes in the dosing of the background medication are often done as the interacting medication is being started. Genetic variability in enzymes that metabolize AEDs, and in the presence of inducible multidrug resistance genes, **pharmacogenomics**, might account for some of the variation among individuals in responding to certain AEDs. Although numerous variants of the cytochrome P450 enzymes have been characterized and although several multidrug resistance genes have been identified, the use of this new knowledge is currently largely restricted to research investigations, and it has yet to be applied in routine clinical practice.

Additional Treatments

The principles of monotherapy indicate that a second medication needs to be considered after the first either is pushed as high as tolerated and still does not control the seizures or results in intolerable adverse effects. In those cases, a second drug is started and the first is tapered and then discontinued. The second drug is then again pushed to the dose that controls the seizure or that results in intolerable side effects. If the second drug fails, monotherapy with a third drug or **dual (combination) therapy** is considered.

Patients with **drug-resistant** (previously referred to as intractable or refractory) **epilepsy** (those who have failed at least 2 fair trials of appropriate medications) warrant a careful diagnostic reevaluation to look for degenerative, metabolic, or inflammatory underlying disorders (e.g., mitochondrial disease, Rasmussen encephalitis; see Chapter 593.2) and to investigate them for candidacy for epilepsy surgery. Treatable metabolic disorders that can manifest as intractable epilepsy include pyridoxine-dependent and pyridoxal-responsive epilepsy; folinic acid–responsive seizures (demonstrated to be the same disorder as pyridoxine-dependent epilepsy); cerebral folate deficiency; neurotransmitter disorders; biotinidase deficiency; glucose transporter 1 deficiency (responds to the ketogenic diet); serine synthesis defects; creatine deficiency syndromes; untreated phenylketonuria; developmental delay, epilepsy and neonatal diabetes; and hyperinsulinemia–hyperammonia. Often patients who do not respond to AEDs are candidates for steroids, IVIG, or the ketogenic diet.

Steroids, usually given as ACTH (see the discussion of West syndrome in "Severe Generalized Epilepsies" in Chapter 593.4) or as prednisone 2 mg/kg/day (or equivalent), are often used in epileptic encephalopathies such as West, Lennox-Gastaut, myoclonic astatic, continuous spike-waves in slow-wave sleep, and Landau-Kleffner syndromes. The course usually is for 2-3 mo with a taper over a similar period. Because relapses occur commonly during tapering, and in such syndromes as Landau-Kleffner and continuous spike-waves in slow-wave sleep, therapy for longer than 1 yr is often needed.

IVIG has also been reported to be similarly effective in non–immunodeficient patients with West, Lennox-Gastaut, Landau-Kleffner, and continuous spike-waves in slow-wave sleep syndromes and may also have efficacy in partial seizures. One should check the IgA levels before starting the infusions (to assess the risk for allergic reactions, because these are increased in patients with complete IgA deficiency) and guard against allergic reactions during the infusion. Low IgA, low IgG_2, and male sex are reported to possibly predict favorable response. The usual regimen is 2 g/kg divided over 4 consecutive days followed by 1 g/kg once a month for 6 mo. The mechanism of action of steroids and of IVIG are not known but is presumed to be antiinflammatory, because it has been demonstrated that seizures increase cytokines and that these, in turn, increase neuronal excitability by several mechanisms, including activation of glutamate receptors. Steroids and ACTH might also stimulate brain neurosteroid receptors that enhance GABA activity and might reduce corticotrophin-releasing hormone, which is known to be epileptogenic.

The **ketogenic diet** is believed to be effective in glucose transporter protein 1 deficiency, pyruvate dehydrogenase deficiency, myoclonic–astatic epilepsy, tuberous sclerosis complex, Rett syndrome, severe myoclonic epilepsy of infancy (Dravet syndrome), and infantile spasms. There is also suggestion of possible efficacy in selected

mitochondrial disorders—glycogenosis type V, Landau-Kleffner syndrome, Lafora body disease, and subacute sclerosing panencephalitis. The diet is absolutely contraindicated in carnitine deficiency (primary); carnitine palmitoyltransferase I or II deficiency; carnitine translocase deficiency; β-oxidation defects; medium-chain acyl dehydrogenase deficiency; long-chain acyl dehydrogenase deficiency; short-chain acyl dehydrogenase deficiency; long-chain 3-hydroxyacyl-coenzyme A deficiency; medium-chain 3-hydroxyacyl-coenzyme A deficiency; pyruvate carboxylase deficiency; and porphyrias. Thus, an appropriate metabolic work-up, depending on the clinical picture, usually needs to be performed before starting the diet (e.g., acyl carnitine profile, total and free carnitine levels). The diet has been used for refractory seizures of various types (partial or generalized) and consists of an initial period of fasting followed by a diet with a 3:1 or 4:1 fat:nonfat ratio, with fats consisting of animal fat, vegetable oils, or medium-chain triglycerides. Many patients do not tolerate it owing to diarrhea, vomiting, hypoglycemia, dehydration, or lack of palatability. Diets such as the low-glycemic-index diet and the Atkins diet are easier to institute, do not require hospitalization, and are also useful, but it is not known yet if they are as effective as the classic diet.

APPROACH TO EPILEPSY SURGERY

If a patient has failed 3 drugs, the chance of achieving seizure freedom using AEDs is generally <10%. Therefore, proper evaluation for surgery is necessary as soon as patients fail 2 or 3 AEDs, usually within 2 yr of the onset of epilepsy and often sooner than 2 yr. Performing epilepsy surgery in children at an earlier stage (e.g., <5 yr of age) allows transfer of function in the developing brain. Candidacy for epilepsy surgery requires proof of resistance to AEDs used at maximum, tolerably nontoxic doses; absence of expected unacceptable adverse consequences of surgery, and a properly defined **epileptogenic zone** (area that needs to be resected to achieve seizure freedom). The epileptogenic zone is identified by careful analysis, by an expert team of epilepsy specialists in an epilepsy center, of the following parameters: seizure semiology, interictal EEG, video-EEG long-term monitoring, neuropsychologic profile, and MRI. Other techniques, such as invasive EEG (depth electrodes, subdurals), single-photon emission CT, magnetoencephalography, and positron emission tomography are also often needed when the epileptogenic zone is difficult to localize or when it is close to eloquent cortex. To avoid resection of eloquent cortex, several techniques can be used, including the **Wada test**. In this test, intracarotid infusion of amobarbital is used to anesthetize 1 hemisphere to lateralize memory and speech by testing them during that unilateral anesthesia. Other tests to localize function include functional MRI, magnetoencephalography, and subdural electrodes with cortical stimulation. Developmental delay or psychiatric diseases must be considered in assessing the potential impact of surgery on the patient. The usual minimal presurgical evaluation includes EEG monitoring, imaging, and age-specific neuropsychologic assessment.

Epilepsy surgery is often used to treat refractory epilepsy of a number of etiologies, including cortical dysplasia, tuberous sclerosis, polymicrogyria, hypothalamic hamartoma, Landau-Kleffner syndrome, and hemispheric syndromes, such as Sturge-Weber syndrome, hemimegalencephaly, and Rasmussen encephalitis. Patients with intractable epilepsy resulting from metabolic or degenerative problems are not candidates for resective epilepsy surgery. **Focal resection** of the epileptogenic zone is the most common procedure. **Hemispherectomy** is used for diffuse hemispheric lesions; **multiple subpial transection**, a surgical technique in which the horizontal connections of the epileptic focus are partially cut without resecting it, is sometimes used for unresectable foci located in eloquent cortex such as in Landau-Kleffner syndrome. In Lennox-Gastaut syndrome, **corpus callosotomy** is used for drop attacks. **Vagal nerve stimulation** is often used for intractable epilepsies of various types and for seizures of diffuse focal or multifocal anatomic origin that do not yield themselves to resective surgery. Focal resection and hemispherectomy result in a high rate (50-80%) of seizure freedom. Corpus callosotomy and vagal nerve stimulation result in lower rates (5-10%) of seizure freedom; however, these procedures do result in significant reductions in the frequency and severity of seizures, decrease in medication requirements, and meaningful improvements in the patient's quality of life in approximately half or more of eligible patients.

DISCONTINUATION OF THERAPY

Discontinuation of AEDs is usually indicated when children are free of seizures for at least 2 yr. In more-severe syndromes, such as temporal lobe epilepsy secondary to mesial temporal sclerosis, Lennox-Gastaut syndrome, or severe myoclonic epilepsy, a prolonged period of seizure freedom on treatment is often warranted before AEDs are withdrawn, if withdrawal is attempted at all. In self-limited (benign) epilepsy syndromes, the duration of therapy can often be as short as 6 mo.

Many factors should be considered before discontinuing medications, including the likelihood of remaining seizure-free after drug withdrawal based on the type of epilepsy syndrome and etiology; the risk of injury in case of seizure recurrence (e.g., if the patient drives); and the adverse effects of AED therapy. Most children who have not had a seizure for 2 yr or longer and who have a normal EEG when AED withdrawal is initiated, remain free of seizures after discontinuing medication, and most relapses occur within the 1st 6 mo.

Certain risk factors can help the clinician predict the prognosis after AED withdrawal. The most important risk factor for seizure relapse is an abnormal EEG before medication is discontinued. Children who have remote structural (symptomatic) epilepsy are less likely to be able to stop AEDs than are children who have a benign genetic (idiopathic) epilepsy. In patients with absences or in patients treated with valproate for primary generalized epilepsy, the risk of relapse might still be high despite a normal EEG because valproate can normalize EEGs with generalized spike-wave abnormalities. Thus, in these patients, repeating the EEG during drug taper can help identify recurrence of the EEG abnormality and associated seizure risk before clinical seizures recur. Older age of epilepsy onset, longer duration of epilepsy, presence of multiple seizure types, and need to use more than 1 AED are all factors associated with a higher risk of seizure relapse after AED withdrawal.

AED therapy should be discontinued gradually; often over a period of 3-6 mo. Abrupt discontinuation can result in withdrawal seizures or status epilepticus. Withdrawal seizures are especially common with phenobarbital and benzodiazepines; consequently, special attention must be given to a prolonged tapering schedule during the withdrawal of these AEDs. Seizures that occur more than 2-3 mo after AEDs are completely discontinued indicate relapse, and resumption of treatment is usually warranted.

The decision to attempt AED withdrawal must be assessed mutually among the clinician, the parents, and the child depending on the child's age. Risk factors should be identified and precautionary measures should be taken. The patient and family should be counseled fully on what to expect, what precautions to take (including cessation of driving for a period of time), and what to do in case of relapse. A prescription for rectal diazepam or of intranasal midazolam to be given at the time of seizures that might occur during and after tapering is usually warranted (see Table 593-12 for dosing).

Sudden Unexpected Death in Epilepsy

SUDEP is the most common epilepsy related mortality in patients with chronic epilepsy; the incidence is unknown but ranges from 1-5 per 1,000 people with epilepsy. Although the precise etiology is unknown, risk factors include polypharmacology, poorly controlled generalized tonic–clonic seizures, male gender, age younger than 16 yr, long duration of epilepsy, and frequent seizures. Patients are usually found dead in their bed in a prone position with evidence suggesting a recent seizure. Potential mechanisms of SUDEP include respiratory arrest or dysfunction, drug-induced cardiac toxicity, CNS dysfunction (hypoventilation, arrhythmia, suppression of brain electrical activity), or pulmonary edema. Table 593-15 lists possible preventive measures.

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Table 593-15 Measures in Clinical Practice to Reduce the Risk of SUDEP

- **Reduction of tonic–clonic seizures:** optimum treatment, good drug compliance, lifestyle advice (e.g., alcohol intake, sleep deprivation)
- **Treatment changes:** change in a gradual staged manner; when switching drugs, introduce the new drug before withdrawing the old drug; the patients should have access to immediate advice in the event of worsening seizures during periods of change
- **Supervision at night for patients at high risk:** attendance, use of alarms (balancing the benefits of independent living and the penalties of intrusive monitoring)
- **Choice of drugs:** caution with antiepileptic drugs with potential cardiorespiratory adverse effects
- **Act on ictal warning signs:** tonic–clonic seizures that are prolonged, associated with marked cyanosis, severe bradycardia or apnea, and postictal EEG suppression; complex partial seizures with marked atonia (drop attacks); seizure in those with preexisting cardiac or respiratory impairment
- **Supervision after a tonic–clonic seizure:** continuous attendance until full consciousness is restored; call emergency services for high-risk seizures
- **Counseling on the risks:** lifestyle and treatment decisions are the patient's prerogative and the physician's role is to provide a risk-vs-benefit analysis

EEG, electroencephalogram; SUDEP, sudden unexpected death in epilepsy.
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593.7 Neonatal Seizures

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Seizures are possibly the most important and common indicator of significant neurologic dysfunction in the neonatal period. Seizure incidence is higher during this period than in any other period in life: 57.5 per 1,000 in infants with birth weights <1,500 g and 2.8 per 1,000 in infants weighing between 2,500 and 3,999 g have seizures.

PATHOPHYSIOLOGY

The immature brain has many differences from the mature brain that render it more excitable and more likely to develop seizures. Based predominantly on animal studies, these are delay in Na^+, K^+-adenosine triphosphatase maturation and increased NMDA and α-amino-3-hydroxy-5-methylisoxazole-4-propionate (AMPA) receptor density. In addition, the specific types of these receptors that are increased are those that are permeable to calcium (GLUR2 AMPA receptors). This contributes to increased excitability and to the long-term consequences associated with seizures, particularly those resulting from perinatal hypoxia. Medications that block AMPA receptors, such as topiramate, may thus prove useful in this clinical setup.

Another difference is delay in the development of inhibitory GABAergic transmission. In fact, GABA in the immature brain has an excitatory function as the chloride gradient is reversed relative to the mature brain, with higher concentrations of chloride being present intracellularly than extracellularly. Thus, opening of the chloride channels in the immature brain results in depolarizing the cell and not in hyperpolarizing it. This phenomenon appears to be more prominent in male neonates, perhaps explaining their greater predisposition to seizures. The reason for this is that the Cl^- transporter, NKCC1, is predominantly expressed in the neonatal period, leading to transport of Cl^- into the cell at rest, and then to cellular depolarization upon activation of $GABA_A$ receptors and opening of Cl^- channels with chloride efflux. This is important for neuronal development but renders the neonatal brain hyperexcitable. With maturation, expression of NCCK1 decreases and KCC2 increases. KCC2 transports Cl^- out of the cell, resulting in reduction of intracellular chloride concentration so that when $GABA_A$ receptors are activated, Cl^- influx and hyperpolarization occur. Bumetanide, a diuretic that blocks NKCC1, can prevent excessive GABA depolarization and avert the neuronal hyperexcitability underlying neonatal seizures. It also prevents, in rats, complex febrile seizure induced hyperactivation of excitatory $GABA_A$ receptors and the resultant granule cell ectopia and temporal lobe epilepsy.

Although it is susceptible to developing seizures, the immature brain appears to be more resistant to the deleterious effects of seizures than the mature brain, as a result of increases in calcium binding proteins that buffer injury-related increases in calcium, increased extracellular space, decreased levels of the second messenger inositol triphosphate, and the immature brain's ability to tolerate hypoxic conditions by resorting to anaerobic energy metabolism.

Many animal studies indicate that seizures are detrimental to the immature brain. Human studies also suggest harmful effects of seizures as shown by MRI and by the association of worse prognosis in neonates with seizures even when correcting for confounding factors. Even electrographic seizures without clinical correlates have been shown to be associated with worse prognosis. However, it is not definite that this association is causal: It is difficult in human studies to distinguish among effects of seizures, of the underlying insult responsible for the seizures (clinical or electrographic), and of the AEDs used to stop the seizures. Most physicians currently believe that it is favorable to control clinical as well as electrographic seizures.

TYPES OF NEONATAL SEIZURES

There are 5 main neonatal seizure types: subtle, clonic, tonic, spasms, and myoclonic. Spasms, focal clonic, focal tonic, and generalized myoclonic seizures are, as a rule, associated with electrographic discharges (epileptic seizures), whereas motor automatisms, the subtle, generalized tonic and multifocal myoclonic episodes are frequently not associated with discharges and thus are thought to often represent release phenomena with abnormal movements secondary to brain injury rather than true epileptic seizures (Table 593-16). To determine clinically whether such manifestations are seizures or release phenomena is often difficult, but precipitation of such manifestations by stimulation and aborting them by restraint or manipulation would suggest that they are not seizures. One needs to keep in mind, however, that epileptic seizures can also be induced by stimulation. Thus, in many cases, specifically in sick neonates with history of neurologic insults, continuous bedside EEG monitoring helps make this distinction. Such monitoring has become the standard of care in most intensive care nurseries.

Subtle Seizures

Subtle seizures include transient eye deviations, nystagmus, blinking, mouthing, abnormal extremity movements (rowing, swimming, bicycling, pedaling, and stepping), fluctuations in heart rate, hypertension episodes, and apnea. Subtle seizures occur more commonly in premature than in full-term infants.

Clonic Seizures

Clonic seizures can be focal or multifocal. Multifocal clonic seizures incorporate several body parts and are migratory in nature. The migration follows a nonjacksonian trend; for example, jerking of the left arm can be associated with jerking of the right leg. Generalized clonic seizures that are bilateral, symmetric, and synchronous are uncommon in the neonatal period presumably due to decreased connectivity associated with incomplete myelination at this age.

Tonic Seizures

Tonic seizures can be focal or generalized (generalized are more common). Focal tonic seizures include persistent posturing of a limb or posturing of trunk or neck in an asymmetric way often with persistent horizontal eye deviation. Generalized tonic seizures are bilateral tonic limb extension or tonic flexion of upper extremities often associated with tonic extension of lower extremities.

Spasms

Spasms are sudden generalized jerks lasting 1-2 sec that are distinguished from generalized tonic spells by their shorter duration and by

Table 593-16 Clinical Characteristics, Classification, and Presumed Pathophysiology of Neonatal Seizures

CLASSIFICATION	CHARACTERIZATION
Focal clonic	Repetitive, rhythmic contractions of muscle groups of the limbs, face, or trunk May be unifocal or multifocal May occur synchronously or asynchronously in muscle groups on 1 side of the body May occur simultaneously but asynchronously on both sides Cannot be suppressed by restraint Pathophysiology: epileptic
Focal tonic	Sustained posturing of single limbs Sustained asymmetrical posturing of the trunk Sustained eye deviation Cannot be provoked by stimulation or suppressed by restraint Pathophysiology: epileptic
Generalized tonic	Sustained symmetrical posturing of limbs, trunk, and neck May be flexor, extensor, or mixed extensor/flexor May be provoked or intensified by stimulation May be suppressed by restraint or repositioning Presumed pathophysiology: nonepileptic
Myoclonic	Random, single, rapid contractions of muscle groups of the limbs, face, or trunk Typically not repetitive or may recur at a slow rate May be generalized, focal, or fragmentary May be provoked by stimulation Presumed pathophysiology: may be epileptic or nonepileptic
Spasms	May be flexor, extensor, or mixed extensor/flexor May occur in clusters Cannot be provoked by stimulation or suppressed by restraint Pathophysiology: epileptic
Motor automatisms	
Ocular signs	Random and roving eye movements or nystagmus (distinct from tonic eye deviation) May be provoked or intensified by tactile stimulation Presumed pathophysiology: nonepileptic
Oral-buccal-lingual movements	Sucking, chewing, tongue protrusions May be provoked or intensified by stimulation Presumed pathophysiology: nonepileptic
Progression movements	Rowing or swimming movements Pedaling or bicycling movements of the legs May be provoked or intensified by stimulation May be suppressed by restraint or repositioning Presumed pathophysiology: nonepileptic
Complex purposeless movements	Sudden arousal with transient increased random activity of limbs May be provoked or intensified by stimulation Presumed pathophysiology: nonepileptic

From Mizrahi EM, Kellaway P. Diagnosis and management of neonatal seizures. *Philadelphia, 1998, Lippincott-Raven. Tab 4, p. 21.*

the fact that spasms are usually associated with a single, very brief, generalized discharge.

Myoclonic Seizures

Myoclonic seizures are divided into focal, multifocal, and generalized types. Myoclonic seizures can be distinguished from clonic seizures by the rapidity of the jerks (<50 msec) and by their lack of rhythmicity. Focal myoclonic seizures characteristically affect the flexor muscles of the upper extremities and are sometimes associated with seizure activity on EEG. Multifocal myoclonic movements involve asynchronous twitching of several parts of the body and are not commonly associated with seizure discharges on EEG. Generalized myoclonic seizures involve bilateral jerking associated with flexion of upper and occasionally lower extremities. The latter type of myoclonic jerks is more commonly correlated with EEG abnormalities than the other types.

Seizures vs Jitteriness

Jitteriness can be defined as rapid motor activities, such as a tremor or shake, that can be ended by flexion or holding the limb. Seizures, on the other hand, generally do not end with tactile or motor suppression. Jitteriness, unlike most seizures, is usually induced by a stimulus. Also unlike jitteriness, seizures often involve eye deviation and autonomic changes.

ETIOLOGY

Table 593-17 lists causes of neonatal seizures.

Hypoxic–Ischemic Encephalopathy

This is the most common cause of neonatal seizures, accounting for 50-60% of patients. Seizures secondary to this encephalopathy occur within 12 hr of birth.

Vascular Events

These include intracranial bleeds and ischemic strokes and account for 10-20% of patients. Three types of hemorrhage can be distinguished: primary subarachnoid hemorrhage, germinal matrix–intraventricular hemorrhage, and subdural hemorrhage. Patients with arterial strokes or venous sinus thrombosis can present with seizure and these can be

Table 593-17 Causes of Neonatal Seizures According to Common Age of Presentation

AGES 1-4 DAYS
Hypoxic–ischemic encephalopathy
Drug withdrawal, maternal drug use of narcotic or barbiturates
Drug toxicity: lidocaine, penicillin
Intraventricular hemorrhage
Acute metabolic disorders
- Hypocalcemia
- Sepsis
- Maternal hyperthyroidism, or hypoparathyroidism
- Hypoglycemia
- Perinatal insults, prematurity, small for gestational age
- Maternal diabetes
- Hyperinsulinemic hypoglycemia
- Hypomagnesemia
- Hyponatremia or hypernatremia
- Iatrogenic or inappropriate antidiuretic hormone secretion

Inborn errors of metabolism
- Galactosemia
- Hyperglycinemia
- Urea cycle disorders

Pyridoxine deficiency and pyridoxal-5-phosphate deficiency (must be considered at any age)

AGES 4-14 DAYS
Infection
- Meningitis (bacterial)
- Encephalitis (enteroviral, herpes simplex)

Metabolic disorders
- Hypocalcemia
- Diet, milk formula
- Hypoglycemia, persistent
- Inherited disorders of metabolism
- Galactosemia
- Fructosemia
- Leucine sensitivity
- Hyperinsulinemic hypoglycemia, hyperinsulinism, hyperammonemia syndrome
- Anterior pituitary hypoplasia, pancreatic islet cell tumor
- Beckwith syndrome

Drug withdrawal, maternal drug use of narcotics or barbiturates
Benign neonatal convulsions, familial and nonfamilial
Kernicterus, hyperbilirubinemia
Developmental delay, epilepsy, neonatal diabetes syndrome

AGES 2-8 WK
Infection
- Herpes simplex or enteroviral encephalitis
- Bacterial meningitis

Head injury
- Subdural hematoma
- Child abuse

Inherited disorders of metabolism
- Aminoacidurias
- Urea cycle defects
- Organic acidurias
- Neonatal adrenoleukodystrophy

Malformations of cortical development
- Lissencephaly
- Focal cortical dysplasia

Tuberous sclerosis
Sturge-Weber syndrome

diagnosed by neuroimaging. Venous sinus thrombosis could be missed unless MR or CT venography studies are requested.

Intracranial Infections

Bacterial and nonbacterial infections account for 5-10% of the cases of neonatal seizures and include bacterial meningitis, TORCH (*t*oxoplasmosis, *o*ther infections, *r*ubella, *c*ytomegalovirus, *h*erpes simplex virus) infections, particularly herpes simplex encephalitis.

Brain Malformations

Brain malformations account for 5-10% of neonatal seizure cases. An example is **Aicardi syndrome**, which affects girls only and consists of retinal lacunae, agenesis of the corpus callosum, and severe seizures including subsequent infantile spasms with hypsarrhythmia that is sometimes initially unilateral on EEG.

Metabolic Disturbances

Metabolic disturbances include disturbances in glucose, calcium, magnesium, other electrolytes, amino acids, or organic acids and pyridoxine dependency.

Hypoglycemia can cause neurologic disturbances and is very common in small neonates and neonates whose mothers are diabetic or prediabetic. The duration of hypoglycemia is very critical in determining the incidence of neurologic symptoms.

Hypocalcemia occurs at 2 peaks. The first peak corresponds to low-birthweight infants and is evident in the 1st 2-3 days of life. The second peak occurs later in neonatal life and often involves large, full-term babies who consume milk that has an unfavorable ratio of phosphorus to calcium and phosphorus to magnesium. **Hypomagnesemia** is often associated with hypocalcemia. **Hyponatremia** can cause seizures and is often secondary to inappropriate antidiuretic hormone secretion.

Local anesthetic intoxication seizures can result from neonatal intoxication with local anesthetics administered into the infant's scalp.

Neonatal seizures can also result from disturbances in **amino acid or organic acid** metabolism. These are usually associated with acidosis and/or hyperammonemia. However, even in the absence of these findings, if a cause of the seizures is not immediately evident, then ruling out metabolic causes requires a full metabolic work-up (see Chapter 593.2) including examination of serum amino acids, acyl carnitine profile, lactate, pyruvate, ammonia, very-long-chain fatty acids (for neonatal adrenoleukodystrophy and Zellweger syndrome), examination of urine for organic acids, α-aminoadipic acid semialdehyde and sulfocysteine, as well as examination of CSF for glucose, protein, cells, amino acids, lactate, pyruvate, α-aminoadipic acid semialdehyde, pyridoxal phosphate, 5-MTHF (5-methyltetrahydrofolate), succinyladenosine, and CSF neurotransmitter metabolites. This is because many inborn errors of metabolism, such as nonketotic hyperglycinemia, can manifest with neonatal seizures (often mistaken initially for hiccups that these patients also have) and can be detected only by performing these tests. Definitive diagnosis of **nonketotic hyperglycinemia**, for example, requires measuring the ratio of CSF glycine to plasma glycine.

Pyridoxine and **pyridoxal dependency disorders** can cause severe seizures. These seizures, which are often multifocal clonic, usually start during the 1st few hr of life. Cognitive impairment is often associated if therapy is delayed (see Chapter 593.6).

Drug Withdrawal

Seizures can rarely be caused by the neonate's passive addiction and then drug withdrawal. Such drugs include narcotic analgesics, sedative–hypnotics, and others. The associated seizures appear during the 1st 3 days of life.

Neonatal Seizure Syndromes

Seizure syndromes include **benign idiopathic neonatal seizures (fifth day fits)**, which are usually apneic and focal motor seizures that start around the fifth day of life. Interictal EEG shows a distinctive pattern called *theta pointu alternant* (runs of sharp 4-7 Hz activity), and ictal EEG shows multifocal electrographic seizures. Patients have a good response to medications and a good prognosis. Autosomal dominant **benign familial neonatal seizures** have onset at 2-4 days of age and usually remit at 2-15 wk of age. The seizures consist of ocular deviation, tonic posturing, clonic jerks, and, at times, motor automatisms. Interictal EEG is usually normal. These are caused by mutations in the *KCNQ2* and *KCNQ3* genes. Approximately 16% of patients develop later epilepsy. **Early myoclonic encephalopathy** and **early infantile epileptic encephalopathy (Ohtahara syndrome)** are discussed in Chapter 593.4.

Miscellaneous Conditions

Miscellaneous conditions include benign neonatal sleep myoclonus and hyperekplexia, which are nonepileptic conditions (see Chapter 594).

DIAGNOSIS

Some cases can be correctly diagnosed by simply taking the prenatal and postnatal history and performing an adequate physical examination. Depending on the case, additional tests or procedures can be performed. EEG is considered the main tool for diagnosis. It can show paroxysmal activity (e.g., sharp waves) in between the seizures and electrographic seizure activity if a seizure is captured. However, some neonatal seizures might not be associated with EEG abnormalities as noted above either because they are "release phenomena" or alternatively because the discharge is deep and is not detected by the scalp EEG. Additionally, electrographic seizures can occur without observed clinical signs **(electroclinical dissociation).** This is presumed to be caused by the immaturity of cortical connections, resulting, in many cases, in no or minimal motor manifestations. Continuously monitoring the EEG at the bedside in the neonatal intensive care unit for neonates at risk for neonatal seizures and brain injury is part of routine clinical practice in most centers, providing real-time measurements of the brain's electrical activity and identifying seizure activity. Many centers apply EEG monitoring to at-risk babies even before seizures develop, which is often desirable; others monitor patients who have manifested or are suspected of having seizures. In addition, there are currently attempts to develop methods for continuous monitoring of cerebral activity with automated detection and background analysis of neonatal seizures, similar to the continuous ECG monitoring in intensive care facilities. In infants started on hypothermia protocols following suspected hypoxic–ischemic injuries, it is recommended to continuously monitor the EEG during the cooling and rewarming periods to detect clinical and subclinical events in this high-risk population. The American Clinical Neurophysiology Society recommends continuous EEG monitoring in the neonatal intensive care unit to monitor evolution of EEG background to help with prognostication, to guide titration of anticonvulsant therapy for infants with established seizures, to screen for seizures among infants deemed to be at risk (hypoxic ischemic encephalopathy, stroke, meningitis, intraventricular hemorrhage, metabolic disorders, and congenital cerebral malformations), to screen for seizures among infants who are paralyzed, to characterize clinical events suspected to represent seizures, and to detect impending cerebral ischemia or hemorrhage.

Careful neurologic examination of the infant might uncover the cause of the seizure disorder. Examination of the **retina** might show the presence of chorioretinitis, suggesting a congenital TORCH infection, in which case titers of mother and infant are indicated. The **Aicardi syndrome** is associated with coloboma of the iris and retinal lacunae. Inspection of the **skin** might show hypopigmented lesions characteristic of tuberous sclerosis (seen best on UV light examination) or the typical crusted vesicular lesions of incontinentia pigmenti; both neurocutaneous syndromes are often associated with generalized myoclonic seizures beginning early in life. An unusual body or urine odor suggests an inborn error of metabolism.

Blood should be obtained for determinations of glucose, calcium, magnesium, electrolytes, and blood urea nitrogen. If hypoglycemia is a possibility, serum glucose testing is indicated so that treatment can be initiated immediately. Hypocalcemia can occur in isolation or in association with hypomagnesemia. A lowered serum calcium level is often associated with birth trauma or a CNS insult in the perinatal period. Additional causes include maternal diabetes, prematurity, DiGeorge syndrome, and high-phosphate feedings. Hypomagnesemia (<1.5 mg/dL) is often associated with hypocalcemia and occurs particularly in infants of malnourished mothers. In this situation, the seizures are resistant to calcium therapy but respond to intramuscular magnesium, 0.2 mL/kg of a 50% solution of $MgSO_4$. Serum electrolyte measurement can indicate significant hyponatremia (serum sodium <115 mEq/L) or hypernatremia (serum sodium >160 mEq/L) as a cause of the seizure disorder.

A **lumbar puncture** is indicated in virtually all neonates with seizures, unless the cause is obviously related to a metabolic disorder such as hypoglycemia or hypocalcemia. The latter infants are normally alert interictally and usually respond promptly to appropriate therapy. The CSF findings can indicate a bacterial meningitis or aseptic encephalitis. Prompt diagnosis and appropriate therapy improve the outcome for these infants. Bloody CSF indicates a traumatic tap or a subarachnoid or intraventricular bleed. Immediate centrifugation of the specimen can assist in differentiating the 2 disorders. A clear supernatant suggests a traumatic tap, and a xanthochromic color suggests a subarachnoid bleed. Mildly jaundiced normal infants can have a yellowish discoloration of the CSF that makes inspection of the supernatant less reliable in the newborn period.

Many **inborn errors of metabolism** cause generalized convulsions in the newborn period. Because these conditions are often inherited in an autosomal recessive or X-linked recessive fashion, it is imperative that a careful family history be obtained to determine if there is consanguinity or whether siblings or close relatives developed seizures or died at an early age. Serum ammonia determination is useful for screening for the hypoglycemic hyperammonemia syndrome and for suspected urea cycle abnormalities. In addition to having generalized clonic seizures, these latter infants present during the 1st few days of life with increasing lethargy progressing to coma, anorexia and vomiting, and a bulging fontanel. If the blood gases show an anion gap and a metabolic acidosis with the hyperammonemia, urine organic acids should be immediately determined to investigate the possibility of methylmalonic or propionic acidemia.

Maple syrup urine disease should be suspected when a metabolic acidosis occurs in association with generalized clonic seizures, vomiting, bulging fontanel, and muscle rigidity during the 1st wk of life. The result of a rapid screening test using 2,4-dinitrophenylhydrazine that identifies keto derivatives in the urine is positive in maple syrup urine disease.

Additional metabolic causes of neonatal seizures include nonketotic hyperglycinemia, an intractable condition characterized by markedly elevated plasma and CSF glycine levels, prominent hiccups, persistent generalized seizures, and lethargy rapidly leading to coma; ketotic hyperglycinemia in which seizures are associated with vomiting, fluid and electrolyte disturbances, and a metabolic acidosis; and Leigh disease suggested by elevated levels of serum and CSF lactate or an increased lactate : pyruvate ratio. Biotinidase deficiency should also be considered. A comprehensive description of the diagnosis and management of these metabolic diseases is discussed in Part XI, Metabolic Disorders.

Unintentional **injection of a local anesthetic** into a fetus during labor can produce intense tonic seizures. These infants are often thought to have had a traumatic delivery because they are flaccid at birth, have abnormal brainstem reflexes, and show signs of respiratory depression that sometimes require ventilation. Examination may show a needle puncture of the skin or a perforation or laceration of the scalp. An elevated serum anesthetic level confirms the diagnosis. The treatment consists of supportive measures and promotion of urine output by administering intravenous fluids with appropriate monitoring to prevent fluid overload.

Benign familial neonatal seizures, an autosomal dominant condition, begins on the 2nd-3rd day of life, with a seizure frequency of 10-20/day. Patients are normal between seizures, which stop in 1-6 mo. These are caused by mutations in the voltage-sensitive potassium channel genes *Kv7.2*, and *Kv7.3* (*KCNQ2* and *KCNQ3*). Other mutations in the *Kv7.2* gene cause severe neonatal epileptic encephalopathy. **Fifth-day fits** occur on day 5 of life (4-6 days) in normal-appearing neonates. The seizures are multifocal and are often present for <24 hr. The diagnosis requires exclusion of other causes of seizures and sequencing of the above genes. The prognosis is good for the benign form.

Pyridoxine dependency, a rare disorder, must be considered when seizures begin shortly after birth with signs of fetal distress in utero and are resistant to conventional anticonvulsants such as phenobarbital or phenytoin. The history may suggest that similar seizures

occurred in utero. When pyridoxine-dependent seizures are suspected, 100-200 mg of pyridoxine or pyridoxal phosphate should be administered intravenously during the EEG, which should be promptly performed once the diagnosis is considered. The seizures abruptly cease, and the EEG often normalizes in the next few hours or longer. Not all cases of pyridoxine dependency respond dramatically to the initial bolus of IV pyridoxine. Therefore, a 6-wk trial of oral pyridoxine (100-200 mg/day) or preferably pyridoxal phosphate (as pyridoxine does not help infants with the related but distinct syndrome of pyridoxal dependency) is recommended for infants in whom a high index of suspicion continues after a negative response to IV pyridoxine. Measurement of serum pipecolic acid and α-aminoadipic acid semialdehyde (elevated) and CSF pyridoxal-5-phosphate (decreased) needs to be performed before initiation of the trials without delay. These children require lifelong supplementation of oral pyridoxine (100 mg/day at times with folinic acid) or pyridoxal phosphate (15-60 mg/kg/day). Cerebral folate deficiency should also be ruled out by medication trial (folinic acid 1-3 mg/kg/day) and by CSF levels of 5-methyltetrahydrofolate assay. Gene sequencing can confirm the diagnosis (see Chapter 593.4). The earlier the therapy is initiated in these vitamin responsive disorders, the more favorable the outcome.

Drug-withdrawal seizures can occur in the newborn nursery but can take several weeks to develop because of prolonged excretion of the drug by the neonate. The incriminated drugs include barbiturates, benzodiazepines, heroin, and methadone. The infant may be jittery, irritable, and lethargic, and can have myoclonus or frank clonic seizures. The mother might deny the use of drugs; a serum or urine drug screen might identify the responsible agent.

Infants with focal seizures, suspected stroke or intracranial hemorrhage, and severe **cytoarchitectural abnormalities** of the brain (including lissencephaly and schizencephaly) who clinically may appear normal or microcephalic should undergo MRI or CT scan. Indeed, it is appropriate to recommend imaging of all neonates with seizures unexplained by serum glucose, calcium, or electrolyte disorders. Infants with chromosome abnormalities and adrenoleukodystrophy are also at risk for seizures and should be evaluated with investigation of a karyotype and serum very-long-chain fatty acids, respectively.

PROGNOSIS

Over the last few decades, prognosis of neonatal seizures has improved owing to advancements in obstetric and intensive neonatal care. Mortality has decreased from 40% to 20%. The correlation between EEG and prognosis is very clear. Although neonatal EEG interpretation is very difficult, EEG was found to be highly associated with the outcome in premature and full-term infants. An abnormal background is a powerful predictor of less-favorable later outcome. In addition, prolonged electrographic seizures (>10 min/hr), multifocal periodic electrographic discharges, and spread of the electrographic seizures to the contralateral hemisphere also correlate with poorer outcome. The underlying etiology of the seizures is the main determinant of outcome. For example, patients with seizures secondary to hypoxic–ischemic encephalopathy have a 50% chance of developing normally, whereas those with seizures caused by primary subarachnoid hemorrhage or hypocalcemia have a much better prognosis.

TREATMENT

A mainstay in the therapy of neonatal seizures is the diagnosis and treatment of the underlying etiology (e.g., hypoglycemia, hypocalcemia, meningitis, drug withdrawal, trauma), whenever one can be identified. There are conflicting approaches regarding the control of neonatal seizures. Most experts advocate complete control of clinical as well electrographic seizures. Others argue for treating clinical seizures only. Most centers favor the first approach. An important consideration before starting anticonvulsants is deciding, based on the severity duration and frequency of the seizures if the patient needs to receive intravenous therapy and loading with an initial bolus or can simply be started on maintenance doses of a long-acting drug. Patients often require assisted ventilation after receiving intravenous or oral loading doses of AEDs, and thus precautions for observations and for needed interventions are necessary.

Lorazepam

The initial drug used to control acute seizures is usually lorazepam. Lorazepam is distributed to the brain very quickly and exerts its anticonvulsant effect in <5 min. It is not very lipophilic and does not clear out from the brain very rapidly. Its action can last 6-24 hr. Usually, it does not cause hypotension or respiratory depression. The dose is 0.05 mg/kg (range: 0.02-0.10 mg/kg) every 4-8 hr.

Diazepam

Diazepam can be used as an alternative initial drug. It is highly lipophilic, so it distributes very rapidly into the brain and then is cleared very quickly out, carrying the risk of recurrence of seizures. Like other intravenous benzodiazepines, it carries a risk of apnea and hypotension, particularly if the patient is also on a barbiturate, so patients need to be observed for 3-8 hr after administration. The usual dose is 0.1-0.3 mg/kg IV over 3-5 min, given every 15-30 min to a maximum total dose of 2 mg. However, because of the respiratory and blood pressure limitations and because the intravenous preparation contains sodium benzoate and benzoic acid, it is currently not recommended as a first-line agent.

Midazolam

Midazolam can be used as an initial drug as a bolus or as a second- or third-line drug as a continuous drip for patients who did not respond to phenobarbital and/or to phenytoin. The doses used have been in the range of 0.05-0.1 mg/kg IV initial bolus, with a continuous infusion of 0.5-1 μg/kg/min IV that can then be gradually titrated upward, if tolerated, every 5 min or longer, to a maximum of approximately 33 μg/kg/min (2 mg/kg/hr).

Phenobarbital

Phenobarbital is considered by many as the first choice long-acting drug in neonatal seizures. Whether to use a benzodiazepine first depends on the clinical situation. The usual loading dose is 20 mg/kg. If this dosage is not effective, then additional doses of 5-10 mg/kg can be given until a dose of 40 mg/kg is reached. Respiratory support may be needed after phenobarbital loading. Twenty-four hours after starting the loading dose, maintenance dosing can be started at 3-6 mg/kg/day usually administered in 2 separate doses. Phenobarbital is metabolized in the liver and is excreted through kidneys. Thus, any abnormality in the function of these organs alters the drug's metabolism and can result in toxicity. In infants with acidosis or critical illness that might alter serum protein content, free (i.e., not protein bound) levels of the drug should be followed carefully.

Phenytoin and Fosphenytoin

For ongoing seizures, if a total loading dose of 40 mg/kg of phenobarbital was not effective, then a loading dose of 15-20 mg/kg of phenytoin can be administered intravenously. The rate at which the dose should be given must not exceed 0.5-1.0 mg/kg/min so as to prevent cardiac problems, and the medication needs to be avoided in patients with significant heart disease. Heart rate should be monitored while administrating the drug. It is not possible to mix phenytoin or fosphenytoin with dextrose solutions. Owing to its reduced solubility, potentially severe local cutaneous reactions, interaction with other drugs, and possible cardiac toxicity, intravenous phenytoin is not widely used.

Fosphenytoin, which is a phosphate ester prodrug, is preferable. It is highly soluble in water, and can be administered very safely intravenously and intramuscularly, without causing injury to tissues. Fosphenytoin is administered in phenytoin equivalents (PE). The usual loading dose of fosphenytoin is 15-20 PE/kg administered over 30 min. Maintenance doses of 4-8 PE/kg/day can be given. As is the case for phenobarbital, free levels of the drug should be monitored in neonates whose serum pH or protein content might not be normal.

Other Medications

Approximately 45% of neonates respond to the first drug used if it is phenobarbital or phenytoin and an additional 15% respond to the second agent. Levetiracetam (which can be given intravenously with later convenient conversion to oral solution) and topiramate (oral) are reported to be the drugs of second and third choice for approximately half of surveyed pediatric neurologists and some have used them even before phenobarbital or phenytoin in selected cases. The dosages used are 10-30 mg/kg/day of levetiracetam, at times higher, and up to 20 mg/kg/day of topiramate. Bumetanide has been used as an adjunct drug, particularly with phenobarbital, because of its effect on the chloride gradient, as discussed above. Lidocaine is another medication used for resistant cases. Primidone, carbamazepine, valproate, and lamotrigine use, although reported in some studies, is rarely warranted. Valproate, for example, is more likely to be toxic in children younger than 2 yr of age than in older children.

Duration of Therapy

Duration of therapy is related to the risk of developing later epilepsy in infants suffering from neonatal seizures, which ranges from 10-30% and depends on the individual neurologic examination, the etiology of the seizures, and the EEG at the time of discharge from the hospital. In general, if the EEG at the time of discharge does not show evidence of epileptiform activity, then medications are usually tapered at that time. If the EEG remains paroxysmal, then the decision is usually delayed for several months after discharge.

Bibliography is available at Expert Consult.

593.8 Status Epilepticus

Mohamad A. Mikati and Abeer J. Hani

Status epilepticus is a medical emergency that should be anticipated in any patient who presents with an acute seizure. It is defined as continuous seizure activity or recurrent seizure activity without regaining of consciousness lasting for more than 5 min as part of an operational definition put forth within the past few years. In the past, the cutoff time was 30 min, but this has been reduced to emphasize the risks involved with the longer durations. The ILAE defines status epilepticus as "a seizure which shows no clinical signs of arresting after a duration encompassing the great majority of seizures of that type in most patients or recurrent seizures without resumption of baseline central nervous system function interictally." The measures used to treat status epilepticus have to be started in any patient with acute seizures that do not stop within a few minutes. The most common type is **convulsive status epilepticus** (generalized tonic, clonic, or tonic–clonic), but other types do occur, including **nonconvulsive status** (complex partial, absence), myoclonic status, epilepsia partialis continua, and neonatal status epilepticus. The incidence of status epilepticus ranges between 10 and 60 per 100,000 population in various studies. Status epilepticus is most common in children younger than 5 yr of age, with an incidence in this age group of >100 per 100,000 children.

Approximately 30% of patients presenting with status epilepticus are having their first seizure, and approximately 40% of these later develop epilepsy. Febrile status epilepticus is the most common type of status epilepticus in children. In the 1950s and 1960s, mortality rates of 6-18% were reported after status epilepticus; currently, with the recognition of status epilepticus as a medical emergency, a lower mortality rate of 4-5% is observed, most of it secondary to the underlying etiology rather than to the seizures. Status epilepticus carries an approximately 14% risk of new neurologic deficits, most of this (12.5%) secondary to the underlying pathology.

Nonconvulsive status epilepticus manifests as a confusional state, dementia, hyperactivity with behavioral problems, fluctuating impairment of consciousness with at times unsteady sitting or walking, fluctuating mental status, confusional state, hallucinations, paranoia, aggressiveness catatonia, and or psychotic symptoms. It should be considered in any of these situations, especially in an unresponsive or encephalopathic child. Epilepsia partialis continua has been defined previously and can be caused by tumor, vascular etiologies, mitochondrial disease (mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes [MELAS]), and Rasmussen encephalitis.

Refractory status epilepticus is status epilepticus that has failed to respond to therapy, usually with at least 2 (such as a benzodiazepine and another medication) medications. Currently, the trend is not to assign a minimum duration, whereas in the past a minimum duration of 30 min, 60 min, or even 2 hr was cited. **New-onset refractory status epilepticus** has been identified as a distinct entity that can be caused by almost any of the causes of status epilepticus in a patient without prior epilepsy. It also is often of unknown etiology, presumed to be encephalitic or postencephalitic, can last several weeks or longer, and often, but not always, has a poor prognosis. Devastating epileptic encephalopathy in school-age children, also called **fever-induced refractory epileptic encephalopathy in school age children (FIRES)** is a syndrome of refractory status epilepticus that is associated with acute febrile infections, appears to be parainfectious in nature, and to be highly drug resistant but responsive to the ketogenic diet.

ETIOLOGY

Etiologies include new-onset epilepsy of any type; drug intoxication (e.g., tricyclic antidepressants) in children and drug and alcohol abuse in adolescents; drug withdrawal or overdose in patients on AEDs; hypoglycemia; hypocalcemia; hyponatremia; hypomagnesemia; acute head trauma; encephalitis; meningitis; autoimmune encephalitis (such as anti-NMDA receptor and anti–voltage-gated potassium channel complex antibody syndromes); ischemic (arterial or venous) stroke; intracranial hemorrhage; folinic acid and pyridoxine and pyridoxal phosphate dependency (these usually present in infancy but childhood onset is also possible); inborn errors of metabolism (see Chapter 593.2) such as nonketotic hyperglycinemia in neonates and mitochondrial encephalopathy with lactic acidosis (MELAS) in infants, children, and adolescents; ion channel–related epilepsies (e.g., sodium and potassium channel mutations reviewed in the sections above); hypoxic–ischemic injury (e.g., after cardiac arrest); systemic conditions (such as hypertensive encephalopathy, posterior reversible encephalopathy, renal or hepatic encephalopathy); brain tumors; and any other disorders that can cause epilepsy (such as brain malformations, neurodegenerative disorders, different types of progressive myoclonic epilepsy, storage diseases).

A rare condition called **hemiconvulsion-hemiplegia-epilepsy syndrome** consists of prolonged febrile status epilepticus presumably caused by focal acute encephalitis with resultant atrophy in the involved hemisphere, contralateral hemiplegia, and chronic epilepsy. It should be suspected early on to attempt to control the seizures as early as possible. This and the somewhat similar condition mentioned above called FIRES are likely to be have a parainfectious-autoimmune etiology. Rasmussen encephalitis often causes epilepsia partialis continua (see Chapter 593.3) and sometimes convulsive status epilepticus. Several types of infections are more likely to cause encephalitis with status epilepticus, such as herpes simplex (complex partial and convulsive status), *Bartonella* (particularly nonconvulsive status), Epstein-Barr virus, and mycoplasma (postinfectious encephalomyelitis with any type of status epilepticus). Postinfectious encephalitis and acute disseminated encephalomyelitis are common causes of status epilepticus, including refractory status epilepticus. HHV6 can cause a distinct epileptic syndrome with limbic status epilepticus in immune-suppressed patients.

MECHANISMS

The mechanisms leading to the establishment of sustained seizure activity seen in status epilepticus appear to involve (1) failure of desensitization of AMPA glutamate receptors, thus persistence of increased excitability, and (2) reduction of GABA-mediated inhibition as a result of intracellular internalization of $GABA_A$ receptors. This explains the

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clinical observation that status epilepticus is often less likely to stop in the next specific period of time the longer the seizure has lasted and why benzodiazepines appear to be decreasingly effective the longer seizure activity lasts. During status epilepticus there is increased cerebral metabolic rate and a compensatory increase in cerebral blood flow that, after approximately 30 min, is not able to keep up with the increases in cerebral metabolic rate. This leads to a transition from adequate to inadequate cerebral oxygen tensions and, together with other factors, contributes to neuronal injury resulting from status epilepticus. Status epilepticus can cause both neuronal necrosis and apoptosis. The mechanisms of apoptosis are thought to be related to increases in intracellular calcium and proapoptotic factors such as ceramide, Bax, and apoptosis-inducing factor. In addition, inflammation through the cytokines (such as interleukin-1β) released during seizure activity can modify neuronal excitability by modifying neurotransmitter function in a number of ways, such as through phosphorylation of the NR2B subunit rendering the NMDA receptors more permeable to calcium influx, increased expression of highly calcium-permeable AMPA receptors, and induction of endocytosis of $GABA_A$ receptors. Prostaglandins (such as prostaglandin E_2) can increase glutamate release and reduce potassium currents leading to increased excitability.

THERAPY

Status epilepticus is a medical emergency that requires initial and continuous attention to securing airway, breathing, and circulation (with continuous monitoring of vital signs including ECG) and determination and management of the underlying etiology (e.g., hypoglycemia). Laboratory studies, including glucose, sodium, calcium, magnesium, complete blood count, basic metabolic panel, CT scan, and continuous EEG, are needed for all patients. Blood and spinal fluid cultures, toxic screens, and tests for inborn errors of metabolism are often needed. AED levels need to be determined in all patients known already to be taking these drugs. Lumbar puncture, comprehensive toxicologic screens, MRI, and other laboratory tests are performed depending on clinical suspicion and need. EEG is helpful in ruling out **pseudo–status epilepticus** (psychologic conversion reaction mimicking status epilepticus) or other movement disorders (chorea, tics), rigors, clonus with stimulation, and decerebrate/decorticate posturing. The EEG can also be helpful in identifying the type of status epilepticus (generalized vs focal), which can guide further testing for the underlying etiology and further therapy. EEG can also help distinguish between postictal depression and later stages of status epilepticus in which the clinical manifestations are subtle (e.g., minimal myoclonic jerks) or absent (electroclinical dissociation), and can help in monitoring the therapy, particularly in patients who are paralyzed and intubated. Neuroimaging must be considered after the child has been stabilized, especially if it is indicated by the clinical manifestations, by an asymmetric or focal nature of the EEG abnormalities, or by lack of knowledge of the underlying etiology. The EEG manifestations of status epilepticus show several stages that consist of initial distinct electrographic seizures (stage I) followed by waxing and waning electrographic seizures (stage II), continuous electrographic seizures (stage III; many patients start with this directly), continuous ictal discharges punctuated by flat periods (stage IV), and periodic epileptiform discharges on flat background (stage V). The last 2 stages are often associated with subtle clinical manifestations and with a lower chance of response to medications.

The initial **emergent** therapy usually involves intravenous diazepam, lorazepam, or midazolam. Diazepam is at least as effective as intravenous lorazepam but has fewer side effects (Table 593-18). The use of midazolam autoinjector as initial therapy for acute seizures was found to be at least as useful and safe as the use intravenous lorazepam and results in earlier response. If intravenous access is not available, buccal or intranasal midazolam, intranasal lorazepam, or rectal diazepam are effective options. Intramuscular midazolam is equally effective as intravenous lorazepam. With all options, respiratory depression is a potential side effect for which the patient should be monitored and managed as needed. In some infants, a trial of pyridoxine may be warranted. The strongest evidence for initial and emergent therapy is for diazepam or

Table 593-18 Doses of Commonly Used Antiepileptic Drugs in Status Epilepticus

DRUG*	ROUTE	DOSAGE
Lorazepam	Intravenous Intranasal	0.1 mg/kg up to 4 mg total, may repeat in 5-10 min 0.1 mg/kg
Midazolam	Intravenous Intramuscular Intranasal Buccal	0.2 mg/kg up to 10 mg total dose, may repeat in 5-10 min 0.08-0.23 mg/kg/hr maintenance 0.2 mg/kg 0.2 mg/kg 0.5 mg/kg
Diazepam	Intravenous Rectal	0.15 mg/kg up to a max total dose of 10 mg, may repeat in 5-10 min 2-5 yr: 0.5 mg/kg 6-11 yr: 0.3 mg/kg ≥12 yr: 0.2 mg/kg
Fosphenytoin	Intravenous	20 mg/kg PE, then 3-6 mg/kg/24 hr, loading rate up to 50 mg PE per min
Phenobarbital†	Intravenous	5-20 mg/kg
Pentobarbital coma†	Intravenous	13.0 mg/kg, then 1-5 mg/kg/hr
Propofol†	Intravenous	1 mg/kg (bolus), then 1-15 mg/kg/hr (infusion)
Thiopental†	Intravenous	5 mg/kg/1st hr, then 1-2 mg/kg/hr
Valproate†	Intravenous	Loading: 25 mg/kg, then 30-60 mg/kg/24 hr
Lacosamide†	Intravenous	Loading: 4 mg/kg then 4-12 mg/kg/24 hr
Levetiracetam	Intravenous	20-60 mg/kg
Topiramate	Enterally	5-10 mg/kg/24 hr (loading dose) then same or lower for maintenance

*Reflects current trends in use which may not be FDA approved. For FDA indications, see Table 593-13.
†May cause PR prolongation.
PE, phenytoin sodium equivalents.

lorazepam, followed by phenytoin/fosphenytoin and phenobarbital, then valproate and levetiracetam.

After the emergent therapy usually with a benzodiazepine, the subsequent **urgent therapy** medication is usually fosphenytoin, and the loading dose is usually 15-20 PE/kg. A level is usually taken 2 hr later to ensure achievement of a therapeutic concentration. Depending on the level, maintenance dose can be started right away or, more commonly, in 6 hr. With phenytoin and phenobarbital, each 1 mg/kg (1 PE/kg for fosphenytoin) increases the serum concentration by approximately 1 µg/mL; for valproate, each 1 mg/kg increases the serum concentration by approximately 4 µg/mL. Precautions about the rate of infusion of fosphenytoin and phenytoin (not >0.5-1.0 mg/kg/min) and the other medications need to be followed because side effects often depend on infusion rate. The subsequent medication is often phenobarbital. The dose used in neonates is usually 20 mg/kg loading dose, but in infants and children the dose is often 5-10 mg/kg (to avoid respiratory depression), with the dose repeated if there is not an adequate response. Current evidence for the urgent therapy is strongest for valproate, followed by phenytoin/fosphenytoin and midazolam continuous infusion, followed by phenobarbital and levetiracetam, the last of which are currently being increasingly used.

After the second or third medication is given, and sometimes before that, the patient might need to be intubated. All patients with status epilepticus, even the ones who respond, need to be admitted to the ICU for completion of therapy and monitoring. Ideally, emergent and urgent therapies should have been received within less than 30 min so as to initiate the subsequent therapy soon, thus reducing the chances of sequelae. For **refractory status epilepticus treatment**, an intravenous bolus followed by continuous infusion of midazolam, propofol, pentobarbital, or thiopental is used. This is done in the ICU. Subsequent boluses and adjustment of the rate of the infusion are usually made depending on clinical and EEG responses. Because most of these patients need to be intubated and paralyzed, the EEG becomes the method of choice by which to follow them. The goal is to stop electrographic seizure activity before reducing the therapy. Usually this implies achievement of complete flattening of the EEG. Some consider that achieving a burst suppression pattern may be enough, and the periods of flattening in such a case need to be 8-20 sec to ensure interruption of electrographic seizure activity. However, this is an area that is in need of further study. Currently, the level of the evidence for refractory treatment is strongest for midazolam and valproate, followed by propofol and pentobarbital/thiopental, followed by levetiracetam, phenytoin/fosphenytoin, lacosamide, topiramate, and phenobarbital.

Patients on these therapies require careful attention to blood pressure and to systemic complications, and some develop multiorgan failure. It is not unusual for patients put into pentobarbital coma to have to be on multiple pressors to maintain their blood pressure during therapy.

The choice among the above options to treat refractory status epilepticus often depends on the experience of the specific center. Midazolam probably has fewer side effects, but is less effective, and barbiturate coma is more effective, but carries a higher risk of side effects. On propofol, some patients develop a propofol infusion syndrome with lactic acidosis, hemodynamic instability, and rhabdomyolysis with higher infusion rates (>67 µg/kg/min). Thus electrolytes, creatine phosphokinase, and organ function studies need to be monitored. Often, barbiturate coma and similar therapies are maintained for 1 or more days before it is possible to gradually taper the therapy, usually over a few days. However, in some cases, including cases of new-onset refractory status epilepticus (new-onset refractory status epilepticus), such therapies need to be maintained for several weeks or even months. Even though the prognosis in new-onset refractory status epilepticus cases is often poor and many patients do not survive, meaningful recovery despite a prolonged course is still possible. This also appears to apply to the FIRES syndrome. Occasionally, inhalational anesthetics are useful. Probably isoflurane is preferable because halothane can increase intracranial pressure and enflurane can induce seizures. Other therapies have included ketamine, corticosteroids (e.g., for Rasmussen encephalitis, Hashimoto encephalopathy, or other autoimmune encephalitides), immunoglobulins, and plasma exchange (e.g., in Rasmussen or other autoimmune encephalitides), ketogenic diet (in patients with FIRES and Landau-Kleffner syndrome), vagus nerve stimulation in catastrophic epilepsy in infants, hypothermia, electroconvulsive therapy, magnetic transcranial stimulation, and surgical management with focal resection. Another potential therapy under study for convulsive status epilepticus is induction of acidosis (e.g., by hypercapnia), which could reduce neuronal excitability.

For nonconvulsive status epilepticus and epilepsia partialis continua, therapy needs to be tailored according to the clinical manifestations and often consists of trials of sequential oral or sometimes parenteral AEDs without resorting to barbiturate coma or overmedication that could result in respiratory compromise. The approach to complex partial status epilepticus is sometimes similar to the approach to convulsive status epilepticus and sometimes intermediate between the approach for epilepsia partialis and that for convulsive status, depending on severity. Long-term consequences after complex partial status epilepticus do occur, but the complications are often less severe than those after convulsive status epilepticus of similar duration. Prolonged nonconvulsive complex partial status epilepticus can last for as long as 12 wk, with patients manifesting psychotic symptoms and confusional states. These cases can be resistant to therapy. Despite that, patients still can have a full recovery. Some of these cases appear to improve with the use of steroids or IVIG, which are used if an autoimmune, parainfectious etiology is suspected.

Bibliography is available at Expert Consult.

593.9 Reflex Seizures (Stimulus Precipitated Seizures)

Robert M. Kliegman

Many patients with epilepsy can identify precipitating or provoking events that predispose them to having a seizure. Common events in patients with epilepsy include stress, lack of sleep, fever, or fatigue.

There is another group of patients who have seizures in response to a very specific, identifiable sensory stimulus or activity and are considered to have reflex seizures. Although no known "reflex" may be involved, more appropriate terms may be sensory precipitated or stimulus sensitive seizures (see Table 593-1). Stimuli may be external (light, patterns, music, brushing teeth) or internal (math, reading, thinking, self-induced). Reflex seizures may be generalized, partial, nonconvulsive, absence or myoclonic. One common pattern is photomyoclonic seizures characterized by forehead muscle twitching or repetitive eye opening or closing.

Photosensitive or pattern-induced seizures are a well-recognized disorder stimulated by bright or flashing lights (TV, video games, discotheques, concert light shows) or by patterns (TV, video games, lines on the road while traveling). Visual sensitivity may occur in 0.3-3% of the population, while photosensitive or pattern-induced seizures may occur in 1 in 4,000 people in the at-risk age group of 5-25 yr. When Japanese children were exposed to a Pokémon cartoon that induced seizures, only 24% had a history of spontaneous seizures. Patients tend to outgrow photosensitive or pattern-induced seizures in their 30s. Photoparoxysmal responses, with an abnormal EEG response to photic stimulation may be more common than photic-induced seizures. There are some photo-induced responses that do not demonstrate EEG abnormalities (nonconvulsive).

For patients with isolated photosensitive or pattern-induced seizures, avoidance or modification of stimuli is the initial approach. Such activities may include blue or polarized sunglasses, avoiding high-contrast flashing-light video games, avoiding discotheques, use a TV remote or watch TV in a well-lit room at a distance of >8 feet, and covering 1 eye when in a provocative situation.

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Table 593-19 Consensus Case Definition and Modified Consensus Case Definition for Nodding Syndrome—Uganda, 2012-2013*

TYPE OF CASE	CONSENSUS CASE DEFINITION	MODIFIED CONSENSUS CASE DEFINITION
Suspected case	Reported head nodding (repetitive involuntary drops of the head toward the chest on 2 or more occasions) in a previously normal person	Reported head nodding (repetitive involuntary drops of the head toward the chest on 2 or more occasions) in a previously normal person
Probable case	Suspected case of head nodding, with both major criteria: • Age of onset of nodding ranging from 3-18 yr • Frequency of nodding 5-20 per minute Plus at least 1 of the following minor criteria: • Other neurologic abnormalities (cognitive decline, school dropout because of cognitive or behavioral problems, other seizures or neurologic abnormalities) • Clustering in space or time with similar cases • Triggering by food or cold weather • Stunting or wasting • Delayed sexual or physical development • Psychiatric symptoms	Suspected case of head nodding, with 1 major criterion: • Age of onset of nodding ranging from 3-18 yr Plus at least 1 of the following minor criteria: • Other neurologic abnormalities (cognitive decline, school dropout because of cognitive or behavioral problems, other seizures or neurologic abnormalities) • Clustering in space or time with similar cases • Triggering by food or cold weather • Stunting or wasting • Psychiatric symptoms
Confirmed case	Probable case, with documented nodding episode • Observed and recorded by a trained healthcare worker, *or* • Videotaped nodding episode, *or* • Video/EEG/EMG documenting head nodding as atonic seizures	Probable case, with documented nodding episode • Observed and recorded by a trained healthcare worker, *or* • Videotaped nodding episode, *or* • Video/EEG/EMG documenting head nodding as atonic seizures

*The consensus case definition was drafted at the first International Scientific Meeting on Nodding Syndrome, held July 30–August 1, 2012, in Kampala, Uganda. Meeting report available at http://www.who.int/neglected_diseases/diseases/Nodding_syndrom_Kampala_Report_2012.pdf. The modified consensus case definition was developed during the March 2013 single-stage cluster survey conducted by Centers for Disease Control and Prevention (CDC) and the Ugandan Ministry of Health to assess prevalence of nodding syndrome in Uganda.

EEG, electroencephalographic; EMG, electromyographic.

From Iyengar PJ, Wamala J, Ratto J, et al: Prevalence of nodding syndrome–Uganda, 2012-2013. MMWR Morb Mortal Wkly Rep *63:603–606, 2014, Table 1.*

593.10 Nodding Syndrome

Robert M. Kliegman

Nodding syndrome appears to be an epidemic progressive epilepsy encephalopathy syndrome of unknown etiology seen predominantly in Uganda, Liberia, Tanzania, and the southern Sudan, with a prevalence of approximately 6.8 per 1,000 children. Age of onset is 6-13 yr. Nodding episodes are characterized by at least daily, rapid, paroxysmal forward head bobbling spells lasting several minutes; some patients are unresponsive whereas others may respond to commands or continue what they were doing before the episode. Children were previously healthy, although there may be a family history of seizures. In addition to episodes of nodding, there may be associated definable generalized tonic–clonic or absence seizures. Furthermore, patients go on to demonstrate severe and global cognitive impairment (see Table 593-19 for case definitions).

The EEG demonstrates a disorganized slow background and interictal generalized 2.5-3.0 Hz spike and slow waves. During a nodding episode, the EEG demonstrates generalized electrodecrement and paraspinal electromyography dropout suggestive of an atonic seizure. Cerebral spinal fluid analysis is usually negative, while the MRI shows cerebral and cerebellar atrophy.

Nodding episodes may be triggered during meals while eating hot foods or drinking cold liquids; cold environmental temperature may also trigger a nodding episode.

Treatment of seizures are indicated; however, the response to treatment is poor.

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Chapter 594

Conditions That Mimic Seizures

Mohamad A. Mikati and Makram M. Obeid

The misdiagnosis of epilepsy is estimated to be as high as 5-40%, implying that many patients may be subjected to unnecessary therapy and tests. Often all that is needed to differentiate nonepileptic paroxysmal disorders from epilepsy is a careful and detailed history in addition to a thorough exam; but sometimes an electroencephalogram (EEG) or more advanced testing may be necessary. The ready availability of video recording on mobile phones and other devices at home or at school can provide invaluable information. Nonepileptic paroxysmal disorders can be classified according to the age of presentation and the clinical manifestations: (1) syncope and other generalized paroxysms, (2) movement disorders and other abnormal movements and postures, (3) oculomotor abnormalities and visual hallucinations, and (4) sleep-related disorders (Table 594-1).

SYNCOPE AND OTHER GENERALIZED PAROXYSMS

Apnea

Apneic episodes in neonates are usually associated with bradycardia as is usually apnea resulting from brainstem compression. In contrast, apnea associated with seizures is usually accompanied by tachycardia. Of note, exceptions do occur as bradycardia can occur during epileptic seizures, and severe apnea of any cause can be followed by anoxic seizures.

Table 594-1 Conditions That Mimic Seizures According to Age of Presentation

AGE	SYNCOPE AND OTHER GENERALIZED PAROXYSMS	MOVEMENT DISORDERS AND OTHER ABNORMAL MOVEMENTS	OCULOMOTOR ABNORMALITIES	SLEEP DISORDERS
Neonate	Apnea Paroxysmal extreme pain disorder	Jitteriness Hyperekplexia Paroxysmal dystonic choreoathetosis	Paroxysmal tonic up gaze Alternating hemiplegia of childhood	Benign neonatal sleep myoclonus Sleep transition disorders
Infants	Reflex anoxic seizures Breath-holding spells Benign paroxysmal vertigo Paroxysmal extreme pain disorder	Jitteriness Sandifer Paroxysmal dystonic choreoathetosis Benign myoclonus of early infancy Pathologic startle Shuddering attacks Benign paroxysmal torticollis Psychologic disorders Alternating hemiplegia of childhood Jactatio capitis head banging Drug reactions	Paroxysmal tonic upgaze Oculomotor apraxia Spasmus nutans Opsoclonus myoclonus syndrome	Non-REM partial arousal disorders REM sleep disorders Narcolepsy Sleep transition disorders (somnambulism, somniloquy)
Children and adolescents	Benign paroxysmal vertigo Compulsive Valsalva Familial hemiplegic migraine Syncope (long QT, vasovagal, vagovagal, orthostatic, migraine-induced) Psychogenic seizures Transient global amnesia Hyperventilation spells	Tics Tremor Pathologic startle Paroxysmal dyskinesias Alternating hemiplegia of childhood Benign paroxysmal torticollis Episodic ataxia Psychologic disorders including factitious disorder imposed on another, malingering Masturbation Psychogenic seizures Cataplexy Jactatio capitis (head banging) Episodic rage Drug reactions	Daydreaming Drug reactions	Non-REM partial-arousal disorders REM sleep disorders Narcolepsy Sleep transition disorders (somnambulism, somniloquy) Sleep myoclonus Restless legs syndrome

REM, rapid eye movement.
From Obeid M, Mikati MA: Expanding spectrum of paroxysmal events in children: potential mimickers of epilepsy, Pediatr Neurol *37(5):309–316, 2007.*

Breath-Holding Spells

The term *breath-holding spells* is actually a misnomer, as these are not self-induced, but result from the immaturity of the autonomic system and occur in 2 different forms. The first type is the **pallid breath-holding spell**, which is caused by reflex vagal–cardiac bradycardia and asystole. The second type is the **cyanotic,** or **"blue," breath-holding spell**, which does not occur during inspiration, but results from prolonged expiratory apnea and intrapulmonary shunting. Episodes usually start with a cry (often, in the case of the pallid type, a "silent" cry with marked pallor), and progress to apnea and cyanosis. Spells usually begin between 6 and 18 mo of age. Syncope, tonic posturing, and even reflex anoxic seizures may follow the more-severe episodes, particularly in breath-holding spells of the pallid type. Injury, anger, and frustration, particularly with surprise, are common triggers. Education and reassurance of the parents is usually all that is needed, as these episodes are, as a rule, self-limited and are outgrown within a few years. However, treatment of coexisting iron deficiency is needed if it is present as the spells are made worse by iron-deficiency anemia. Anticholinergic drugs (e.g., atropine sulfate 0.01 mg/kg/24 hr in divided doses with a maximum daily dose of 0.4 mg), or antiepileptic drug therapy for coexisting anoxic seizures that are recurrent and not responding to other measures may, rarely, be needed. It is important also to educate parents on how to handle more-severe spells by first-aid measures, or even basic CPR when needed. In severe cases of asystole, a cardiac pacemaker implantation may be needed. All parents should be taught not to provide secondary gain when the episodes occur, because this can reinforce the episodes. Also, preparation for unpleasant experiences (such as receiving a shot) rather than surprising the child with them, can help limit the number of spells (see Chapter 69).

Compulsive Valsalva

In children with intellectual disability, including Rett syndrome, syncopal convulsions may be self-induced by maneuvers like Valsalva. In this case, true breath-holding occurs, and it usually lasts for approximately 10 sec during inspiration. Some clinicians advocate the use of naloxone in such cases.

Neurally Mediated Syncope

Syncope can present with drop attacks and can also lead to generalized convulsions, termed *anoxic seizures*. These convulsions, triggered by a sudden reduction of oxygen to the brain, are clinically similar to and can be misdiagnosed as generalized epileptic seizures. **Vasovagal (neurocardiogenic) syncope** is one of the most common mimickers of generalized tonic–clonic seizures and is usually triggered by dehydration, heat, standing for a long time without movement, hot showers, the sight of blood, pain, swallowing, vomiting, and or sudden stress. History is usually the clue to distinguishing syncope from epileptic seizures: There is initially pallor and sweating followed by blurring of vision, dizziness, nausea, and then gradual collapse with loss of consciousness. These symptoms are present in most, although not necessarily all patients with syncope and can sometimes be manifestations of complex partial seizures. Much more important is the fact that such prodromal features have an insidious onset and build up gradually, often arising from a state of malaise when they precede syncope. However when they precede an epileptic convulsion, such features usually start suddenly are short in duration, paroxysmal and are followed by other manifestations of complex partial seizures such as stereotyped automatisms. Abdominal pain, a common aura in temporal lobe epilepsy, occurs in vasovagal syncope, and can be a trigger or a consequence of that process (intestinal vagal discharge). Urinary incontinence and a brief period of convulsive jerks are not uncommon in vasovagal syncope. These occur with a frequency of 10% and 50%, respectively. Postictal confusion only rarely occurs, and the rule is the occurrence of only brief postictal tiredness with a subsequent remarkable ability to resume planned activities. Most children with vasovagal syncope have an affected 1st-degree relative; reports demonstrate

autosomal dominant inheritance at least in some families. The EEG is normal and the tilt test has been used for diagnostic purposes in selected cases. In most cases with typical history, this test is not needed. **Vagovagal syncope** can progress to convulsive seizure if the asystole is sufficiently prolonged. Sudden cold exposure to the face or to the body can also trigger vagal syncope. Syncope has been reported (rarely) to occur in association with cough, tight hair braiding, and hair combing. **Orthostatic hypotension and orthostatic intolerance** manifest symptoms that develop during upright standing and can be relieved by recumbence. **Postural tachycardia syndrome,** the pathophysiology of which presumably involves an excessive sympathetic discharge resulting in increased heart rate and vasoconstriction that can lead to decreased peripheral perfusion, is usually a disease of adolescent females that is characterized by upright syncope/near syncope, and tachycardia with normal or even increased blood pressure during the episode. Primary autonomic failure is rare in children, and familial dysautonomia is the only relatively common form. **Familial dysautonomia** is a disease common in Ashkenazi Jews and is characterized by absence of overflow emotional tears, depressed patellar reflexes, and lack of a flare reaction following intradermal histamine. **Dopamine β-hydroxylase deficiency** is a very rare cause of primary autonomic failure, and is characterized by a complicated perinatal course (hypotension, hypotonia, hypothermia), ptosis, highly arched palate, hyperflexible joints, impaired ejaculation, and nocturia. The tilt test causes a drop in both blood pressure and heart rate in patients with classic vasovagal syncope. It results in a blood pressure drop with minimal change in heart rate in autonomic failure, and in blood pressure drop and an increase in heart rate in postural tachycardia syndrome. Management of syncope centers on avoidance of precipitating factors (maintenance of hydration, avoidance of standing still, rising slowly from sitting, first-aid measures, raising of the legs, positioning) and treatment of any accompanying or underlying medical conditions (anemia, adrenal insufficiency, cardiac, etc.). In addition, **salt supplementation (2-4 g/day),** β-blockers (e.g., metoprolol at a starting dose of 1-2 mg/kg once per day up to a maximum of 6 mg/kg/day), or fluorohydrocortisone (0.05-0.1 mg/day) therapy may be needed in selected cases.

Cardiac Syncope

See Chapter 435.5.

Long QT syndromes (LQT) can cause life-threatening "pallid" or white syncope. Accompanying this are ventricular arrhythmias, usually torsades de pointes or even ventricular fibrillation. There are more than 10 types of prolonged QT syndrome. When accompanied by congenital deafness, it is part of the autosomal recessive Jervell and Lange-Nielson syndrome (type 1, LQT 1, associated with *KvLQT1* potassium channel mutation). The Romano-Ward syndrome is an autosomal dominant syndrome with incomplete penetrance that is characterized by episodes of lying still like a dead body for several seconds before the anoxic convulsive episode (LQT 2 associated with an *HERG* potassium channel mutation). LQT 3 is associated with an *SCN1A* sodium channel mutation, LQT 4 with ankyrin protein mutation, LQT 5 (milder form) with *KCNE1* mutations, LQT 6 with *KCNE2* potassium gene mutations, LQT 9 with caveolin sodium channel–related protein mutations, and LQT 10 with *SCN4B* sodium channel mutations. LQT 7 and LQT 8 are of particular interest because of associated clinical and neurologic manifestations. LQT 7 (Andersen-Tawil) syndrome is associated with periodic paralysis, skeletal developmental abnormalities, clinodactyly, low-set ears, and micrognathia (mutations in *KCNJ2* gene). LQT 8 or the Timothy syndrome (mutations in the calcium channel gene *CACNA1c*) manifests congenital heart disease, autism, syndactyly, and immune deficiency. All family members of an affected LQT syndrome individual should be investigated. Affected individuals need insertion of cardiac defibrillators, and their families should be taught CPR. As a rule, children with new-onset seizure disorder should get an electrocardiogram to rule out LQT syndrome masquerading as seizure disorder. Cardiac syncope is usually sudden without the gradual onset and the symptoms that accompany vagal syncope. Aortic stenosis can cause sudden syncope at the height of the exercise (usually hypertrophic), or directly at the end (usually valvular) and, if suspected, warrants an echocardiogram.

Other Causes of Syncope

Syncope that is not neurally mediated or cardiac in origin is caused by a decrease in blood volume, or a mechanical disruption of brain perfusion. Systemic diseases that lead to syncope by affecting blood volume (e.g., adrenal insufficiency) are usually first brought to medical attention by other accompanying signs and symptoms. In **stretch syncope**, which occurs mostly in adolescents while stretching the neck and the trunk backward and the arms outward, or during flexion of the neck, the presumed mechanism is mechanical disruption of brain perfusion caused by compression of the vertebral arteries. In some cases, this may be associated with an abnormally prolonged stylomastoid process compressing the carotids. If the latter condition is suspected, then neuroimaging (CT, MRI) is required for proper diagnosis of the stylomastoid anomaly.

Sporadic and Familial Hemiplegic Migraine

This is a rare type of migraine with a motor aura of weakness. Attacks begin as early as 5-7 yr of age. In a genetically susceptible person, attacks may be precipitated by head trauma, exertion, or emotional stress. The 3 genes so far identified are *SCN1A* (neuronal sodium channel subunit), *CACNA1*A (neuronal calcium channel subunit), and *ATP1A2* (sodium potassium adenosine triphosphatase subunit). However at least a quarter of the affected families, and most of the sporadic cases do not carry a mutations in these 3 genes. Headaches occur in all attacks in most patients. The presence of negative phenomena (e.g., numbness, visual scotomas) in addition to positive phenomena (pins and needles, flickering lights), and the progressive and successive occurrence of visual, sensory, motor, aphasic, and basilar signs and symptoms, in that order, help differentiate these attacks from epileptic seizures. Persistent cerebellar deficits (e.g., nystagmus, ataxia) may be present. Verapamil, acetazolamide, and lamotrigine have been successfully used to prevent attacks and verapamil and ketamine have been used for the acute episode, while ergot derivatives, nimodipine, Midrin (isometheptene mucate, dichloralphenazone, and paracetamol), and probably triptans and propranolol are to be avoided because of concerns of exacerbating the attacks. Interestingly, the co-occurrence of epileptic seizures has been reported in a minority of patient with hemiplegic migraine. It is important also to note that recurrent attacks akin to hemiplegic migraine can be symptomatic of Sturge-Weber syndrome or various metabolic diseases (e.g., mitochondrial encephalopathy with lactic acidosis and stroke-like episodes).

Benign Paroxysmal Vertigo of Childhood

This is a common migraine equivalent that consists of brief seconds-to-minutes episodes of vertigo that is often accompanied by postural imbalance and nystagmus. It is important to note that vertigo does not always refer to a spinning motion; it can also refer to a backward or forward motion (vertigo titubant) where children sometimes report that objects are moving toward them. The child appears frightened during the episode. Diaphoresis, nausea, vomiting, and, rarely, tinnitus may be present. Episodes usually remit by 6 yr of age. MRI and EEG are normal, but caloric testing, if done, can show abnormal vestibular function. Diphenhydramine, 5 mg/kg/day (maximum of 300 mg/day) may be used for a cluster of attacks. Preventive therapy with cyproheptadine may be rarely needed for frequent attacks.

Cyclic Vomiting Syndrome

This syndrome is another related periodic migraine variant that can respond to antimigraine or antiepileptic drugs. This and other periodic syndromes have been associated with mutations that also can cause hemiplegic migraine.

The "Alice in Wonderland" Syndrome

This is the episodic experience of transient distortions of body image or visual images that, most often, constitute a migraine equivalent. It also can be an epileptic phenomenon.

Migraine-Induced Syncope

Migraine, usually of the basilar variety, can trigger vasovagal syncope and, less commonly, epileptic seizures. Careful elicitation of the history of a migrainous prelude to the syncope helps in identifying these phenomena.

Psychologic Disorders

Psychogenic nonepileptic seizures are conversion reactions that are usually suspected clinically based on the characteristics of the spells (Table 594-2). The diagnosis can be confirmed by video EEG with capture of an episode to eliminate any residual doubts about their nature, as they can often occur in patients who also have epileptic seizures. They are best managed acutely by reassurance about their relatively benign nature and by a supportive attitude while at the same time avoiding positive reinforcement of the episodes. Psychiatric evaluation and follow-up are needed to uncover underlying psychopathology, and to establish continued support as psychogenic seizures can persist over long periods of time. **Malingering** and **factitious disorder imposed on another (formerly called Munchausen syndrome by proxy)** are often difficult to diagnose but an approach similar to that for psychogenic seizures, including video-EEG monitoring, is often helpful.

Paroxysmal Extreme Pain Disorder

Paroxysmal extreme pain disorder was previously called familial rectal pain syndrome. This syndrome (caused by the *SCN9A* sodium channel gene mutation) usually starts in the neonatal period or infancy and persists throughout life. Autonomic manifestations predominate initially, with skin flushing in all cases and harlequin color change and tonic attacks in most. Dramatic syncope with bradycardia and sometimes asystole are common. Later, the disorder is characterized by attacks of excruciating deep burning pain often in the rectal, ocular, or jaw areas, but also diffusely in some. Attacks are triggered by defecation, cold, wind, eating, and emotion. Carbamazepine is used, but the response is often incomplete. Gain-of-function Na(v)1.7 mutations are known to cause two neuropathic **pain** syndromes: inherited **erythromelalgia** and **paroxysmal extreme pain syndrome**. These syndromes are inherited in a dominant trait; they usually begin in childhood or infancy, and are characterized by attacks of severe neuropathic **pain** accompanied with autonomic symptoms. In addition, small fiber neuropathy and chronic nonparoxysmal **pain** have been described in patients harboring gain-of-function mutations in Na(v)1.7 channel. Loss-of-function mutations in Na(v)1.7 are extremely rare and invariably cause **congenital inability to perceive pain.**

Autonomic Storms (Diencephalic Seizures)

Spells of hyperhidrosis, changes in blood pressure, temperature and autonomic instability occur in patients with severe diffuse brain injury or localized hypothalamic injury and have been termed autonomic storms. The term *diencephalic seizures* is discouraged as these are not truly seizures. Therapy is difficult and has included, with mixed results, clonidine, anticonvulsants, cyproheptadine, morphine, and sympathectomy. Serotonin syndrome caused by antidepressants, stimulants, opioids, certain herbs like St. John's Wart and some other medications can produce similar symptoms, and if not recognized, can at times be fatal as can be the similar neuroleptic malignant syndrome caused by antipsychotic medications.

MOVEMENT DISORDERS AND OTHER ABNORMAL MOVEMENTS AND POSTURES

Neonatal Jitteriness and Clonus

Jitteriness consists of equal backward and forward movements of limbs, occurring spontaneously, or triggered by touch or loud sounds. Movement suppression by stimulus removal or by relaxing the affected limbs, the lack of autonomic symptoms, and the clear difference from the 2-phased (fast contraction, slow relaxation) clonic activity and the very quick myoclonic jerks, point to a nonepileptic event.

Table 594-2 Comparison of Generalized Seizures and Some Disorders That Can Mimic Them

CONDITION	PRECIPITANTS (MAY NOT APPLY TO ALL PATIENTS)	PRODROME	ICTAL SYMPTOMS	POSTICTAL SYMPTOMS
Generalized seizures	Sleep deprivation, television, video games, visual patterns, and photic stimulation	Rarely irritability or nonspecific behavioral changes	Usually 2-3 min Consciousness might be preserved if atonic, or in some, tonic seizures Synchronous bilateral movements Tongue biting	Delayed recovery with postictal depression, incontinence (may be ictal also)
Syncope: vasovagal Syncope with reflex anoxic seizures Syncope: trigeminal vagal Syncope: orthostatic	Fatigue, emotional stress, dehydration, vomiting, choking, swallowing Minor bump to head, upsetting surprises Cold water on face Standing up, bathing, awakening	Blurring of vision, tinnitus, dizziness Crying in breath-holding spells	Loss of consciousness for seconds, pallor and rarely reflex anoxic seizures	Rapid recovery with no postictal depression
Hyperekplexia	Auditory and tactile stimuli	None	Tonic stiffening, cyanosis if severe, nonfatigable nose-tap–induced startles	Depending on severity, may have postictal depression
Cardiac	Exercise	None	Loss of consciousness, often only few seconds, pallor	Rarely
Psychogenic	Suggestion, stress	None	Eyes closed Asynchronous flailing limb movements that vary between attacks No injury, closed eyelids May respond to suggestion during "loss of consciousness" Usually longer than 2-3 min	No postictal depression

Adapted from Obeid M, Mikati MA: Expanding spectrum of paroxysmal events in children: potential mimickers of epilepsy, Pediatr Neurol *37(5):309–316, 2007.*

Hypocalcemia, hypoglycemia, drug withdrawal, and hypoxic–ischemic encephalopathy are possible etiologies. **Clonus** as a result of corticospinal tract injury usually occurs in later infancy and childhood and can be stopped by change in position.

Hyperekplexia (Stiff Baby Syndrome) and Pathologic Startles

Hyperekplexia is a rare, sporadic or dominantly inherited disorder with neonatal onset of life-threatening episodes of tonic stiffening that precipitate apnea and convulsive hypoxic seizures.

Stiffness may result in difficulty in swallowing, choking spells, hip dislocations, umbilical or inguinal hernias, and delayed motor development. Stiffness in the neonatal form improves by 1 yr of age and may disappear during sleep.

The genetic cause is a defect in the α or β subunits of the strychnine-sensitive glycine receptors. It is characterized by a triad of generalized stiffness, nocturnal myoclonus, and later a pathologic startle reflex. A specific diagnostic sign can be elicited by tapping the nose, which produces a nonfatigable startle reflex with head retraction. Bathing, sudden awakening, and auditory or tactile stimuli can induce attacks. The differential diagnosis includes congenital stiff person syndrome, startle epilepsy, myoclonic seizures, neonatal tetany, phenothiazine toxicity, and Schwartz-Jampel syndrome. Making a prompt diagnosis is extremely important to initiate treatment with clonazepam as hypoxic brain injury can result from a prolonged episode. Other antiepileptics have also been effective. Repeatedly flexing the baby at the neck and hips (the Vigevano maneuver) can abort the episodes.

In other children after brain injury, and in many patients with cerebral palsy, an exaggerated startle reflex can occur. This is more common than hyperekplexia. In Tay-Sachs disease and similar gangliosidoses, exaggerated startle to sound occurs and has been, inappropriately, interpreted as hyperacusis.

Benign Paroxysmal Torticollis of Infancy

This condition typically presents as morning episodes of painless retrocollis, and later, torticollis, often triggered by changes in posture. Attacks may start with abnormal ocular movements, and progress to stillness in an abnormal posture. This usually lasts for minutes or hours and, at times, days. Neurologic exam between attacks, EEG, and neuroimaging are normal. It affects girls more than boys (3:1), often begins before 3 mo of age, and spontaneously remits before the age of 5 yr. Medical therapy is not needed. It is considered to be a migraine equivalent and cosegregates with migraine in families.

Sandifer Syndrome

Gastroesophageal reflux in infants may cause paroxysmal episodes of generalized stiffening and opisthotonic posturing that may be accompanied by apnea, staring, and minimal jerking of the extremities. Episodes often occur 30 min after a feed. In older children, this syndrome manifests with episodic dystonic or dyskinetic movements consisting of latero-, retro-, or torticollis, the exact pathophysiology of which remains elusive.

Alternating Hemiplegia of Childhood

This is a rare, often severe, disorder that consists of attacks of flaccid hemiplegia affecting 1 or both sides lasting minutes to days, starting in the 1st 18 mo of life. Earlier manifestations include paroxysmal nystagmus, which is often monocular and ipsilateral to the hemiplegia. Dystonic and tonic spells often occur and can be confused with seizures and the hemiplegia with Todd paralysis. Attacks can be triggered by bathing, cold, fatigue, hyperthermia, and emotional stress, and they remit during sleep and for about 15 minutes or so after waking up. Most cases are caused by mutations in the *ATP1A3* gene while, rarely, a similar clinical picture can occur as a result of mutations in *ATP1A2* or in the glucose transporter 1 *(GLUT1/SLC2AI)* gene mutations. Flunarizine 2.5-15 mg/day reduces the frequency of the attacks. Most children ultimately develop ataxia, developmental delay, and persistent choreoathetosis.

Paroxysmal Dyskinesias and Other Movement Disorders

These disorders are characterized by sudden attacks that consist of choreic, dystonic, ballistic, or mixed movements (Table 594-3). A sensation of fatigue or weakness confined to 1 side may herald an attack. Consciousness is preserved and patients may be able perform a motor activity, like walking, despite the attack. The variability in the pattern of severity and localization between different attacks may also help in differentiating them from seizures. The frequency of attacks increases in adolescence, and steadily decreases in the 3rd decade. Neurologic exam between attacks, EEG, laboratory investigations, and imaging studies are normal. These dyskinesias often respond to phenytoin, carbamazepine, clonazepam, or to antidopaminergic drugs such as haloperidol. **Drug reactions** can result in abnormal movements such as **oculogyric crisis** with many antiemetics, choreoathetosis with phenytoin, dystonia and facial dyskinesias with antidopaminergic drugs, and tics with carbamazepine. Strokes, focal brain lesions, connective tissue disorders (e.g., systemic lupus erythematosus), vasculitis, or metabolic and genetic disorders can also cause movement disorders. Mutations of the glucose transporter 1 *(GLUT1/SLC2AI)* gene have been described in patients with **exercise-induced dyskinesia**.

Motor Tics

These are movements that are under partial control, and are associated with an urge to do them and with a subsequent relief. They are usually exacerbated by emotions, and often change in character over time. In patients with tics who have Tourette syndrome, there is often a family history of tics and/or obsessive compulsive disorder or personality traits.

Episodic Ataxias

Episodic ataxia encompasses 7 clinically and genetically heterogeneous syndromes, only 2 of which (types 1 and 2) have been described in a large number of families. Type 1 is caused by mutations in the voltage-gated potassium channel Kv1.1. It consists of brief episodes (seconds to minutes) of cerebellar ataxia, and occasional partial seizures with interictal myokymia as a main diagnostic feature. Type 2 is characterized by longer attacks (minutes to hours) and interictal cerebellar signs. It is caused by mutations in the voltage-gated calcium channel gene *CACNA1A*. This type is more responsive than type 1 to acetazolamide that reduces the frequency and severity of attacks, but not the interictal signs and symptoms.

Benign Myoclonus of Early Infancy, Shuddering Attacks, and Chin Trembling

Benign myoclonus consists of myoclonic jerks of the extremities in wakefulness and sometimes also in sleep. It has been suggested by some that these attacks are in the same spectrum as shuddering attacks. **Shuddering attacks** are characterized by rapid tremor of the head, shoulder, and trunk, lasting a few seconds, often associated with eating, and recurring many times a day. Others have considered shuddering as an early manifestation of essential tremor as family history of essential tremor is often present. The clinical events in either of these can be mistaken for infantile spasms, but ictal and interictal EEG, MRI, and development are normal. Spontaneous remission occurs in both usually within a few months. **Hereditary chin trembling** at a frequency faster than 3 Hz starting shortly after birth and precipitated by stress has been described in several families.

A novel type of nonepileptic attack with infantile onset characterized in 3 patients as clusters of repeated head drops, mimicking epileptic negative myoclonus of the neck, accompanied by crying. The episodes occurred for 5 or 6 mo and disappeared by the end of the 1st yr. Language and cognition were normal This is a different form of myoclonic activity that may complicate the diagnosis of infantile spasms and West syndrome; thorough EEG investigation is needed in such cases.

Brainstem Dysfunction

Decorticate or decerebrate posturing that mimics epileptic tonic seizures may be secondary to decompensated hydrocephalus,

Table 594-3 Differential Diagnoses of Various Types of Paroxysmal Dyskinesia

Features	PKD	PNKD MR1+	PNKD MR1–	PED	PHD
Nomenclature	PKC	PDC, FPC	PDC, FPC	PEDt	ADNFLE
Inheritance	AD–16q	AD–2q35	AD–2q13	AD/AR	AD–20q13, 15q24, 1q21, 8p21
Age at onset (yr)	1-20	<1-12	1-23	Usually childhood	Usually childhood
Triggers	Sudden whole-body movement	Coffee, alcohol, stress	Exercise	After 10-15 minutes of exercise	Sleep
Clinical features	Chorea, athetosis, ballismus, dystonia	Chorea, athetosis, dystonia, ballismus	Chorea, athetosis, dystonia, ballismus	Mainly leg dystonia	Wakes up with dystonic posture
Usual duration	<1-5 min	10 min to 1 hr	10 min to 2-3 hr	10-15 min	<1 min
Frequency	1-20/day	1/week	1/week	Unclear	Several/night
Associations	Infantile seizures, migraine, writer's cramp, essential tremor	Migraine	Epilepsy	RE-PED-WC	
Medication	Carbamazepine Phenytoin Oxcarbazepine	Clonazepam Benzodiazepine	Clonazepam Benzodiazepine	Acetazolamide L-DOPA	Carbamazepine Oxcarbazepine
Prognosis	Excellent	Excellent, worse than PKD	Minimally worse than PNKD MR1+	Poor medication response	Excellent

AD, autosomal-dominant; ADNFLE, autosomal-dominant nocturnal frontal lobe epilepsy; AR, autosomal-recessive; FPC, familial paroxysmal choreoathetosis; MR1+, myofibrillogenesis regulator 1-positive; MR1–, myofibrillogenesis regulator 1-negative; PDC, paroxysmal dystonic choreoathetosis; PED, paroxysmal exercise-induced dyskinesia; PEDt, paroxysmal exercise-induced dystonia; PHD, paroxysmal hypnogenic dyskinesia; PKC, paroxysmal kinesigenic choreoathetosis; PKD, paroxysmal kinesigenic dyskinesia; PNKD, paroxysmal nonkinesigenic dyskinesia; RE-PED-WC, rolandic epilepsy–paroxysmal exercise-induced dystonia–writer's cramp.

From Friedman NR, Ghosh D, Moodley M: Syncope and paroxysmal disorders other than epilepsy. In Swaiman KF, Ashwal S, Ferriero DM, Schor NF, editors: Swaiman's pediatric neurology, *ed 5, Philadelphia, 2012, WB Saunders, Table 65-1.*

hemorrhage, or other causes of sudden rises in intracranial pressure that lead to brainstem dysfunction. In addition, crowding of the posterior fossa and near herniation, the so-called cerebellar fits can also lead to abnormal extensor posturing, drop attacks, and varying degrees of altered consciousness and respiratory compromise. Historically secondary to undiagnosed posterior fossa tumors in the preneuroimaging era, "cerebellar fits" mostly occur in the context of Chiari I malformations.

Psychologic Disorders

Many psychologic disorders can be mistaken for epileptic seizures. Pleasurable behavior similar to masturbation may occur from infancy onward, and may consist of rhythmical rocking movement in a sitting or lying position, or rhythmic hip flexion and adduction. **Masturbation** may occur in girls 2-3 yr of age and is often associated with perspiration, irregular breathing, and grunting, but no loss of consciousness. Occasionally this is associated with child abuse or with other psychopathology. **Stereotypies,** or repetitive movements that are more complex than tics and do not change and wax and wane like tics (e.g., head banging, head rolling, body rocking, and hand flapping), usually occur in neurologically impaired children. **A mannerism** is a pattern of socially acceptable, situational behavior that is seen in particular situations such as gesturing when talking. Mannerisms should not be confused with stereotypies which are generally pervasive over almost every other activity such as head-shaking or hand-flapping in multiple situations. Stereotypies, unlike mannerisms, increase with stress. Unlike tics and mannerisms, stereotypies usually start before the age of 3 yr, involve more body parts, are more rhythmic and most importantly occur with engrossment with an object or activity of interest and do not have a premonitory urge that increases with attempts to suppress them as children rarely try to suppress stereotypies. **Panic and anxiety attacks** have been described in children; at times, these may be clinically indistinguishable from actual epileptic seizures, and therefore may necessitate video-EEG monitoring. **Rage attacks** usually occur in patients with personality disorder and are usually not seizures although rare cases of partial seizures can manifest as rage attacks. **Hyperventilation spells** can be precipitated by anxiety and are associated with dizziness, tingling, and, at times, carpopedal spasm. **Transient global amnesia** consists of isolated short-term memory loss for minutes to hours that occurs mostly in the elderly. The etiology can be epileptic, vascular, or drug related.

OCULOMOTOR ABNORMALITIES AND VISUAL HALLUCINATIONS

Paroxysmal Tonic Upgaze of Childhood

This usually starts before 3 mo of age, and consists of protracted attacks (hours to days) of continuous or episodic upward gaze deviation, during which horizontal eye movements are preserved. A downbeating nystagmus occurs on downward gaze. Symptoms are reduced or relieved by sleep, exacerbated by fatigue and infections, and spontaneously remit after a few years. Up to 50% of patients may have psychomotor and language delay. Imaging, laboratory, and neuropsychologic examinations are usually nonrevealing. Therapy with low-dose levodopa/carbidopa may be helpful.

Oculomotor Apraxia and Saccadic Intrusions

In oculomotor apraxia saccadic eye movements are impaired. Sudden head turns compensating for lateral gaze impairment mimic seizures. This disorder may be idiopathic (Cogan oculomotor apraxia) or may occur in the context of ataxia telangiectasia or lysosomal storage diseases. Genetic defects in DNA repair mechanisms have been implicated in at least 4 spinocerebellar ataxia disorders that are accompanied by oculomotor apraxia. A selective loss of Purkinje cells required to suppress omnipause neurons and initiate saccadic eye movement is believed to occur in those disorders. Saccadic intrusions are involuntary sudden conjugate eye movements away from the desired eye position. These are not necessarily pathologic.

Spasmus Nutans

This disorder presents with a triad of nystagmus, head tilt, and head nodding. If diurnal fluctuation occurs, symptoms may look like epileptic seizures. Brain MRI should be performed, as the triad has been

associated with masses in the optic chiasm and third ventricle. Retinal disease should also be ruled out. In the absence of these associations, remission occurs before 5 yr of age.

Opsoclonus Myoclonus Syndrome

The so-called dancing eyes refers to continuous, random, irregular, and conjugate eye movements that may fluctuate in intensity. They usually accompany myoclonus and ataxia ("dancing feet"). Encephalitis and neuroblastoma are possible causes. Therapy is by treating the underlying etiology, but adrenocorticotropic hormone (ACTH), corticosteroids, and clonazepam may be needed. Rituximab has been studied and preliminary trials suggest it may be effective as well.

Daydreaming and Behavioral Staring

Staring may be a manifestation of absence seizures, which should be differentiated from daydreaming, behavioral staring because of fatigue, and inattention. Episodes of staring only in certain settings (e.g., school) are unlikely to be seizures. In addition, responsiveness to stimulation such as touch and lack of interruption of playing activity characterizes nonepileptic staring.

Visual Hallucinations

Visual perceptions in the absence of external stimuli, or visual hallucinations, are usually accompanied by other neurologic signs and symptoms when they occur in the context of seizures. An exception is occipital seizures, which can manifest with isolated and unformed visual hallucinations and may be accompanied by headache and nausea, making them difficult to differentiate from migraine. However, occipital seizures are characterized by colorful, shapes, circles and spots lasting seconds and confined to 1 hemifield, while migrainous auras usually last minutes, and consist of black-and-white lines, scotomas, and or fortification spectra that start in the center of vision. Hallucinations can also be secondary to drug exposure, midbrain lesions, and psychiatric illnesses. In addition, retinal-associated hallucinations can occur in the form of flashes of light in the context of inflammatory etiologies, trauma, or optic nerve edema.

SLEEP DISORDERS

Paroxysmal nonepileptic sleep events are more common in epileptic patients than in the general population, which makes their diagnosis difficult. Semiology, timing of events, and if needed video-EEG and polysomnography help in distinguishing epileptic from nonepileptic events. Parasomnias typically occur less than once or twice a night; more frequent episodes suggest epileptic seizures. Of note, the EEG pattern of frontal lobe epileptic seizures may be similar to the one seen in a normal arousals, making their diagnosis challenging, especially that they have nonspecific hypermotor manifestations such as thrashing, body rocking, kicking, boxing, pedaling, bending, running, and various vocalizations. The diagnosis of such epileptic seizures is made on the basis of highly stereotyped events arising several times a night from nonrapid eye movement sleep.

Benign Sleep Myoclonus and Neonatal Sleep Myoclonus

Neonatal sleep myoclonus consists of repetitive, usually bilateral rhythmic jerks involving the upper and lower limbs during nonrapid eye movement sleep, sometimes mimicking clonic seizures. A slow (1 Hz) rocking of the infant in a head-to-toe direction is a specific diagnostic test that may reproduce the myoclonus. The lack of autonomic changes, occurrence only in sleep, and suppression by awakenings may help in differentiating these events from epileptic seizures. Remission is spontaneous at 2-3 mo of age. In older children and adults, sleep myoclonus consists of random myoclonic jerks of the limbs.

Nonrapid Eye Movement Partial Arousal Disorders

Brief **nocturnal confusional arousals** occurring 1-2 hr after sleep in stage 4 sleep are normal in children. Such episodes can vary from chewing, sitting up, and mumbling to agitated sleep walking, and usually last for 10-15 min. **Night terrors** similarly occur a few hours after going to sleep in stage 3 or 4 of sleep, most often at 2-7 yr of age and more so in boys. The child screams; appears terrified; has dilated pupils, tachycardia, tachypnea, unresponsiveness, agitation, and thrashing that increase with attempts to be consoled; is difficult to arouse; and may have little or no vocalization. In older children with persistent night terrors, an underlying psychologic etiology may be present. Diagnosis is based on the history. However, rarely, video EEG monitoring may be needed. At times, the use of bedtime diazepam (0.2-0.3 mg/kg) or clonazepam (0.01 mg/kg) may help control the problem while psychologic factors are being investigated. **Restless leg syndrome** can cause painful leg dysesthesias that cause nocturnal arousals and insomnia. It can be either genetic or associated with iron deficiency, systemic illness, or some drugs. Therapy depends upon treating the underlying cause and, if needed, on dopaminergic drugs such as levodopa/carbidopa, or antiepileptics like gabapentin.

Rapid Eye Movement Sleep Disorders

Nightmares and **sleep paralysis** are common disorders. Unlike night terrors, nightmares tend to occur later during the night and the child has a memory of the event.

Sleep Transition Disorders

Nocturnal head banging **(jactatio capitis nocturna)**, rolling, or body rocking often occurs in infants and toddlers as they are trying to fall asleep. These usually remit spontaneously by 5 yr of age. No specific therapy is needed.

Narcolepsy-Cataplexy Syndrome

Narcolepsy is characterized by excessive daytime sleepiness, cataplexy, sleep paralysis, hypnogogic hallucinations, and disturbed nighttime sleep. The persistence of rapid eye movement sleep atonia upon awakening or its intrusion during wakefulness lead to sleep paralysis or cataplexy, respectively. Loss of tone in cataplexy occurs in response to strong emotions, and spreads from the face downwards leading to a fall in a series of stages rather than a sudden one. Consciousness is maintained in cataplexy. A selective loss of hypocretin-secreting neurons in the hypothalamus is at the origin of this disorder. The fact that DQB1*0602 is a predisposing HLA allele identified in 85-95% of patients with narcolepsy-cataplexy suggests an autoimmune-mediated neuronal loss. Diagnosis is based on the **multiple sleep latency test**, and therapy relies on scheduled naps, amphetamines, methylphenidate, tricyclic antidepressants, and counseling about precautions in work and driving.

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Chapter 595

Headaches

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Headache is a common complaint in children and adolescents. Headaches can be a primary problem or occur as a symptom of another disorder, representing a secondary problem. Recognizing this difference is essential for choosing the appropriate evaluation and treatment to ensure successful management of the headache. Primary headaches are most often recurrent, episodic headaches and for most children are sporadic in their presentation.

The most common forms of primary headache of childhood are migraine and tension-type headaches (Table 595-1). Other forms of

Table 595-1 Classification of Headaches (ICHD-3 Beta Code Diagnosis)

MIGRAINE
Migraine with or without aura
Migraine with typical aura (with or without headache)
Migraine with brainstem aura
Hemiplegic migraine (sporadic or familial types 1, 2, 3, or other genetic loci)
Retinal migraine
Chronic migraine
Complications of Migraine
Status migrainosus
Persistent aura without infarction
Migrainous infarction
Migraine aura-triggered seizure
Episodic Syndromes That May Be Associated with Migraine
Recurrent gastrointestinal disturbance
Cyclical vomiting syndrome
Abdominal migraine
Benign paroxysmal vertigo
Benign paroxysmal torticollis

TENSION-TYPE HEADACHE (TTH)
Infrequent episodic tension-type headache associated with or without pericranial tenderness
Frequent episodic tension-type headache associated with or without pericranial tenderness
Chronic tension-type headache associated with or without pericranial tenderness
Probable tension-type headaches

TRIGEMINAL AUTONOMIC CEPHALALGIAS (TACS)
Cluster headache (episodic or cluster)
Paroxysmal hemicrania (episodic or cluster)
Short-lasting unilateral neuralgiform headache attacks with or without conjunctival injection and tearing (SUNCT)
Episodic SUNCT
Chronic SUNCT
Short-lasting unilateral neuralgiform headache attacks with or without cranial autonomic symptoms (SUNA)
Episodic SUNA
Chronic SUNA
Hemicrania continua
Probable trigeminal autonomic cephalalgias

OTHER PRIMARY HEADACHE DISORDERS
Primary cough headache
Primary exercise headache
Primary headache associated with sexual activity
Primary thunderclap headache
Cold-stimulus headache (external application, ingestion, or inhalation)
External-pressure headache
External-compression headache
External-traction headache
Primary stabbing headache
Nummular headache
Hypnic headache
New daily persistent headache (NDPH)

HEADACHE ATTRIBUTED TO TRAUMA OR INJURY TO THE HEAD AND/OR NECK
Acute headache attributed to traumatic (mild, moderate, or severe) injury to the head
Persistent headache attributed to traumatic (mild, moderate, or severe) injury to the head
Acute or persistent headache attributed to whiplash
Acute or persistent headache attributed to craniotomy

HEADACHE ATTRIBUTED TO CRANIAL OR CERVICAL VASCULAR DISORDER
Headache attributed to ischemic stroke or transient ischemic attack
Headache attributed to nontraumatic intracerebral hemorrhage
Headache attributed to nontraumatic subarachnoid hemorrhage (SAH)
Headache attributed to nontraumatic acute subdural hemorrhage (ASDH)
Headache attributed to unruptured vascular malformation
Headache attributed to unruptured saccular aneurysm
Headache attributed to arteriovenous malformation (AVM)
Headache attributed to dural arteriovenous fistula (DAVF)
Headache attributed to cavernous angioma
Headache attributed to encephalotrigeminal or leptomeningeal angiomatosis (Sturge-Weber syndrome)
Headache attributed to arteritis
Headache attributed to giant cell arteritis (GCA)
Headache attributed to primary angiitis of the central nervous system (PACNS)
Headache attributed to secondary angiitis of the central nervous system (SACNS)
Headache attributed to cervical carotid or vertebral artery disorder
Headache or facial or neck pain attributed to cervical carotid or vertebral artery dissection
Post-endarterectomy headache
Headache attributed to carotid or vertebral angioplasty
Headache attributed to cerebral venous thrombosis (CVT)
Headache attributed to other acute intracranial arterial disorder
Headache attributed to an intracranial endovascular procedure
Angiography headache
Headache attributed to reversible cerebral vasoconstriction syndrome (RCVS)
Headache attributed to intracranial arterial dissection
Headache attributed to genetic vasculopathy
Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL)
Mitochondrial encephalopathy, lactic acidosis and stroke-like episodes (MELAS)
Headache attributed to another genetic vasculopathy
Headache attributed to pituitary apoplexy

HEADACHE ATTRIBUTED TO NONVASCULAR INTRACRANIAL DISORDER
Headache attributed to increased cerebrospinal fluid pressure
Headache attributed to idiopathic intracranial hypertension (IIH)
Headache attributed to intracranial hypertension secondary to metabolic, toxic, or hormonal causes
Headache attributed to intracranial hypertension secondary to hydrocephalus
Headache attributed to low cerebrospinal fluid pressure
Postdural puncture headache
Cerebrospinal fluid fistula headache
Headache attributed to spontaneous intracranial hypotension
Headache attributed to noninfectious inflammatory disease
Headache attributed to neurosarcoidosis
Headache attributed to aseptic (noninfectious) meningitis
Headache attributed to other noninfectious inflammatory disease
Headache attributed to lymphocytic hypophysitis
Syndrome of transient headache and neurological deficits with cerebrospinal fluid lymphocytosis (HaNDL)
Headache attributed to intracranial neoplasm
Headache attributed to colloid cyst of the third ventricle
Headache attributed to carcinomatous meningitis
Headache attributed to hypothalamic or pituitary hyper- or hyposecretion
Headache attributed to intrathecal injection
Headache attributed to epileptic seizure
Hemicrania epileptica
Postictal headache
Headache attributed to Chiari malformation type I (CM1)
Headache attributed to other nonvascular intracranial disorder

Table 595-1 Classification of Headaches (ICHD-3 Beta Code Diagnosis)—cont'd

HEADACHE ATTRIBUTED TO A SUBSTANCE OR ITS WITHDRAWAL
Headache attributed to use of or exposure to a substance
Nitric oxide (NO) donor-induced headache
Phosphodiesterase (PDE) inhibitor-induced headache
Carbon monoxide (CO)-induced headache
Alcohol-induced headache
Monosodium glutamate (MSG)-induced headache
Cocaine-induced headache
Histamine-induced headache
Calcitonin gene-related peptide (CGRP)-induced headache
Headache attributed to exogenous acute pressor agent
Headache attributed to occasional or long-term use of nonheadache medication
Headache attributed to exogenous hormone
Medication-Overuse Headache (MOH)
Ergotamine-overuse headache
Triptan-overuse headache
Simple analgesic-overuse headache
Paracetamol (acetaminophen)-overuse headache
Acetylsalicylic acid-overuse headache
Other non-steroidal antiinflammatory drug (NSAID)-overuse headache
Opioid-overuse headache
Combination analgesic-overuse headache
Headache Attributed to Substance Withdrawal
Caffeine-withdrawal headache
Opioid-withdrawal headache
Estrogen-withdrawal headache

HEADACHE ATTRIBUTED TO INFECTION
Acute or chronic headache attributed to bacterial meningitis or meningoencephalitis
Persistent headache attributed to past bacterial meningitis or meningoencephalitis
Acute or chronic headache attributed to intracranial fungal or other parasitic infection
Headache attributed to brain abscess
Headache attributed to subdural empyema
Headache attributed to systemic infection (acute or chronic)

HEADACHE ATTRIBUTED TO DISORDER OF HOMEOSTASIS
Headache attributed to hypoxia and/or hypercapnia
High-altitude headache
Headache attributed to airplane travel
Diving headache
Sleep apnea headache
Dialysis headache
Headache attributed to arterial hypertension
Headache attributed to pheochromocytoma
Headache attributed to hypertensive crisis with or without hypertensive encephalopathy
Headache attributed to preeclampsia or eclampsia
Headache attributed to autonomic dysreflexia
Headache attributed to hypothyroidism
Headache attributed to fasting
Cardiac cephalalgia
Headache attributed to other disorder of homoeostasis

HEADACHE OR FACIAL PAIN ATTRIBUTED TO DISORDER OF THE CRANIUM, NECK, EYES, EARS, NOSE, SINUSES, TEETH, MOUTH, OR OTHER FACIAL OR CERVICAL STRUCTURE
Headache attributed to disorder of cranial bone
Headache attributed to retropharyngeal tendonitis
Headache attributed to craniocervical dystonia
Headache attributed to acute glaucoma
Headache attributed to refractive error
Headache attributed to heterophoria or heterotropia (latent or persistent squint)
Headache attributed to ocular inflammatory disorder
Headache attributed to trachelitis
Headache attributed to disorder of the ears
Headache attributed to acute or chronic or recurring rhinosinusitis
Headache attributed to temporomandibular disorder (TMD)
Head or facial pain attributed to inflammation of the stylohyoid ligament
Headache or facial pain attributed to other disorder of cranium, neck, eyes, ears, nose, sinuses, teeth, mouth, or other facial or cervical structure

HEADACHE ATTRIBUTED TO PSYCHIATRIC DISORDER
Headache attributed to somatization disorder
Headache attributed to psychotic disorder

PAINFUL CRANIAL NEUROPATHIES AND OTHER FACIAL PAINS
Classical trigeminal neuralgia
Classical trigeminal neuralgia, purely paroxysmal or with concomitant persistent facial pain
Painful trigeminal neuropathy
Painful trigeminal neuropathy attributed to acute herpes zoster
Postherpetic trigeminal neuropathy
Painful posttraumatic trigeminal neuropathy
Painful trigeminal neuropathy attributed to multiple sclerosis (MS) plaque
Painful trigeminal neuropathy attributed to space-occupying lesion
Painful trigeminal neuropathy attributed to other disorder
Glossopharyngeal neuralgia
Classical nervus intermedius (facial nerve) neuralgia
Nervus intermedius neuropathy attributed to herpes zoster
Occipital neuralgia
Optic neuritis
Headache attributed to ischemic ocular motor nerve palsy
Tolosa-Hunt syndrome
Paratrigeminal oculosympathetic (Raeder) syndrome
Recurrent painful ophthalmoplegic neuropathy
Burning mouth syndrome (BMS)
Persistent idiopathic facial pain (PIFP)
Central neuropathic pain
Central neuropathic pain attributed to multiple sclerosis (MS)
Central post-stroke pain (CPSP)

From Headache Classification Committee on the International Headache Society (IHS): The International Classification of Headache Disorders, ed 3 (beta version). Cephalalgia *33(9):629–808, 2013.*

primary headache, including the trigeminal autonomic cephalalgias, occur much less commonly. Primary headache can progress to very frequent or even daily headaches with chronic migraine and chronic tension-type headaches being increasingly recognized. These more frequent headaches can have an enormous impact on the life of the child and adolescent, as reflected in school absences and decreased school performance, social withdrawal, and changes in family interactions. To reduce this impact, a treatment strategy that incorporates acute treatments, preventive treatments, and biobehavioral therapies must be implemented.

Secondary headache involves headaches that are a symptom of an underlying illness (see Table 595-1). The underlying illness should be clearly present as a direct cause of the headaches. This is often difficult when 2 or more common conditions occur in close temporal association. This frequently leads to the misdiagnosis of a primary headache as a secondary headache. This is, for example, the case when migraine is misdiagnosed as a sinus headache. In general, the key components of a secondary headache are the likely direct cause-and-effect relationship between the headache and the precipitating condition, and the lower likelihood in a specific patient and circumstance of the headaches being the result of a recurrent headache disorder. In addition, once the underlying suspected cause is treated, the secondary headache should resolve. If this does not occur, either the diagnosis must be reevaluated or the effectiveness of the treatment reassessed. *One key clue that additional investigation is warranted is the presence of an abnormal neurologic examination or unusual neurologic symptoms.*

595.1 Migraine

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Migraine is the most frequent type of recurrent headache that is brought to the attention of parents and primary care providers, but it remains underrecognized and undertreated, particularly in children. Migraine is characterized by episodic attacks that may be moderate to severe in intensity, focal in location on the head, have a throbbing quality, and may be associated with nausea, vomiting, light sensitivity, and sound sensitivity. Compared to adults, pediatric migraine is shorter in duration and has a bilateral, often bifrontal, location. Migraine can also be associated with an aura that may be typical (visual, sensory, or dysphasic) or atypical (i.e., hemiplegic, "Alice in Wonderland" syndrome) (Tables 595-2 to 595-6). In addition, a number of migraine variants have been described and, in children, include abdominal related symptoms without headache, and components of the painless periodic syndromes of childhood (see Table 595-1). Treatment of migraine requires the incorporation of an acute treatment plan, a preventive treatment plan if the migraine occurs frequently or is disabling, and a biobehavioral plan to help cope with both the acute attacks and frequent or persistent attacks if present.

EPIDEMIOLOGY

Up to 75% of children report having a significant headache by the time they are 15 yr old. Recurrent headaches are less common, but remain highly frequent. Migraine has been reported to occur in up to 10.6% of children between the ages of 5 and 15 yr, and up to 28% of older

Table 595-2 Migraine Without Aura

A. At least 5 attacks fulfilling criteria B to D
B. Headache attacks lasting 4-72 hr (untreated or unsuccessfully treated)
C. Headache has at least 2 of the following 4 characteristics:
   1. Unilateral location
   2. Pulsating quality
   3. Moderate or severe pain intensity
   4. Aggravation by or causing avoidance of routine physical activity (e.g., walking or climbing stairs)
D. During headache at least 1 of the following:
   1. Nausea and/or vomiting
   2. Photophobia and phonophobia
E. Not better accounted for by another ICHD-3 diagnosis

From Headache Classification Committee on the International Headache Society (IHS): The International Classification of Headache Disorders, ed 3 (beta version). Cephalalgia *33(9):629–808, 2013, Table 4.*

Table 595-3 Migraine with Typical Aura

A. At least 2 attacks fulfilling criteria B and C
B. Aura consisting of visual, sensory and/or speech/language symptoms, each fully reversible, but no motor, brainstem or retinal symptoms
C. At least 2 of the following 4 characteristics:
   1. At least 1 aura symptom spreads gradually over 5 or more minutes, and/or 2 or more symptoms occur in succession
   2. Each individual aura symptom lasts 5-60 minutes
   3. At least 1 aura symptom is unilateral
   4. The aura is accompanied, or followed within 60 minutes, by headache
D. Not better accounted for by another ICHD-3 diagnosis, and transient ischemic attack has been excluded

From Headache Classification Committee on the International Headache Society (IHS): The International Classification of Headache Disorders, ed 3 (beta version). Cephalalgia *33(9):629–808, 2013, Table 6.*

Table 595-4 Migraine with Brainstem Aura

A. At least 2 attacks fulfilling criteria B to D
B. Aura consisting of visual, sensory and/or speech/language symptoms, each fully reversible, but no motor or retinal symptoms
C. At least 2 of the following brainstem symptoms:
   1. Dysarthria
   2. Vertigo
   3. Tinnitus
   4. Hypacusis
   5. Diplopia
   6. Ataxia
   7. Decreased level of consciousness
D. At least 2 of the following 4 characteristics:
   1. At least 1 aura symptom spreads gradually over 5 or more minutes, and/or 2 or more symptoms occur in succession
   2. Each individual aura symptom lasts 5-60 minutes
   3. At least 1 aura symptom is unilateral
   4. The aura is accompanied, or followed within 60 minutes, by headache
E. Not better accounted for by another ICHD-3 diagnosis, and transient ischemic attack has been excluded.

From Headache Classification Committee on the International Headache Society (IHS): The International Classification of Headache Disorders, ed 3 (beta version). Cephalalgia *33(9):629–808, 2013, Table 7.*

Table 595-5 Vestibular Migraine with Vertigo

A. At least 5 episodes fulfilling criteria C and D
B. A current or past history of 1.1 *Migraine without aura* or 1.2 *Migraine with aura*
C. Vestibular symptoms of moderate or severe intensity, lasting between 5 min and 72 hr
D. At least 50% of episodes are associated with at least 1 of the following 3 migrainous features:
   1. Headache with at least 2 of the following 4 characteristics:
      a. Unilateral location
      b. Pulsating quality
      c. Moderate or severe intensity
      d. Aggravation by routine physical activity
   2. Photophobia and phonophobia
   3. Visual aura
E. Not better accounted for by another ICHD-3 diagnosis or by another vestibular disorder

From Headache Classification Committee on the International Headache Society (IHS): The International Classification of Headache Disorders, ed 3 (beta version). Cephalalgia *33(9):629–808, 2013 (Table 8).*

Table 595-6 Chronic Migraine

A. Headache (tension-type-like and/or migraine-like) on 15 or more days per month for more than 3 mo and fulfilling criteria B and C
B. Occurring in a patient who has had at least 5 attacks fulfilling criteria B to D for 1.1 *Migraine without aura* and/or criteria B and C for 1.2 *Migraine with aura*
C. On 8 or more days per month for more than 3 mo, fulfilling any of the following:
   1. Criteria C and D for 1.1 *Migraine without aura*
   2. Criteria B and C for 1.2 *Migraine with aura*
   3. Believed by the patient to be migraine at onset and relieved by a triptan or ergot derivative
D. Not better accounted for by another ICHD-3 diagnosis

From Headache Classification Committee on the International Headache Society (IHS): The International Classification of Headache Disorders, ed 3 (beta version). Cephalalgia *33(9):629–808, 2013, Table 9.*

adolescents. When the headaches become frequent, they convert into chronic daily headaches in up to 1% of children. When headaches are occurring more than 15 days a month the risk of conversion to a daily headache becomes more prominent. This explains the necessity to treat the headaches aggressively or prevent the headaches altogether, trying to block transformation to chronic daily headaches.

Migraine can impact a patient's life through school absences, limitation of home activities, and restriction of social activities. As headaches become more frequent, their negative impact increases in magnitude. This can lead to further complications including anxiety and school avoidance, requiring a more extensive treatment plan.

CLASSIFICATION AND CLINICAL MANIFESTATIONS

Criteria have been established to guide the clinical and scientific study of headaches; these are summarized in *The International Classification of Headache Disorders*, 3rd edition (ICHD-3 beta). Table 595-1 contrasts the different clinical types of migraine; Tables 595-2 to 595-6 list the specific criteria for migraine types.

Migraine Without Aura

Migraine without aura is the most common form of migraine in both children and adults. The ICHD-3 beta (see Table 595-2) requires this to be recurrent (at least 5 headaches that meet the criteria, but there is no time limit over which this must occur). The recurrent episodic nature helps differentiate this from a secondary headache, as well as separates migraine from tension-type headache, but may limit the diagnosis in children as they may just be beginning to have headaches.

The duration of the headache is defined as 4-72 hr for adults. It has been recognized that children may have shorter-duration headaches, so an allowance has been made to reduce this duration to 2-72 hr or 1-72 hr with diary confirmation. Note that this duration is for the untreated or unsuccessfully treated headache. Furthermore, if the child falls asleep with the headache, the entire sleep period is considered part of the duration. These duration limits help differentiate migraine from both short-duration headaches, including the trigeminal autonomic cephalalgias, and prolonged headaches, like those caused by idiopathic intracranial hypertension (pseudotumor cerebri). Some prolonged headaches may still be migraine, but a migraine that persists beyond 72 hr is classified as a variant termed **status migrainosus.**

The quality of migraine pain is often, but not always, throbbing or pounding. This may be difficult to elicit in young children and drawings or demonstrations may help confirm the throbbing quality.

The location of the pain has classically been described as **unilateral (hemicrania)**; in young children it is more commonly bilateral. A more appropriate way to think of the location would therefore be focal, to differentiate it from the diffuse pain of tension-type headaches. Of particular concern is the exclusively occipital headache because although these can be migraines, they are more frequently secondary to another more proximate etiology such as posterior fossa abnormalities.

Migraine, when allowed to fully develop, often worsens in the face of and secondarily results in altered activity level. For example, worsening of the pain occurs classically in adults when going up or down stairs. This history is often not elicited in children. A change in the child's activity pattern can be easily observed as a reduction in play or physical activity. Older children may limit or restrict their sports activity or exercise during a headache attack.

Migraine may have a variety of associated symptoms. In younger children, nausea and vomiting may be the most obvious symptoms and often outweigh the headache itself. This often leads to the overlap with several of the gastrointestinal periodic diseases, including recurrent abdominal pain, recurrent vomiting, cyclic vomiting, and abdominal migraine. The common feature among all of these related conditions is an increased propensity among children with them for the later development of migraine. Oftentimes, early childhood recurrent vomiting may in fact be migraine, but the child is not asked about or is unable to describe headache pain. Once this becomes clear, the earlier diagnosis of a gastrointestinal disorder is no longer appropriate. When headache is present, vomiting raises the concern of a secondary headache, particularly related to increased intracranial pressure. *One of the red flags for this is the daily or near daily early morning vomiting, or headaches waking the child up from sleep.* When the headaches associated with vomiting episodes are sporadic and not worsening, it is more likely that the diagnosis is migraine. Vomiting and headache caused by increased intracranial pressure are frequently present on first awakening and remit with maintenance of upright posture. In contrast, if a migraine is present on first awakening *(a relatively infrequent occurrence in children)*, getting up and going about normal, upright activities usually makes the headache and vomiting worse.

As the child matures, light and sound sensitivity (**photophobia** and **phonophobia**) may become more apparent. This is either by direct report of the patient, or the interpretation by the parents of the child's activity. These symptoms are likely a component of the hypersensitivity that develops during an acute migraine attack and may also include smell sensitivity **(osmophobia)** and touch sensitivity **(cutaneous allodynia with central sensitization).** Although only the photophobia and phonophobia are components of the ICHD-3 beta criteria, these other symptoms are helpful in confirming the diagnosis and may be helpful in understanding the underlying pathophysiology and determining the response to treatment. The final ICHD-3 beta requirement is the exclusion of causes of secondary headaches, and this should be an integral component of the headache history.

Migraine typically runs in families with reports up to 90% of children having a 1st- or 2nd-degree relative with recurrent headaches. Given the underdiagnosis and misdiagnosis in adults, this is often not recognized by the family and a headache family history is required. When a family history is not identified, this may be the result of either a lack of awareness of migraine within the family or an underlying secondary headache in the child. Any child whose family, upon close and both direct and indirect questioning, does not include individuals with migraine or related syndromes (e.g., motion sickness, cyclic vomiting, menstrual headache) should have an imaging procedure performed to look for anatomic etiologies for headache.

In addition to the classifying features, there may additional markers of a migraine disorder. These include such things as triggers (skipping meals, inadequate or irregular sleep, dehydration and weather changes are the most common), pattern recognition (associated with menstrual periods in adolescents or Monday-morning headaches resulting from changes in sleep patterns over the weekend and nonphysiologic early waking on Monday mornings for school), and premonitory symptoms (a feeling of irritability, tiredness, and food cravings prior to the start of the headache). Although these additional features may not be consistent, they do raise the index of suspicion for migraine and provide a potential mechanism of intervention. In the past, food triggers were considered widely common, but the majority have either been discredited with scientific study or represent such a small number of patients that they only need to be addressed when consistently triggering the headache.

Migraine with Aura

The aura associated with migraine is a neurologic warning that a migraine is going to occur. In the common forms this can be the start of a typical migraine or a headache without migraine, or it may even occur in isolation. For a typical aura, the aura needs to be visual, sensory, or dysphasic, lasting longer than 5 min and less than 60 min with the headache starting within 60 min (see Table 595-3). The importance of the aura lasting longer than 5 min is to differentiate the migraine aura from a seizure with a postictal headache, while the 60 min maximal duration is to separate migraine aura from the possibility of a more prolonged neurologic event such as a transient ischemic attack.

The most common type of visual aura in children and adolescents is **photopsia** (flashes of light or light bulbs going off everywhere). These photopsias are often multicolored and when gone, the child may report not being able to see where the flash occurred. Less likely in children are the typical adult auras including *fortification spectra* (brilliant white

zigzag lines resembling a starred pattern castle) or *shimmering scotoma* (sometimes described as a shining spot that grows or a sequined curtain closing). In adults, the auras typically involve only half the visual field, whereas in children they may be randomly dispersed. Blurred vision is often confused as an aura but is difficult to separate from photophobia or difficulty concentrating during the pain of the headache.

Sensory auras are less common. They typically occur unilaterally. Many children describe this sensation as insects are worms crawling from their hand, up their arm to their face with a numbness following this sensation. Once the numbness occurs, the child may have difficulty using the arm as they have lost sensory input, and a misdiagnosis of hemiplegic migraine may be made.

Dysphasic auras are the least-common type of typical aura and have been described as an inability or difficulty to respond verbally. The patient afterwards will describe an ability to understand what is being asked, but cannot answer back. This may be the basis of what in the past has been referred to as confusional migraine and special attention needs to be paid to asking the child about this possibility and their degree of understanding during the initial phases of the attack. Most of the time, these episodes are described as a motor aphasia and they are often associated with sensory or motor symptoms.

Much less commonly, *atypical forms of aura can occur,* including hemiplegia (true weakness, not numbness, and may be familial), vertigo or lower cranial nerve symptoms (basilar-type, formerly thought to be caused by basilar artery dysfunction, now thought to be more brainstem based) (see Table 595-4), and distortion ("Alice in Wonderland" syndrome). Whenever these rarer forms of aura are present, further investigation is warranted. Not all motor auras can be classified as hemiplegic migraine spectrum and they should be differentiated from those very specific migrainous events, as the diagnosis of hemiplegic migraine has genetic, pathophysiologic, and therapeutic implications.

Hemiplegic migraine is one of the better known forms of rare auras. This transient unilateral weakness usually lasts only a few hours but may persist for days. Both familial and sporadic forms have been described. The familial hemiplegic migraine is an autosomal dominant disorder with mutations described in 3 separate genes: (1) *CACNA1A*, (2) *ATP1A2*, and (3) *SCN1A*. Some patients with familial hemiplegic migraine have other yet-to-be-identified genetic mutations. Multiple polymorphisms have been described for these genes. Hemiplegic migraines may be triggered by minor head trauma, exertion, or emotional stress. The motor weakness is usually associated with another aura symptom and may progress slowly over 20-30 min first with visual and then followed in sequence by sensory, motor, aphasic, and then basilar auras. Headache is present in more than 95% of patients and usually begins during the aura; headache may be unilateral or bilateral and may have no relationship to the motor weakness. Some patients may develop attacks of coma with encephalopathy, cerebrospinal fluid (CSF) pleocytosis, and cerebral edema. Long-term complications may include seizures, repetitive daily episodes of blindness, cerebellar signs with the development of cerebellar atrophy, and mental retardation.

Basilar-type migraine was formerly considered a disease of the basilar artery as many of the unique symptoms were attributed to dysfunction in this area of the brainstem. Some of the symptoms described include vertigo, tinnitus, diplopia, blurred vision, scotoma, ataxia, and an occipital headache. The pupils may be dilated, and ptosis may be evident.

Syndrome of transient headache and neurological deficits with CSF lymphocytosis (HaNDL) describes transient headaches associated with neurologic deficits, and CSF showing pleocytosis. It is considered a self-limited migraine-like syndrome, and is rarely reported in the pediatric population.

Childhood periodic syndromes are a group of potentially related symptoms that occur with increased frequency in children with migraine. The hallmark of these symptoms is the recurrent episodic nature of the events. Some of these have included gastrointestinal-related symptoms (motion sickness, recurrent abdominal pain, recurrent vomiting including cyclic vomiting, and abdominal migraine), sleep disorders (sleepwalking, sleeptalking, and night terrors), unexplained recurrent fevers, and even seizures.

The gastrointestinal symptoms span the spectrum from the relatively mild (motion sickness on occasional long car rides) to severe episodes of uncontrollable vomiting that may lead to dehydration and the need for hospital admission to receive fluids. These latter episodes may occur on a predictable time schedule and hence have been called cyclic vomiting. During these attacks, the child may appear pale and frightened but does not lose consciousness. After a period of deep sleep, the child awakens and resumes normal play and eating habits as if the vomiting had not occurred. Many children with cyclic vomiting have a positive family history of migraine, and as they grow older have a higher than average likelihood of developing migraine. Cyclic vomiting may be responsive to migraine-specific therapies with careful attention to fluid replacement if the vomiting is excessive. Cyclic vomiting of migraine must be differentiated from gastrointestinal disorders including intestinal obstruction (malrotation, intermittent volvulus, duodenal web, duplication cysts, superior mesenteric artery compression, and internal hernias), peptic ulcer, gastritis, giardiasis, chronic pancreatitis, and Crohn disease. Abnormal gastrointestinal motility and pelviureteric junction obstruction can also cause cyclic vomiting. Metabolic causes include disorders of amino acid metabolism (heterozygote ornithine transcarbamylase deficiency), organic acidurias (propionic acidemia, methylmalonic acidemia), fatty acid oxidation defects (medium-chain acyl-coenzyme A dehydrogenase deficiency), disorders of carbohydrate metabolism (hereditary fructose intolerance), acute intermittent porphyria, and structural central nervous system lesions (posterior fossa brain tumors, subdural hematomas or effusions). The diagnosis is a diagnosis of exclusion and children will need a full work up prior to be labeled of cyclic vomiting syndrome. Cyclic vomiting syndrome is more frequent in younger children and will gradually transform into a typical migraine attack by puberty.

The diagnosis of **abdominal migraine** can be confusing but can be thought of as a migraine without the headache. Like a migraine, it is an episodic disorder characterized by midabdominal pain with pain-free periods between attacks. At times this pain is associated with nausea and vomiting (thus crossing into the recurrent abdominal pain or cyclic vomiting spectrum). The pain is usually described as "dull" and may be moderate to severe. The pain may persist from 1-72 hr and, although usually midline, may be periumbilical or poorly localized by the child. To meet the criteria of abdominal migraine, the child must complain at the time of the abdominal pain of at least 2 of the following: anorexia, nausea, vomiting, or pallor. As with cyclic vomiting, a thorough history and physical examination with appropriate laboratory studies must be completed to rule out an underlying gastrointestinal disorder as a cause of the abdominal pain. Careful questioning about the presence of headache or head pain needs to be addressed directly with the child, as many times this is truly a migraine, but in the child's mind (as well as the parents' observation) the abdominal symptoms are paramount.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

A thorough history and physical examination including a neurologic examination with special focus on headache has been shown to be the most sensitive indicator of an underlying etiology. The history needs to include a thorough evaluation of the premonitory symptoms, any potential triggering events or timing of the headaches, associated neurologic symptoms, and a detailed characterization of the headache attacks, including frequency, severity, duration, associated symptoms, use of medication, and disability. The disability assessment should include the impact on school, home, and social activities and can easily be assessed with tools such as PedMIDAS. Family history of headaches and any other neurologic, psychiatric, and general health conditions is also important both for identification of migraine within the family as well as the identification of possible secondary headache disorders. The familial penetrance of migraine is so robust that the absence of a family history of migraine or its equivalent phenomena should trigger obtaining of an imaging procedure. When headaches are refractory, a history of potential comorbid conditions, which includes mood disorders and

illicit substance use, especially in teenagers, that may influence adherence and acceptability of the treatment plan, may also need to be addressed.

Neuroimaging is warranted when the neurologic examination is abnormal or unusual neurologic features occur during the migraine; when the child has headaches that awaken the child from sleep or that are present on first awakening and remit with upright posture; when the child has brief headaches that only occur with cough or bending over; when the headache is mostly in the occipital area; and when the child has migrainous headache with an absolutely negative family history of migraine or its equivalent (e.g., motion sickness, cyclic vomiting; Table 595-7). In this case, an MRI is the imaging of choice as it provides the highest sensitivity for detecting posterior fossa lesions and does not expose the child to radiation.

In the child with a headache that is instantaneously at its worst at onset, a CT scan looking for blood is the best initial test; and, if it is negative, a lumbar puncture should be done looking especially for xanthochromia of the CSF. There is no evidence that laboratory studies or an electroencephalogram is beneficial in a typical migraine without aura or migraine with aura.

TREATMENT

Table 595-8 outlines the drugs used to manage migraine headaches in children.

The American Academy of Neurology established useful practice guidelines for the management of migraine as follows:

1. Reduction of headache frequency, severity, duration, and disability
2. Reduction of reliance on poorly tolerated, ineffective, or unwanted acute pharmacotherapies
3. Improvement in quality of life
4. Avoidance of acute headache medication escalation
5. Education and enabling of patients to manage their disease to enhance personal control of their migraine
6. Reduction of headache-related distress and psychologic symptoms

Table 595-7 Indications for Neuroimaging in a Child with Headaches

Abnormal neurologic examination
Abnormal or focal neurologic signs or symptoms
• Focal neurologic symptoms or signs developing during a headache (i.e., complicated migraine)
• Focal neurologic symptoms or signs (except classic visual symptoms of migraine) develop during the aura, with fixed laterality; focal signs of the aura persisting or recurring in the headache phase
Seizures or very brief auras (<5 min)
Unusual headaches in children
• Atypical auras including basilar-type, hemiplegic
• Trigeminal autonomic cephalalgia including cluster headaches in child or adolescent
• An acute secondary headache (i.e., headache with known underlying illness or insult)
Headache in children younger than 6 yr old or any child who cannot adequately describe his or her headache
Brief cough headache in a child or adolescent
Headache worst on first awakening or that awakens the child from sleep
Migrainous headache in the child with no family history of migraine or its equivalent

Table 595-8 Drugs Used in the Management of Migraine Headaches in Children

DRUG	DOSE	MECHANISM	SIDE EFFECTS	COMMENTS
ACUTE MIGRAINE				
Analgesics				
Acetaminophen	15 mg/kg/dose	Analgesic effects	Overdose, fatal hepatic necrosis	Effectiveness limited in migraine
Ibuprofen	7.5-10 mg/kg/dose	Antiinflammatory and analgesic	GI bleeding stomach upset, kidney injury	Avoid overuse (2-3 times per wk)
Triptans				
Almotriptan* (ages 12-17 yr)	12.5 mg	5-$HT_{1b/1d}$ agonist	Vascular constriction, serotonin symptoms such as flushing, paresthesias, somnolence, GI discomfort	Avoid overuse (more than 4-6 times per mo)
Eletriptan	40 mg	Same	Same	Avoid overuse (more than 4-6 times per mo)
Frovatriptan	2.5 mg	Same	Same	May be effective for menstrual migraine prevention Avoid overuse (more than 4-6 times per mo)
Naratriptan	2.5 mg	Same	Same	May be effective for menstrual migraine prevention Avoid overuse (more than 4-6 times per mo)
Rizatriptan* (ages 6-17 yr)	5 mg for child weighing <40 kg, 10 mg	Same	Same	Available in tablets and melts Avoid overuse (more than 4-6 times per mo)
Sumatriptan	Oral: 25 mg, 50 mg, 100 mg Nasal: 10 mg SC: 6 mg	Same	Same	Avoid overuse (more than 4-6 times per mo)
Zolmitriptan	Oral: 2.5 mg, 5 mg Nasal: 5 mg	Same	Same	Available in tablets and melts Avoid overuse (more than 4-6 times per mo)

Continued

Table 595-8 Drugs Used in the Management of Migraine Headaches in Children—cont'd

DRUG	DOSE	MECHANISM	SIDE EFFECTS	COMMENTS
PROPHYLAXIS (NONE APPROVED BY FDA FOR CHILDREN)				
Calcium Channel Blockers				
Flunarizine†	5 mg hs	Calcium channel blocking agent	Headache, lethargy, dizziness	May ↑ to 10 mg hs
Anticonvulsants				
Valproic acid	20 mg/kg/24 hr (begin 5 mg/kg/24 hr)	↑ Brain GABA	Nausea, pancreatitis, fatal hepatotoxicity	↑ 5 mg/kg every 2 wk
Topiramate	100-200 mg divided bid	↑ Activity of GABA	Fatigue, nervousness	Increase slowly over 12-16 wk
Levetiracetam	20-60 mg/kg divided bid	Unknown	Irritability, fatigue	Increase every 2 wk starting at 20 mg/kg divided bid
Gabapentin	900-1800 mg divided bid	Unknown	Somnolence, fatigue aggression, weight gain	Begin 300 mg, ↑ 300 mg/wk
Antidepressants				
Amitriptyline	1 mg/kg/day	↑ CNS serotonin and norepinephrine	Cardiac conduction, abnormalities and dry mouth, constipation, drowsiness, confusion	Increase by 0.25 mg/kg every 2 wk Morning sleepiness reduced by administration at dinnertime
Antihistamines				
Cyproheptadine	0.2-0.4 mg/kg divided bid; max: 0.5 mg/kg/24 hr	H_1-receptor and serotonin agonist	Drowsiness, thick bronchial secretions	Preferred in children who cannot swallow pills; not well tolerated in adolescents
Antihypertensive				
Propranolol	10-20 mg tid	Nonselective β-adrenergic blocking agent	Dizziness, lethargy	Begin 10 mg/24 hr ↑ 10 mg/wk (contraindicated in asthma and depression)
Others				
Coenzyme Q10	1-3 mg/kg/day	Increases fatty acid oxidation in mitochondria	No adverse effects reported	Fat soluble; ensure brand contains small amount of vitamin E to help absorption
Riboflavin	50-400 mg daily	Cofactor in energy metabolism	Bright yellow urine, polyuria and diarrhea	
Magnesium	9 mg/kg divided tid	Cofactor in energy metabolism	Diarrhea or soft stool	
Butterbur	50-150 mg daily	May act similar to a calcium channel blocker	Burping	
OnabotulinumtoxinA	100 units (age 11-17 yr)	Inhibits acetylcholine release from nerve endings	Ptosis, blurred vision, hematoma at injection site	Used off label in children
SEVERE INTRACTABLE				
Prochlorperazine	0.15 mg/kg/IV; max dose 10 mg	Dopamine antagonist	Agitation, drowsiness, muscle stiffness, akinesia and akathisia	May have increased effectiveness when combined with ketorolac and fluid hydration
Metoclopramide	0.2 mg/kg IV; 10 mg max dose	Dopamine antagonist	Drowsiness, urticaria, agitation, akinesia and akathisia	Caution in asthma patients
Ketorolac	0.5 mg/kg IV; 15 mg max dose	Antiinflammatory and analgesic	GI upset, bleeding	
Valproate sodium injection	15 mg/kg IV: 1,000 mg max dose	↑ Brain GABA	Nausea, vomiting, somnolence, thrombocytopenia	Would avoid in hepatic disease
Dihydroergotamine IV	0.5 mg/dose every 8 hr (<40 kg) 1.0 mg/dose every 8 hr (>40 kg)		Nausea, vomiting, vascular constriction, phlebitis	Dose may need to be adjusted for side effects (decrease) or limited effectiveness (increase).
Nasal spray	0.5-1.0 mg/dose 0.5 mg/spray			

*FDA approved in the pediatric population.
†Available in Europe.
↑, Increase; CNS, central nervous system; GABA, γ-aminobutyric acid; GI, gastrointestinal; hs, at night; SC, subcutaneous.

To accomplish these goals, 3 components need to be incorporated into the treatment plan:

1. An acute treatment strategy should be developed for stopping a headache attack on a consistent basis with return to function as soon as possible with the goal being 2 hr maximum.
2. A preventive treatment strategy should be considered when the headaches are frequent (1 or more per week) and disabling.
3. Biobehavioral therapy should be started, including a discussion of adherence, elimination of barriers to treatment, and healthy habit management.

Acute Treatment

Management of an acute attack is to provide headache freedom as quickly as possible with return to normal function. This mainly includes 2 groups of medicines: nonsteroidal antiinflammatory drugs (NSAIDs) and triptans. Most migraine headaches in children will respond to appropriate doses of NSAIDs when administered at the onset of the headache attack. Ibuprofen has been well documented to be effective at a dose of 7.5-10.0 mg/kg and is often preferred; however, acetaminophen (15 mg/kg) can be effective in those with a contraindication to NSAIDs. Special concern for the use of ibuprofen or other NSAIDs includes ensuring that the children can recognize and respond to onset of the headache. This means discussing with the child the importance of telling the teacher when the headache starts at school and ensuring that proper dosing guidelines and permission have been provided to the school. In addition, overuse needs to be avoided, limiting the NSAID (or any combination of nonprescription analgesics) to not more than 2-3 times per week. The limitation of any analgesic to not more than 3 headaches a week is necessary to prevent the transformation of the migraines into medication overuse headaches. If a patient has maximized the weekly allowance of analgesics, the patient's next step is to only use hydrating fluids for the rest of the week as an abortive approach. If ibuprofen is not effective, naproxen sodium also may be tried in similar doses. Aspirin is also a reasonable option but is usually reserved for older children (older than age 15 yr). Use of other NSAIDs have yet to be studied in pediatric migraine. The goal of the primary acute medication should be headache relief within 1 hr with return to function in 10 of 10 headaches.

When a migraine is especially severe, NSAIDs alone may not be sufficient. In this case, a triptan may be considered. Multiple studies have demonstrated their effectiveness and tolerability. There are currently 2 triptans that are approved by the FDA for the treatment of episodic migraine in the pediatric population. Almotriptan is approved for the treatment of acute migraine in adolescents (ages 12-17 yr). Rizatriptan is approved for the treatment of migraine in children as young as age 6 yr. The combination of naproxen sodium and sumatriptan has been studied and may be effective in children. Controlled clinical trials demonstrate that intranasal sumatriptan is safe and effective in children older than age 8 yr with moderate to severe migraine. At present, pediatric studies showing the effectiveness of oral sumatriptan are lacking and there is insufficient evidence to support the use of subcutaneous sumatriptan in children. For most adolescents, dosing is the same as for adults; a reduction in dose is made for children weighing less than 40 kg. The triptans vary by rapidity of onset and biologic half-life. This is related to both their variable lipophilicity and dose. Clinically, 60-70% of patients respond to the first triptan tried, with 60-70% of the patients who did not respond to the first triptan responding to the next triptan. Therefore, in the patient who does not respond to the first triptan in the desired way (rapid reproducible response without relapse or side effects), it is worthwhile to try a different triptan. The most common side effects of the triptans are caused by their mechanism of action—tightness in the jaw, chest, and fingers as a result of vascular constriction and a subsequent feeling of grogginess and fatigue from the central serotonin effect. The vascular constriction symptoms can be alleviated through adequate fluid hydration during an attack.

The most effective way to administer abortive treatment is to use NSAIDs first in mild to severe cases, restricting their use to fewer than 2-3 attacks per week, and adding the triptan for moderate to severe, or attacks that have failed NSAID use, restricting to not more than 4-6 attacks per month. For an acute attack, the NSAIDs can be repeated once in 3-4 hr if needed for that specific attack, and the triptans can be repeated once in 2 hr if needed. It is important to consider the various formulations available and a discussion of these options should be made with pediatric patients and their parents, especially if a child is unable to swallow pills or take an oral dose because of nausea.

As vascular dilation is a common feature of migraine that may be responsible for some of the facial flushing followed by paleness and the lightheaded feeling accompanying the attacks, fluid hydration should be integrated into the acute treatment plan. For oral hydration this can include the sports drinks that combine electrolytes and sugar to provide the intravascular rehydration.

Antiemetics were used for acute treatment of the nausea and vomiting. Further study has identified that their unique mechanism of effectiveness in headache treatment is related to their antagonism of dopaminergic neurotransmission. Therefore, the antiemetics with the most robust dopamine antagonism (i.e., prochlorperazine and metoclopramide) have the best efficacy. These can be very effective for status migrainosus or a migraine that is unresponsive to the NSAIDs and triptans. They require intravenous administration, as other forms of administration of these drugs are less effective than the NSAIDs or triptans. When combined with ketorolac and intravenous fluids in the emergency department or an acute infusion center, intravenous antiemetics can be very effective. When they are not effective, further inpatient treatment may be required using dihydroergotamine (DHE) which will mean an admission to an inpatient unit for more aggressive therapy of an intractable attack.

Emergency Department Treatments for Intractable Headaches

When an acute migraine attack does not respond to an outpatient regimen and is disabling, other therapeutic approaches are available and may be necessary to prevent further increases in the frequency of headaches. These migraines fall into the classification of status migrainosus and need infusion therapy and admission to the emergency room department or to an inpatient unit.

Available specific treatments for migraine headache in an emergency room setting include the following: antidopaminergic medications such as prochlorperazine and metoclopramide; NSAIDs such as ketorolac and DHE; antiepileptic drugs such as sodium valproate; and triptans.

Antidopaminergic Drugs: Prochlorperazine and Metoclopramide. The use of these medications is not limited to controlling the nausea and vomiting often present during a migraine headache. Their potential pharmacologic effect may be a result of their antidopamine property and the underlying pathologic process involving the dopaminergic system during a migraine attack. Prochlorperazine is very effective in aborting an attack in the emergency room when given intravenously with a bolus of IV fluid. Results show a 75% improvement with 50% headache freedom at 1 hr and 95% improvement with 60% headache freedom at 3 hr. Prochlorperazine may be more effective than metoclopramide. The average dose of metoclopramide use is 0.13-0.15 mg/kg with a maximum dose of 10 mg given intravenously over 15 min. The average dose of prochlorperazine is 0.15 mg/kg with a maximum dose of 10 mg. These medications are usually well tolerated, but *extrapyramidal reactions* are more frequent in children compared to the older population. An acute extrapyramidal reaction can be controlled in the emergency room with 25-50 mg of diphenhydramine given IV.

Nonsteroidal Antiinflammatory Drugs: Ketorolac. It is known that an aseptic inflammation occurs in the central nervous system as a result of the effect of multiple reactive peptides in patients with migraines. Ketorolac is often used in the emergency department as monotherapy for a migraine attack or in combination with other drugs. In monotherapy, the response to ketorolac is 55.2% improvement. When combined to prochlorperazine, the response rate jumps to 93%.

Antiepileptic Drugs: Sodium Valproate. Antiepileptic drugs have been used as prophylactic treatment for migraine headache for years with adequate double-blinded, controlled studies on their efficacy in adults. The mechanism in which sodium valproate acutely aborts migraine headaches is not well understood. Sodium valproate is given as a bolus of 15-20 mg/kg push (over 10 min). This intravenous load is followed by an oral dose (15-20 mg/day) in the 4 hr after the injection. Patients may benefit from a short-term preventive treatment with an extended release form after discharge from the emergency room. Sodium valproate is usually well tolerated. Patients should be receiving a fluid load during the procedure to prevent a possible hypotensive episode.

Triptans. Subcutaneous sumatriptan (0.06 mg/kg) has an overall efficacy of 72% at 30 min and 78% at 2 hr, with a recurrence rate of 6%. Because children tend to have a shorter duration of headache, a recurrence rate of 6% would seem appropriate for this population. DHE, if recommended for the recurrences, should not be given in the 24 hr after triptan use. Triptans are contraindicated in patients treated with ergotamine within 24 hr and within 2 wk of treatment with monoamine oxidase inhibitors. Triptans may potentially produce a serotonin syndrome in patients taking a serotonin syndrome reuptake inhibitor. Both triptans and ergotamine are contraindicated in hemiplegic migraines.

Dihydroergotamine. DHE is an old migraine medication used as a vasoconstrictor to abort the vascular phase of migraine headache. The effectiveness is discussed in detail in the section "Inpatient Management of Intractable Migraine and Status Migrainosus" below. One dose of DHE can be effective for abortive treatment in the emergency department. Emergency room treatment of migraine shows a recurrence rate of 29% at 48-72 hr, with 6% who need more aggressive therapy in an inpatient unit.

Inpatient Management of Intractable Migraine and Status Migrainosus

Six percent to 7% of patients fail acute treatment in the emergency department. These patients are usually admitted for a 3-5 day stay and receive extensive parenteral treatment. A child should be admitted to the hospital for a primary headache when the child is in status migrainous, has an exacerbation of a chronic severe headache, or is in an analgesic rebound headache. The goal of inpatient treatment is to control a disabling headache that has been unresponsive to other abortive therapy and is disabling to the child. Treatment protocols include the use of DHE, antiemetics, sodium valproate and other drugs.

Dihydroergotamine. Ergots are one of the oldest treatments for migraine headache. DHE is a parenteral form used for acute exacerbations. Its effect is because of the $5HT_{1A\text{-}1B\text{-}1D\text{-}1F}$ receptor agonist affinity and central vasoconstriction. DHE has a greater α-adrenergic antagonist activity and is less vasoconstrictive peripherally. Before initiation of an IV ergot protocol, a full history and neurologic examination should be obtained. Girls of childbearing age should be evaluated for pregnancy before administering ergots.

The DHE protocol consists of the following: Patients are premedicated with 0.13-0.15 mg/kg of prochlorperazine 30 min prior to the DHE dose (maximum of 3 prochlorperazine doses to prevent extrapyramidal syndrome, then other types of antiemetics should be used, such as ondansetron). A dose of 0.5-1.0 mg of DHE is used (depending on age and tolerability) every 8 hr until headache freedom. When headache ceases, an extra dose is given in an attempt to prevent recurrence after discharge. The response to this protocol is a 97% improvement and 77% headache freedom. Response starts being noticeable by the fifth dose and can reach its maximum effects after the 10th dose. Side effects of DHE include nausea, vomiting, abdominal discomfort, flushed face, increased blood pressure. The maximum dose used in this protocol is 15 mg total of DHE. During the hospital admission the patient is usually started on migraine prophylaxis depending on the patient's history and comorbid problems.

Sodium Valproate. Sodium valproate is used when DHE is contraindicated or has been ineffective. One adult study recommends the use of valproate sodium as follows: Bolus with 15 mg/kg (maximum of 1,000 mg), followed by 5 mg/kg every 8 hr until headache freedom or up to a maximum of 10 doses. Always give an extra dose after headache ceases. This protocol was studied in adults with chronic daily headaches and showed an 80% improvement. It is well tolerated and is useful in children when DHE is ineffective, contraindicated, or not tolerated.

Preventive Therapy

When the headaches are frequent (more than 1 headache/wk) or there are more than 1 disabling headache a month (missing school, home, or social activities, or a PedMIDAS score higher than 20), preventive or **prophylactic therapy** is warranted. The goal of this therapy should to be to reduce frequency (1-2 headaches or fewer per month) and disability (PedMIDAS score <10). Prophylactic agents should be given for at least 4-6 mo at an adequate dose and then weaned over several weeks. Evidence in adult studies has begun to demonstrate that persistent frequent headaches foreshadow an increased risk of progression with decreased responsiveness and increased risk of refractoriness in the future. It is unclear whether this also occurs in children and/or adolescents and whether early treatment of headache in childhood prevents development of refractory headache in adulthood.

Multiple preventive medications have been utilized for migraine prophylaxis in children. When analyzed as part of a practice parameter, only 1 medication, **flunarizine** (a calcium channel blocking agent), demonstrated a level of effectiveness viewed as substantial; it is not available in the United States. Flunarizine is typically dosed at 5 mg orally daily and increased after 1 mo to 10 mg orally daily, with a month off of the drug every 4-6 mo.

The most commonly used preventive therapy for headache and migraine is amitriptyline. Typically, a dose of 1 mg/kg daily at dinner or in the evening is effective. However, this dose needs to be reached slowly (i.e., over weeks: with an increase every 2 wk until goal is reached) to minimize side effects and improve tolerability. The most common side effects are sleepiness and those related to amitriptyline's anticholinergic activity. Weight gain has been observed in adults using amitriptyline but is a less frequent occurrence in children. Amitriptyline does have the potential to exacerbate prolonged QT syndrome, so it should be avoided in patients with this diagnosis and looked for in patients on the drug who complain of rapid or irregular heart rate.

Antiepileptic medications are also used for migraine prophylaxis, with topiramate, valproic acid, and levetiracetam having been demonstrated to be effective in adults. There are limited studies in children for migraine prevention, but all of these medications have been assessed for safety and tolerability in children with epilepsy.

Topiramate has become widely used for migraine prophylaxis in adults. Topiramate was also demonstrated to be effective in an adolescent study. This study demonstrated that a 25 mg dose twice a day was equivalent to placebo, whereas a 50 mg dose twice a day was superior. Thus it appears that the adult dosing schedule is also effective in adolescents with an effective dosage range or 50 mg twice a day to 100 mg twice a day. This dose needs to be reached slowly to minimize the cognitive slowing associated with topiramate use. Additional side effects include weight loss, paresthesias, kidney stones, lowered bicarbonate levels, decreased sweating, and rarely glaucoma and changes in serum transaminases. In addition, in adolescent girls taking birth control pills, the lowering of the effectiveness of the birth control by topiramate needs to be discussed.

Valproic acid has long been used for epilepsy in children and has been demonstrated to be effective in migraine prophylaxis in adults. The effective dose in children appears to be 10 mg/kg orally twice a day. Side effects of weight gain, ovarian cysts, and changes in serum transaminases and platelet counts need to be monitored. Other antiepileptics, including lamotrigine, levetiracetam, zonisamide, gabapentin, and pregabalin, are also used for migraine prevention.

β-Blockers have long been used for migraine prevention. The studies on β-blockers have a mixed response pattern with variability both between β-blockers and between patients with a given β-blocker. Propranolol is the best studied for pediatric migraine prevention with unequivocally positive results. The contraindication for use of

propranolol in children with asthma or allergic disorders or diabetes and the increased incidence of depression in adolescents using propranolol limit its use somewhat. It may be very effective for a mixed subtype of migraine (basilar-type migraine with postural orthostatic tachycardia syndrome). This syndrome has been reported to be responsive to propranolol. α-Blockers and calcium channel blockers, aside from flunarizine, also have been used in pediatric migraine; their effectiveness, however, remains unclear.

In very young children, cyproheptadine may be effective in prevention of migraine or the related variants. Young children tend to tolerate the increased appetite induced by the cyproheptadine and tend not to be subject to the lethargy seen in older children and adults; the weight gain is limiting once children start to enter puberty. Typical dosing is 0.1-0.2 mg/kg orally twice a day.

Nutraceuticals have become increasingly popular over the past few years, especially among families who prefer a more "natural" approach to headache treatment. Despite studies showing success of these therapies in adults, few studies have shown effectiveness in pediatric headaches. Riboflavin (vitamin B_2), at doses ranging from 25-400 mg, is the most widely studied with good results. Side effects are minimal and include bright yellow urine, diarrhea, and polyuria. Coenzyme Q10 supplementation may be effective in reducing migraine frequency at doses of 1-2 mg/kg/day. Butterbur is also effective in reducing headaches with minimal side effects, including burping. Use in children has been limited to avoid the potential toxicity of butterbur containing pyrrolizidine alkaloids, which are naturally contained and are a known carcinogen and toxic to the liver.

OnabotulinumtoxinA is the first medication FDA-approved for chronic migraine in adults. There are studies in children indicating its effectiveness; use in children is considered off-label. The limited available studies revealed the following: Average dose used was 188.5 units ± 32 units with a minimum dose of 75 units and maximum of 200 units. The average age of patients receiving the treatment was 16.8 ± 2.0 yr (minimum: 11; maximum: 21 yr old). OnabotulinumtoxinA injections improved disability scores (PedMIDAS) and headache frequency in pediatric chronic daily headache patients and chronic migraine in this age group. OnabotulinumtoxinA not only had a positive effect on the disability scoring for these young patients with headache, but was also able to transform the headaches from chronic daily to intermittent headache in more than 50% of the patients.

Biobehavioral Therapy

Biobehavioral evaluation and therapy is essential for effective migraine management. This includes identification of behavioral barriers to treatment, like a child's shyness or limitation in notifying a teacher of the start of a migraine or a teacher's unwillingness to accept the need for treatment. Additional barriers include a lack of recognition of the significance of their headache problem and reverting to "bad habits" once the headaches have responded to treatment. Adherence is equally important for acute and preventive treatment. The need to have a sustained response for long enough to prevent relapse (i.e., to stay on preventive medication) is often difficult when the child starts to feel better. Establishing a defined treatment goal (1-2 or fewer headaches per month for 4-6 mo) helps with acceptance.

As many of the potential triggers for frequent migraines (skipping meals, dehydration, decreased or altered sleep) are related to a child's daily routine, a discussion of healthy habits is a component of biobehavioral therapy. This should include adequate fluid intake without caffeine, regular exercise, not skipping meals and making healthy food choices, and adequate (8-9 hr) sleep on a regular basis. Sleep is often difficult in adolescents, as middle and high schools often have very early start times, and the adolescent's sleep architecture features a shift to later sleep onset and waking. This has been one of the explanations for worsening headaches during the school year in general and at the beginning of the school year and week.

Biofeedback-assisted relaxation and cognitive behavioral therapy (usually in combination with amitriptyline) are effective for both acute and preventive therapy and may be incorporated into this multiple treatment strategy. This provides the child with a degree of self-control over the headaches and may further help the child cope with frequent headaches.

Bibliography is available at Expert Consult.

595.2 Secondary Headaches

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Headaches can be a common symptom of other underlying illnesses. In recognition of this, the ICHD-3 beta has classified the potential secondary headaches (see Table 595-1). The key to the diagnosis of a secondary headache is to recognize the underlying cause and demonstrate a direct cause and effect. Until this has been demonstrated the diagnosis is speculative. This is especially true when the suspected etiology is common.

Common causes or suspected causes of secondary headaches in children include the sequelae of head trauma and sinusitis. **Posttraumatic headaches** sometimes occur in children who have not had a prior history of headaches and are temporally related to the initiating head injury. Frequently, though, these children have a family history of migraine or its equivalent. The head injury may be minor or major and the subsequent headache may be acute (resolves within 3 mo, most typically within 10 days) or chronic (longer than 15 days per month for more than 3 mo). Bed rest appears to be the most effective treatment for acute posttraumatic headache; magnesium supplementation and migraine prophylaxis may also be effective. When a child has a history of episodic headaches, the head trauma or the overuse of daily medications may lead to status migrainosus or chronic migraine and the diagnosis may be difficult to sort out.

Sinus headache is the most overdiagnosed form of recurrent headaches. Although no studies have evaluated the frequency of misdiagnosis of an underlying migraine as a sinus headache in children, in adults, it has been found that up to 90% of adults diagnosed as having a sinus headache by either themselves or their physician appear to have migraine. When headaches are recurrent and respond within hours to analgesics, migraine should be considered first. In the absence of purulent nasal discharge, fever, or chronic cough, the diagnosis of sinus headache should not be made.

Medication overuse headaches frequently complicate primary and secondary headaches. A medication overuse headache is defined as a headache present for more than 15 days/mo for longer than 3 mo and intake of a simple analgesic on more than 15 days/mo and/or prescription medications including triptans or combination medications on more than 10 days/mo. Some of the signs that should raise suspicion of medication overuse are the increasing use of analgesics (nonprescription or prescription) with either decreased effectiveness or frequently wearing off (i.e., analgesic rebound). This can be worsened by using ineffective medications and underdosing or misdiagnosing the headache. Patients should be cautioned against the frequent use of antimigraine medications, including combination analgesics or triptans.

Serious causes of secondary headaches are likely to be related to increased intracranial pressure. This can be caused by a mass (tumor, vascular malformation, cystic structure) or an intrinsic increase in pressure (idiopathic intracranial hypertension also known as pseudotumor cerebri). In the former case, the headache is caused by the mass effect and local pressure on the dura; in the latter case, the headache is caused by diffuse pressure on the dura. The etiology of idiopathic intracranial hypertension may be the intake of excessive amounts of fat-soluble compounds (e.g., vitamin A, retinoic acid, and minocycline), hormonal changes (increased incidence in females) or blockage of venous drainage (as with inflammation of the transverse venous sinus from mastoiditis). When increased pressure is suspected, either by historical suspicion or the presence of papilledema, an MRI with magnetic resonance angiography and magnetic resonance venography should be performed, followed by a lumbar puncture if no mass or

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vascular anomaly is noted. The lumbar puncture can be diagnostic and therapeutic of idiopathic intracranial hypertension but must be performed with the patient in a relaxed recumbent position with legs extended, as abdominal pressure can artificially raise intracranial pressure. If headache persists or there are visual field changes, pharmaceutical treatment with a carbonic anhydrase inhibitor, optic nerve fenestration, or a shunt needs to be considered.

Additional causes of secondary headaches in children that may not be associated with increased intracranial pressure include arteriovenous malformations, berry aneurysm, collagen vascular diseases affecting the central nervous system, hypertensive encephalopathy, infectious or autoimmune etiologies, acute subarachnoid hemorrhage, and stroke. The management of secondary headache depends on the cause. Helpful laboratory tests and neuroradiologic procedures depend on the clues provided by the history and physical examination. By definition, a secondary headache has a specific cause and should resolve once this cause is treated. If the headache persists, the diagnosis and treatment should be questioned as either the diagnosis, which may include a primary headache, and/or treatment may be incorrect.

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595.3 Tension-Type Headaches

Andrew D. Hershey, Marielle A. Kabbouche, and Hope L. O'Brien

Tension-type headaches (TTHs) may be very common in children and adolescents with prevalence in some studies shown as high as 48%, with those having a combination of migraine and TTH around 20%. Because of their mild to moderate nature, relative lack of associated symptoms and lower degree of associated disability they are often ignored or have a minimal impact. The ICHD-3 beta subclassifies TTHs as infrequent (<12 times/yr) (Table 595-9), frequent (1-15 times/mo), and chronic (>15 headaches/mo). They can further be separated into headaches with or without pericranial muscle tenderness. The classification of TTH can be likened to the opposite of migraine. Whereas migraines are typically moderate to severe, are focal in location, are worsened by physical activity or limit physical activity, and have a throbbing quality, TTH are mild to moderate in severity, are diffuse in location, are not affected by activity (although the patient may not feel like being active), and are nonthrobbing (often described as a constant pressure). TTH is much less frequently associated with nausea, photophobia, or phonophobia and is never associated with more than 1 of these at a time or with vomiting. TTH must be recurrent, but at least 10 headaches are required and the duration can be 30 min to 7 days. Secondary headaches with other underlying etiologies must be ruled out.

Table 595-9 Infrequent Episodic Tension-Type Headache

A. At least 10 episodes of headache occurring on <1 day per month on average (<12 days per year) and fulfilling criteria B to D
B. Lasting from 30 min to 7 days
C. At least 2 of the following 4 characteristics:
   1. Bilateral location
   2. Pressing or tightening (nonpulsating) quality
   3. Mild or moderate intensity
   4. Not aggravated by routine physical activity such as walking or climbing stairs
D. Both of the following:
   1. No nausea or vomiting
   2. No more than 1 of photophobia or phonophobia
E. Not better accounted for by another ICHD-3 beta diagnosis

From Headache Classification Committee on the International Headache Society (IHS): The International Classification of Headache Disorders, ed 3 (beta version). Cephalalgia *33(9):629–808, 2013, Table 10.*

Evaluation of patients with suspected TTHs requires a detailed headache history and complete general and neurologic examination. This is to establish the diagnosis and ensure exclusion of secondary etiologies. When secondary headaches are suspected, further, directed evaluation is indicated.

Treatment of TTHs can require acute therapy to stop attacks, preventive therapy when frequent or chronic, and behavioral therapy. It is often suspected that there may be underlying psychologic stressors (hence the misnomer as a "stress" headache), but this is often difficult to identify in children, and although it may be suspected by the parents, it cannot be confirmed in the child. Studies of and conclusive evidence to guide the treatment of TTH in children are lacking, but the same general principles and medications used in migraine can be applied to children with TTHs (see Chapter 595.1). Oftentimes, simple analgesics (ibuprofen or acetaminophen) can be effective for acute treatment. Flupirtine is a nonopioid analgesic that has been approved in Europe for the treatment of TTH in children as young as age 6 yr, but is not available in the United States. Amitriptyline has the most evidence of effective prevention of TTH; biobehavioral intervention, including biofeedback-assisted relaxation training and coping skills, can be useful as well.

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Chapter 596

Neurocutaneous Syndromes

Mustafa Sahin

The neurocutaneous syndromes include a heterogeneous group of disorders characterized by abnormalities of both the integument and central nervous system. Many of the disorders are familial and believed to arise from a defect in differentiation of the primitive ectoderm. Disorders classified as neurocutaneous syndromes include neurofibromatosis, tuberous sclerosis, Sturge-Weber syndrome, von Hippel-Lindau disease, PHACE (posterior fossa malformations, hemangiomas, arterial anomalies, coarctation of aorta, cardiac defects, eye abnormalities) syndrome, ataxia telangiectasia, linear nevus syndrome, hypomelanosis of Ito, and incontinentia pigmenti.

596.1 Neurofibromatosis

Mustafa Sahin

Neurofibromatoses are autosomal dominant disorders that cause tumors to grow on nerves and result in other abnormalities such as skin changes and bone deformities. It was believed that there were 2 types of neurofibromatosis (type 1 and type 2), but it is recognized that they are clinically and genetically distinct diseases and should be considered separate entities: neurofibromatosis type 1 (NF-1) and neurofibromatosis type 2 (NF-2).

CLINICAL MANIFESTATIONS AND DIAGNOSIS

NF-1 is the most prevalent type, with an incidence of 1 in 3,000 live births, and is caused by dominant loss-of-function mutations in the *NF-1* gene. The disease is clinically diagnosed when any 2 of the following 7 features are present: (1) six or more café-au-lait macules larger than 5 mm in greatest diameter in prepubertal individuals and larger than 15 mm in greatest diameter in postpubertal individuals (Fig. 596-1). Café-au-lait spots are the hallmark of neurofibromatosis

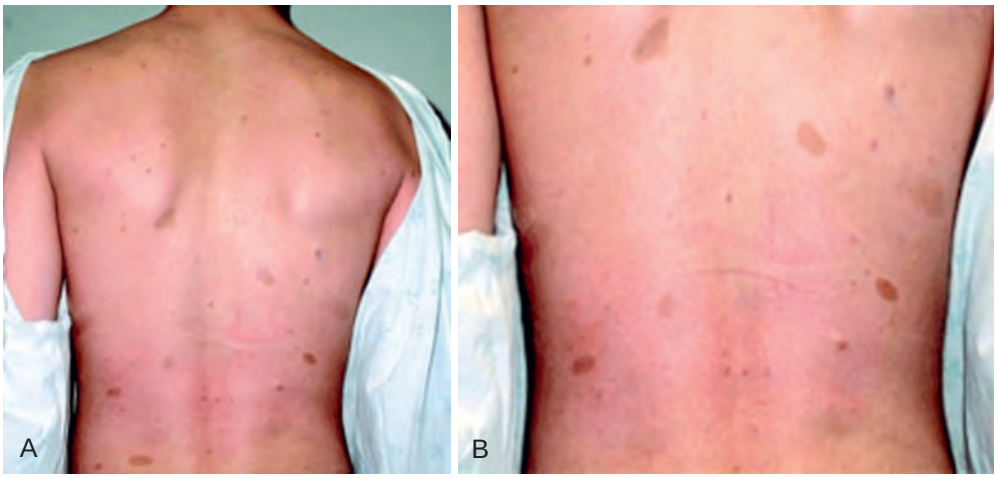


Figure 596-1 **A** and **B,** Multiple café-au-lait spots over the back. Note the dermal neurofibromas below the right scapula and right side of the lower back. *(From Hersh JH, Committee on Genetics: Health supervision for children with neurofibromatosis,* Pediatrics *121:633–642, 2008, Fig. 1.)*

Table 596-1 Diseases Associated with Multiple Café-Au-Lait Spots

DISEASE	MAJOR FEATURES
Ataxia telangiectasia	Progressive ataxia, lymphoreticular malignancy
Bannayan-Riley-Ruvalcaba syndrome	Macrosomia, megalencephaly, lipomas, intestinal polyps
Basal cell nevus syndrome	Multiple basal cell epitheliomas, jaw cysts, skeletal anomalies
Bloom syndrome	Short stature, photosensitivity, chromosome breaks, malignancy
Fanconi anemia	Limb anomalies, renal anomalies, pancytopenia
Gaucher disease	Jewish predilection, ataxia, mental retardation
Hunter syndrome	Thickened skin, coarse facies, skin papules, joint contractures
Jaffe-Campanacci syndrome	Fibromas of long bones, hypogonadism, mental retardation, ocular/cardiac anomalies
Maffucci syndrome	Venous malformations, enchondromas
McCune-Albright syndrome	Polyostotic fibrous dysplasia, precocious puberty
Multiple lentigines syndrome	Multiple lentigines, hypertelorism, pulmonic stenosis
Multiple mucosal neuroma syndrome	Mucosal neuromas, thyroid carcinoma, pheochromocytoma, parathyroid adenoma, dysautonomia
Neurofibromatosis	Neurofibromas, central nervous system tumors, iris hamartomas, axillary freckles, skeletal anomalies
Russell-Silver syndrome	Short stature, asymmetry, limb anomalies
Tuberous sclerosis	White macules, multiple hamartomas, central nervous system anomalies
Watson syndrome	Pulmonic stenosis, axillary freckles, low intelligence
Legius syndrome	Axillary freckling macrocephaly, a Noonan-like facial dysmorphism, lipomas

From Marcoux DA, Duran-McKinster C, Baselga E, et al: Pigmentary abnormalities. In: Schachner LA, Hansen RC, editors: Pediatric dermatology, *ed 4, Philadelphia, 2011, Mosby, Table 10-2.*

and are present in almost 100% of patients. They are present at birth but increase in size, number, and pigmentation, especially during the 1st few yr of life. The spots are scattered over the body surface, with predilection for the trunk and extremities but sparing the face. (2) Axillary or inguinal freckling consisting of multiple hyperpigmented areas 2-3 mm in diameter. Skinfold freckling usually appears between 3 and 5 yr of age. The frequency of axillary and inguinal freckling is reported to be >80% by 6 yr of age. Café-au-lait macules are not specific for NF-1; they may be seen in Noonan syndrome, constitutional mismatch repair deficiency syndrome, Legius syndrome, Peutz-Jeghers syndrome, Carney complex, and those diseases listed in Table 596-1. (3) Two or more iris Lisch nodules. Lisch nodules are hamartomas located within the iris and are best identified by a slit-lamp examination (Fig. 596-2). They are present in more than 74% of patients with NF-1 but are not a characteristic of NF-2. The prevalence of Lisch nodules increases with age, from only 5% of children younger than 3 yr of age, to 42% among children 3-4 yr of age, and virtually 100% of adults older than 21 yr of age. (4) Two or more neurofibromas or 1 plexiform neurofibroma. Neurofibromas typically involve the skin, but they may be situated along peripheral nerves and blood vessels and within viscera including the gastrointestinal tract. These lesions appear characteristically during adolescence or pregnancy, suggesting a hormonal influence. They are usually small, rubbery lesions with a slight purplish discoloration of the overlying skin. Plexiform neurofibromas are usually evident at birth and result from diffuse thickening of nerve trunks that are frequently located in the orbital or temporal region of the face. The skin overlying a plexiform neurofibroma may be hyperpigmented to a greater degree than a café-au-lait macule. Plexiform

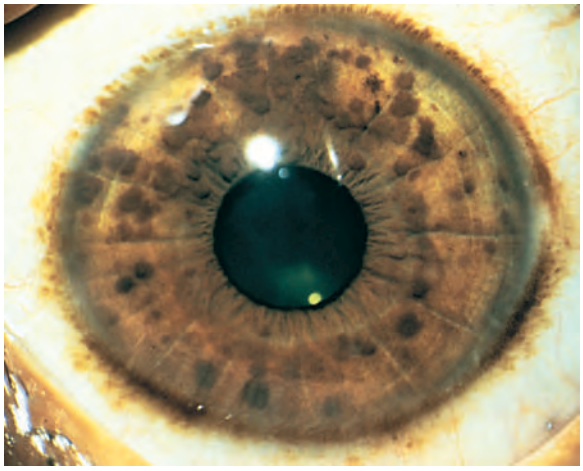


Figure 596-2 Neurofibromatosis type 1 (NF-1). Pigmented hamartomas of the iris (Lisch nodules). *(From Zitelli BJ, McIntire S, Nowalk AJ, editors:* Zitelli and Davis' atlas of pediatric physical diagnosis, *ed 6, Philadelphia, 2012, Mosby, Fig. 15-9.)*

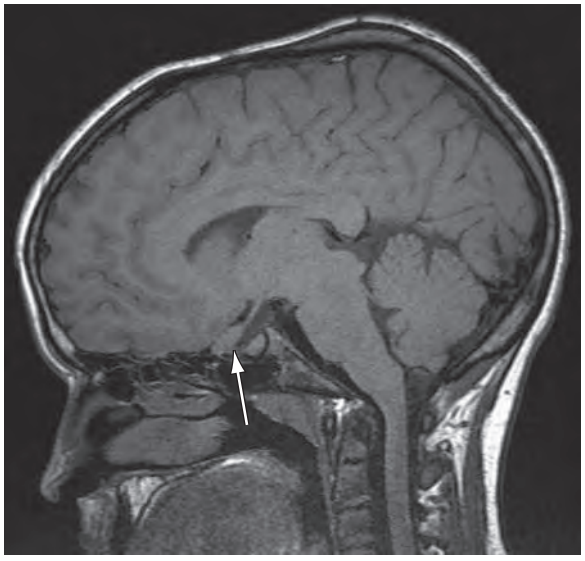


Figure 596-3 Optic glioma. Sagittal T1-weighted MRI scan of a patient with NF-1 shows thickening of the optic nerve *(arrow)*.

neurofibromas may produce overgrowth of an extremity and a deformity of the corresponding bone. (5) A distinctive osseous lesion such as sphenoid dysplasia (which may cause pulsating exophthalmos) or cortical thinning of long bones with or without pseudoarthrosis (e.g., tibia). (6) Optic gliomas are present in approximately 15% of patients with NF-1 and represent mostly low-grade astrocytomas. They are the main central nervous system tumor with a marked increased frequency in NF-1. Because of their growth, it is recommended that all children age 10 yr or younger with NF-1 undergo annual ophthalmologic examinations. When they progress, visual symptoms occur because the tumors enlarge and put pressure on the optic nerves and chiasm resulting in impaired visual acuity and visual fields. Extension into the hypothalamus can lead to endocrine deficiencies or failure to thrive. The MRI findings of an optic glioma include diffuse thickening, localized enlargement, or a distinct focal mass originating from the optic nerve or chiasm (Fig. 596-3). (7) A 1st-degree relative with NF-1 whose diagnosis was based on the aforementioned criteria.

Children with NF-1 are susceptible to **neurologic complications.** MRI studies of selected children have shown abnormal hyperintense T2-weighted signals in the optic tracts, brainstem, globus pallidus,

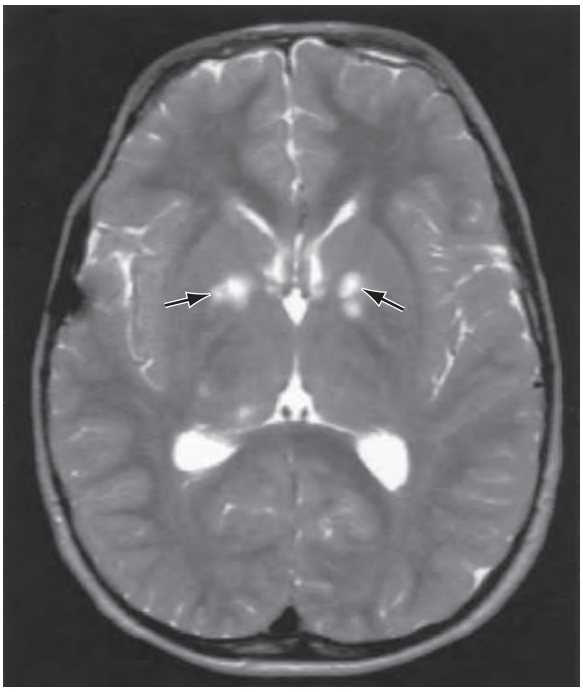


Figure 596-4 T2-weighted MRI scan of a patient with NF-1. Note the high-signal areas (unidentified bright objects) in the basal ganglia *(black arrows)*.

thalamus, internal capsule, and cerebellum (Fig. 596-4). These signals, **"unidentified bright objects,"** tend to disappear with age; most have disappeared by 30 yr of age. It is unclear what the unidentified bright objects represent pathologically, and there is disagreement as to the relationship between the presence and number of unidentified bright objects and the occurrence of learning disabilities, attention-deficit disorders, behavioral and psychosocial problems, and abnormalities of speech among affected children. Therefore, imaging studies such as brain MRIs should be reserved for patients with clinical symptoms only.

One of the most common complications is learning disability affecting approximately 30% of children with NF-1. Seizures are observed in approximately 8% of NF-1 patients. The cerebral vessels may develop aneurysms or stenosis resulting in moyamoya syndrome (see Chapter 601). Neurologic sequelae of these vascular abnormalities include transient cerebrovascular ischemic attacks, hemiparesis, and cognitive defects. Precocious puberty may become evident in the presence or absence of lesions of the optic pathway tumors. Malignant neoplasms are also a significant problem in patients with NF-1, affecting approximately 3% of patients. A neurofibroma occasionally differentiates into a malignant peripheral nerve sheath tumor. The incidence of pheochromocytoma, rhabdomyosarcoma, leukemia, and Wilms tumor is higher than in the general population. Scoliosis is a common complication found in approximately 10% of the patients. Patients with NF-1 are at risk for hypertension, which may result from renal vascular stenosis or a pheochromocytoma.

MANAGEMENT

Because of the diverse and unpredictable complications associated with NF-1, close multidisciplinary follow-up is necessary. Patients with NF-1 should have regular clinical assessments at least yearly, focusing the history and examination on the potential problems for which they are at increased risk. These assessments include yearly ophthalmologic examination, neurologic assessment, blood pressure monitoring, and scoliosis evaluation. Neuropsychologic and educational testing should be considered as needed. The National Institutes of Health (NIH) Consensus Development Conference has advised against routine imaging studies of the brain and optic tracts because treatment in these

Table 596-2 Frequency of Lesions Associated with Neurofibromatosis Type 2

	FREQUENCY OF ASSOCIATION WITH NF-2
NEUROLOGIC LESIONS	
Bilateral vestibular schwannomas	90-95%
Other cranial nerve schwannomas	24-51%
Intracranial meningiomas	45-58%
Spinal tumors	63-90%
Extramedullary	55-90%
Intramedullary	18-53%
Peripheral neuropathy	Up to 66%
OPHTHALMOLOGIC LESIONS	
Cataracts	60-81%
Epiretinal membranes	12-40%
Retinal hamartomas	6-22%
CUTANEOUS LESIONS	
Skin tumors	59-68%
Skin plaques	41-48%
Subcutaneous tumors	43-48%
Intradermal tumors	Rare

From Asthagiri AR, Parry DM, Butman JA, et al: Neurofibromatosis type 2, Lancet 373:1974–1984, 2009, Table 1.

asymptomatic NF-1 children is rarely required. However, all symptomatic cases (i.e., those with visual disturbance, proptosis, increased intracranial pressure) must be studied without delay.

GENETIC COUNSELING

Although NF-1 is an autosomal dominant disorder, more than half the cases are sporadic, representing de novo mutations. The *NF-1* gene on chromosome region 17q11.2 encodes for a protein also known as neurofibromin. Neurofibromin acts as an inhibitor of the oncogene Ras. The diagnosis of NF-1 is based on the clinical features. However, molecular testing for the *NF-1* gene mutations is available and can be useful in a number of cases. Some scenarios in which genetic testing is helpful include for patients who meet only 1 of the criteria for clinical diagnosis, those with unusually severe disease, and those seeking prenatal/preimplantation diagnosis.

NF-2 is a rarer condition, with an incidence of 1 in 25,000 births, and may be diagnosed when 1 of the following 4 features is present: (1) bilateral vestibular schwannomas; (2) a parent, sibling, or child with NF-2 and either unilateral vestibular schwannoma or any 2 of the following: meningioma, schwannoma, glioma, neurofibroma, posterior subcapsular lenticular opacities; (3) unilateral vestibular schwannoma and any 2 of the following: meningioma, schwannoma, glioma, neurofibroma, posterior subcapsular lenticular opacities; or (4) multiple meningiomas (2 or more) and unilateral vestibular schwannoma or any 2 of the following: schwannoma, glioma, neurofibroma, cataract. Symptoms of tinnitus, hearing loss, facial weakness, headache, or unsteadiness may appear during childhood, although signs of a cerebellopontine angle mass are more commonly present in the 2nd and 3rd decades of life. Although café-au-lait macules and skin neurofibromas are classic findings in NF-1, they are much less common in NF-2. Posterior subcapsular lens opacities are identified in approximately 50% of patients with NF-2. The NF-2 gene (which codes for a protein known as merlin or schwannomin) is located on chromosome 22q1.11. Table 596-2 notes the frequency of lesions in NF-2.

Legius syndrome (caused by *SPRED1* mutations) resembles a mild form of NF-1. Patients with Legius syndrome present with multiple café-au-lait macules and macrocephaly, with and without skinfold freckling. However, other typical features of NF-1, such as Lisch nodules, neurofibromas, optic nerve gliomas, and malignant peripheral nerve sheath tumors, are not seen with *SPRED1* mutations.

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596.2 Tuberous Sclerosis

Mustafa Sahin

Tuberous sclerosis complex (TSC) is inherited in an autosomal dominant manner with variable expression and a prevalence of 1 in 6,000 newborns. Spontaneous genetic mutations occur in 65% of the cases. Molecular genetic studies have identified 2 foci for TSC: the *TSC1* gene is located on chromosome 9q34, and the *TSC2* gene is on chromosome 16p13. The *TSC1* gene encodes a protein called *hamartin,* while the *TSC2* gene encodes the protein *tuberin.* Within a cell, these 2 proteins bind to one another and work together. Consequently, a mutation in either the *TSC1* gene or the *TSC2* gene results in a similar disease in patients. The *TSC1* and *TSC2* genes are tumor-suppressor genes. The loss of either tuberin or hamartin protein results in the formation of numerous benign tumors (hamartomas). Tuberin and hamartin are involved in a key pathway in the cell that regulates protein synthesis and cell size. One of the ways cells regulate their growth is by controlling the rate of protein synthesis. A protein called mTOR (mammalian target of rapamycin) was identified as one of the master regulators of cell growth. mTOR, in turn, is controlled by rheb, a small cytoplasmic guanosine triphosphatase. When rheb is activated, the protein synthesis machinery is turned on, most likely via mTOR, and the cell grows in size. Of interest in TSC, rheb is activated by the protein complex formed by hamartin and tuberin.

TSC is an extremely heterogeneous disease with a wide clinical spectrum varying from severe intellectual disability and intractable epilepsy to normal intelligence and a lack of seizures; this variation is often seen within the same family, thus with individuals carrying the same mutation. The disease affects many organ systems other than the skin and brain, including the heart, kidney, eyes, lungs, and bone (Fig. 596-5).

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Definite TSC is diagnosed when at least 2 major or one major plus 2 minor features are present (Tables 596-3 and 596-4 list the major and minor features).

The hallmark of TSC is the involvement of the central nervous system. Retinal lesions consist of two types: hamartomas (elevated mulberry lesions or plaque-like lesions; Fig. 596-6) and white depigmented patches (similar to the hypopigmented skin lesions). The characteristic brain lesion is a cortical tuber (Fig. 596-7). Brain MRI is the best way of identifying cortical tubers, which can form before birth.

Subependymal nodules are lesions found along the wall of the lateral ventricles where they undergo calcification and project into the ventricular cavity, producing a candle-dripping appearance. These lesions do not cause any problems; however, in 5-10% of cases, these benign lesions can grow into subependymal giant cell astrocytomas (SEGAs). These tumors can grow and block the circulation of cerebrospinal fluid around the brain and cause hydrocephalus, which requires immediate neurosurgical intervention. Thus, it is recommended that all asymptomatic TSC patients undergo brain MRI every 1-3 yr to monitor for new occurrence of SEGA. Patients with large or growing SEGA, or with SEGA causing ventricular enlargement but yet are still asymptomatic, should undergo MRI scans more frequently and the patients and their families should be educated regarding the potential of new symptoms due to increased intracranial pressure. Surgical resection should be performed for acutely symptomatic SEGA. For growing but otherwise asymptomatic SEGA, either surgical resection or medical treatment with an mTOR inhibitor may be used. Presymptomatic treatment with everolimus is effective in slowing the growth or even reducing the size of SEGAs. Everolimus is also effective in treating refractory seizures and reducing the volume of renal angiomyolipomas and lymphangioleiomyomatosis as well as facial angiofibromas.

The most common neurologic manifestations of TSC consist of epilepsy, cognitive impairment, and autism spectrum disorders. TSC may present during infancy with infantile spasms and a hypsarrhythmic electroencephalogram pattern. However, it is important to remember

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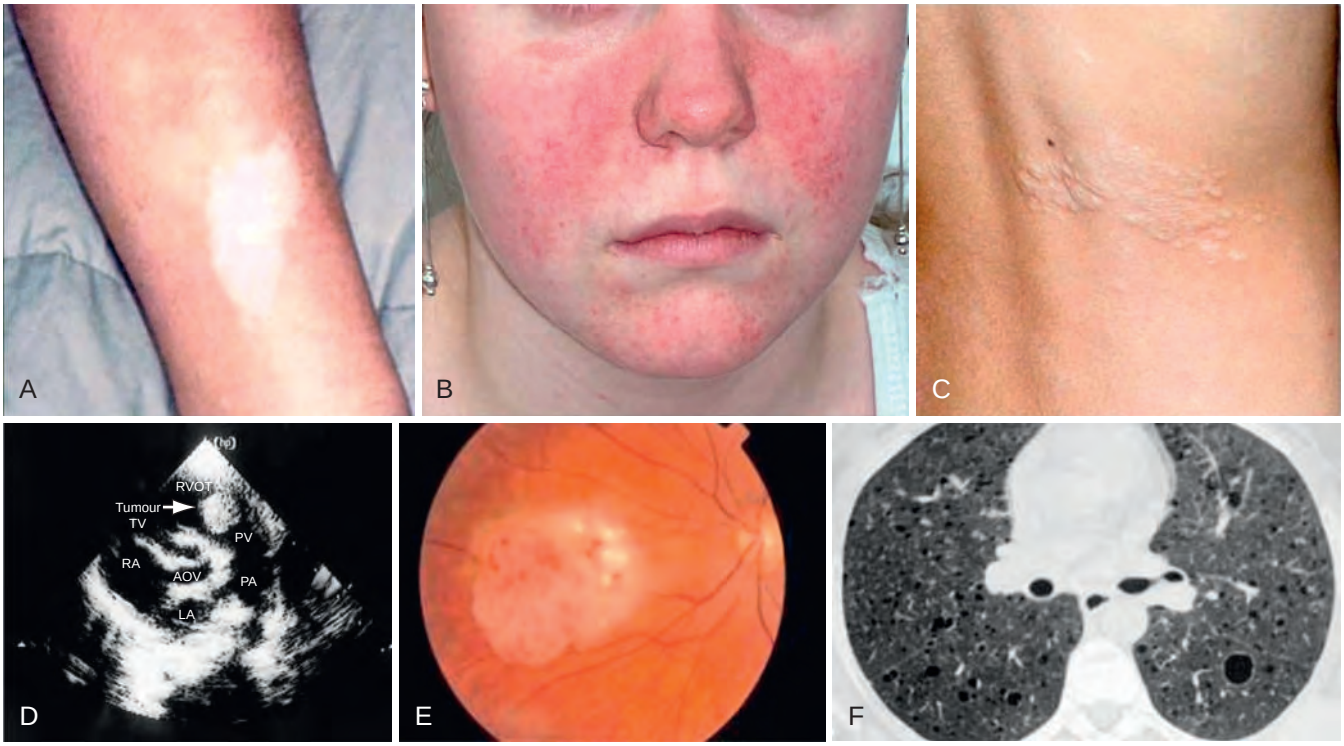


Figure 596-5 Dermatologic, cardiac, and pulmonary manifestations of tuberous sclerosis. **A,** Hypomelanotic macules. **B,** Facial angiofibromas. **C,** Shagreen patch. **D,** Hyperechoic rhabdomyoma detected by echocardiography. **E,** Retinal hamartoma. **F,** Lymphangioleiomyomatosis. *(From Curatolo P, Bombardieri R, Jozwiak S: Tuberous sclerosis,* Lancet *372:657–668, 2008, Fig. 7.)*

Table 596-3 Major Features of TSC

Cortical tuber
Subependymal nodule
Subependymal giant cell astrocytoma
Facial angiofibroma or forehead plaque
Ungual or periungual fibroma (non-traumatic)
Hypomelanotic macules (>3)
Shagreen patch
Multiple retinal hamartomas
Cardiac rhabdomyoma
Renal angiomyolipoma
Pulmonary lymphangioleiomyomatosis

Table 596-4 Minor Features of TSC

Cerebral white matter migration lines
Multiple dental pits
Gingival fibromas
Bone cysts
Retinal achromatic patch
Confetti skin lesions
Nonrenal hamartomas
Multiple renal cysts
Hamartomatous rectal polyps

that you can have infantile spasms without hypsarrhythmia in TSC patients. The seizures may be difficult to control and, at a later age, they may develop into myoclonic epilepsy (see Chapter 593). Vigabatrin is the first-line therapy for infantile spasms. ACTH can be used if treatment with vigabatrin fails. Anticonvulsant therapy of other seizure types in TSC should generally follow that of other epilepsies, and epilepsy surgery should be considered for medically refractory TSC patients.

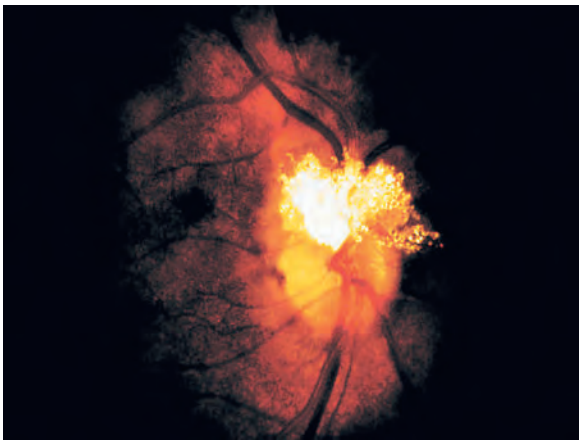


Figure 596-6 A mulberry lesion involving the superior part of the optic nerve in a patient with tuberous sclerosis. *(From Yanoff M, Sassani JW:* Ocular pathology*, ed 7, Philadelphia, 2015, WB Saunders, Fig. 2-7.)*

SKIN LESIONS

More than 90% of patients show the typical hypomelanotic macules that have been likened to an ash leaf on the trunk and extremities. Visualization of the hypomelanotic macule is enhanced by the use of a Wood ultraviolet lamp (see Chapter 653). To count as a major feature, at least three hypomelanotic macules must be present (see Fig. 596-5). Facial angiofibromas develop between 4 and 6 yr of age; they appear as tiny red nodules over the nose and cheeks and are sometimes confused with acne (see Fig. 596-5). Later, they enlarge, coalesce, and assume a fleshy appearance. A shagreen patch is also characteristic of TSC and consists of a roughened, raised lesion with an orange-peel consistency located primarily in the lumbosacral region (see Fig. 596-5). During adolescence or later, small fibromas or nodules

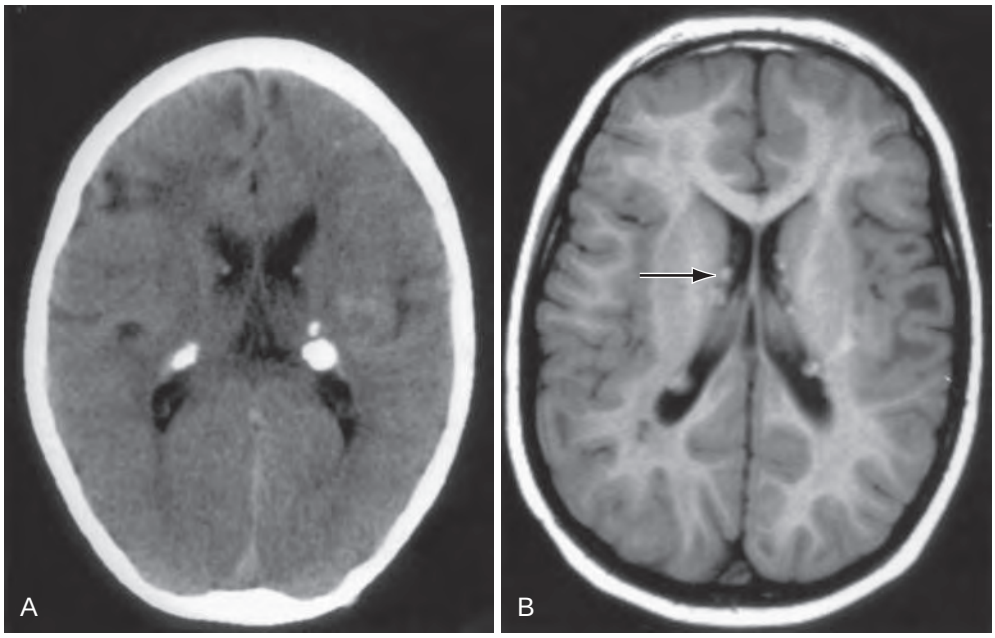


Figure 596-7 Tuberous sclerosis. **A,** CT scan with subependymal calcifications characteristic of tuberous sclerosis. **B,** The MRI demonstrates multiple subependymal nodules in the same patient *(black arrow)*. Parenchymal tubers are also visible on both the CT and the MRI scan as low-density areas in the brain parenchyma.



Figure 596-8 Periungual fibroma in a patient tuberous sclerosis complex (TSC).

of skin may form around fingernails or toenails in 15-20% of the TSC patients (Fig. 596-8).

OTHER ORGAN INVOLVEMENT

Approximately 50% of children with TSC have cardiac rhabdomyomas, which may be detected in the fetus at by an echocardiogram. The rhabdomyomas may be numerous or located at the apex of the left ventricle, and although they can cause congestive heart failure and arrhythmias in a minority of patients, they tend to slowly resolve spontaneously. In 75-80% of patients older than 10 yr of age, the kidneys display angiomyolipomas that are usually benign tumors. Angiomyolipomas begin in childhood in many individuals with TSC, but they may not be problematic until young adulthood. By the third decade of life, they may cause lumbar pain and hematuria from slow bleeding, and rarely they may result in sudden retroperitoneal bleeding. Embolization followed by corticosteroids is first-line therapy for angiomyolipoma presenting with acute hemorrhage. Nephrectomy should be avoided. For asymptomatic, growing angiomyolipomas measuring larger than 3 cm in diameter, an mTOR inhibitor, everolimus, is FDA-approved for treatment. Selective embolization or kidney-sparing resection is alternative therapies for asymptomatic angiomyolipoma. The current recommendation is to follow the angiomyolipoma by yearly imaging, and when the size of the lesion reaches more than 4 cm, to use transcatheter tumor embolization for treatment. Single or multiple renal cysts are also commonly present in TSC. Lymphangioleiomyomatosis is the classical pulmonary lesion in TSC and only affects women after the age of 20 yr.

Diagnosis of TSC relies on a high index of suspicion when assessing a child with infantile spasms. A careful evaluation for the typical skin and retinal lesions should be completed in all patients with a seizure disorder or autism spectrum disorder. Brain MRI confirms the diagnosis in most cases. Genetic testing for *TSC1* and *TSC2* mutations is available and may be considered when the individual patient does not meet all the clinical criteria. Prenatal testing may be offered when a known TSC mutation exists in that family.

MANAGEMENT

As for routine follow-up of individuals with TSC, the following are recommended in addition to physical examination: brain MRI every 1-3 yr, renal imaging (US, CT or MRI) every 1-3 yr and neurodevelopmental testing at the time of beginning 1st grade. Based on the complications of the disease, additional follow-up testing may be required for each individual. Symptoms and signs of increased intracranial pressure suggest obstruction of the foramen of Monro by a SEGA and warrant immediate investigation and surgical intervention.

Bibliography is available at Expert Consult.

596.3 Sturge-Weber Syndrome

Mustafa Sahin

Sturge-Weber syndrome (SWS) is a sporadic vascular disorder and consists of a constellation of symptoms and signs including a facial capillary malformation (port-wine stain), abnormal blood vessels of the brain (leptomeningeal angioma) and abnormal blood vessels of the eye leading to glaucoma. Patients present with seizures, hemiparesis, stroke-like episodes, headaches, and developmental delay. Approximately 1 in 50,000 live births are affected with SWS.

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ETIOLOGY

The sporadic incidence and focal nature of SWS suggests the presence of somatic mutations. Whole-genome sequencing from affected and unaffected skin of 3 patients with SWS identified a single-nucleotide variant (c.548G→A, p.Arg183Gln) in the *GNAQ* gene. This mutation has been confirmed in samples of affected tissue from 88% of a larger cohort of SWS patients as well as 92% of the participants with apparently nonsyndromic port-wine stains. Brain tissue from SWS patients also demonstrated the same change in the *GNAQ* gene. These results strongly suggest that SWS occurs as a result of mosaic mutations in *GNAQ*.

The condition is thought to result from anomalous development of the embryonic vascular bed in the early stages of facial and cerebral development. There are hypotheses about aberrant sympathetic innervation, increased vascular growth factors and defects in extracellular matrix, but these remain to be tested. Low flow angiomatosis of the leptomeninges appears to result in a chronic hypoxic state leading to cortical atrophy and calcifications.

CLINICAL MANIFESTATIONS

The facial port-wine stain is present at birth, tends to be unilateral, and always involves the upper face and eyelid, in a distribution consistent with the ophthalmic division of the trigeminal nerve (Fig. 596-9). The capillary malformation may also be evident over the lower face, trunk, and in the mucosa of the mouth and pharynx. It is important to note that not all children with facial port-wine stain have SWS even though the genetic defect appears to be the same. In fact, the overall incidence of SWS has been reported to be 8-33% in those with a port-wine stain. Buphthalmos and glaucoma of the ipsilateral eye are common complications. The incidence of epilepsy in patients with SWS is 75-90%, and seizures develop in most patients in the 1st yr of life. They are typically focal tonic–clonic and contralateral to the side of the facial capillary malformation. The seizures may become refractory to anticonvulsants and are associated with a slowly progressive hemiparesis in many cases. Transient stroke-like episodes or visual defects persisting for several days and unrelated to seizure activity are common and probably result from thrombosis of cortical veins in the affected region. Although neurodevelopment appears to be normal in the 1st yr of life, intellectual disability or severe learning disabilities are present in at least 50% in later childhood, probably the result of intractable epilepsy and increasing cerebral atrophy.

DIAGNOSIS

MRI with contrast is the imaging modality of choice for demonstrating the leptomeningeal angioma in SWS (Fig. 596-10). White matter abnormalities are common and are thought to be a result of chronic hypoxia. Often, atrophy is noted ipsilateral to the leptomeningeal angiomatosis. Calcifications can be seen best with a head CT (Fig. 596-11).

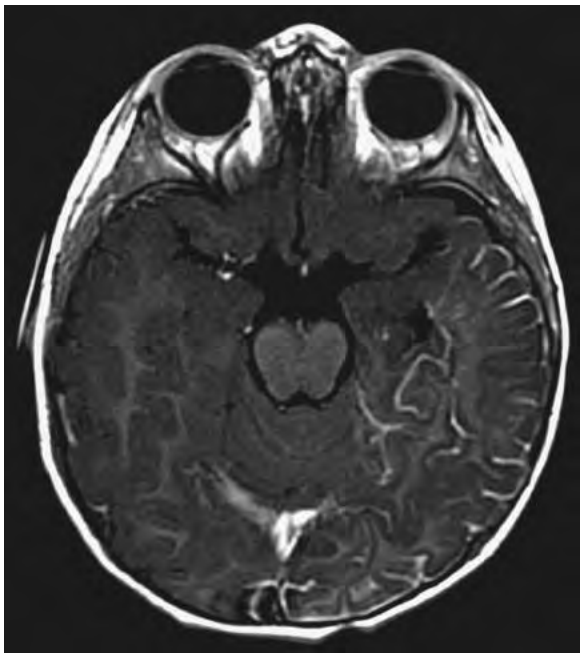


Figure 596-10 Gadolinium-enhanced axial T1 fluid-attenuated inversion recovery (FLAIR) images of a 15 mo old with Sturge-Weber syndrome shows leptomeningeal enhancement in left hemisphere.



Figure 596-9 Port-wine stain involving both V1 and V2 dermatomes. *(Courtesy of Dr. Anne W. Lucky, Cincinnati Children's Hospital.)*

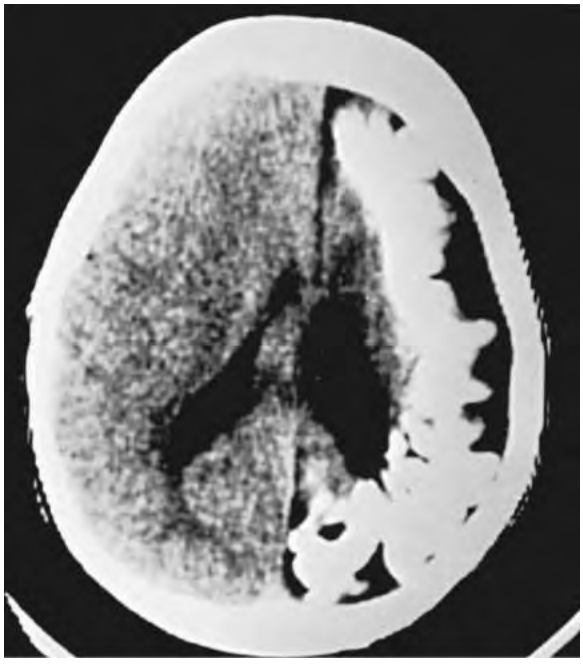


Figure 596-11 CT scan of a patient with Sturge-Weber syndrome showing unilateral calcification and underlying atrophy of a cerebral hemisphere.

Ophthalmologic evaluation examining for glaucoma is also necessary. Based on the involvement of the brain and the face, there are 3 types of SWS according to the Roach Scale:

1. Type I—Both facial and leptomeningeal angiomas; may have glaucoma
2. Type II—Facial angioma alone (no central nervous system involvement); may have glaucoma
3. Type III—Isolated leptomeningeal angiomas; usually no glaucoma

MANAGEMENT

Management of SWS is symptomatic and multidisciplinary but not well studied by prospective studies. It is aimed at seizure control, treatment of headaches, and prevention of stroke-like episodes, as well as monitoring of glaucoma and laser therapy for the cutaneous capillary malformations. Seizures beginning in infancy are not always associated with a poor neurodevelopmental outcome. For patients with well-controlled seizures and normal or near-normal development, management consists of anticonvulsants and surveillance for complications including glaucoma, buphthalmos, and behavioral abnormalities. If the seizures are refractory to anticonvulsant therapy, especially in infancy and the 1st 1-2 yr, and arise from primarily 1 hemisphere, most medical centers advise a hemispherectomy. Because of the risk of glaucoma, regular measurement of intraocular pressure is indicated. The facial port-wine stain is often a target of ridicule by classmates, leading to psychologic trauma. Pulsed-dye laser therapy often provides excellent clearing of the port-wine stain, particularly if it is located on the forehead.

Bibliography is available at Expert Consult.

596.4 Von Hippel-Lindau Disease

Mustafa Sahin

von Hippel-Lindau disease affects many organs, including the cerebellum, spinal cord, retina, kidney, pancreas, and epididymis. Its incidence is around 1 in 36,000 newborns. It results from an autosomal-dominant mutation affecting a tumor suppressor gene, *VHL*. Approximately 80% of individuals with von Hippel-Lindau syndrome have an affected parent, and approximately 20% have a de novo gene mutation. Molecular testing is available and detects mutations in almost 100% of probands.

The major neurologic features of the condition include cerebellar hemangioblastomas and retinal angiomas. Patients with cerebellar hemangioblastoma present in early adult life with symptoms and signs of increased intracranial pressure. A smaller number of patients have hemangioblastoma of the spinal cord, producing abnormalities of proprioception and disturbances of gait and bladder dysfunction. A CT or MRI scan typically shows a cystic cerebellar lesion with a vascular mural nodule. Total surgical removal of the tumor is curative.

Approximately 25% of patients with cerebellar hemangioblastoma have retinal angiomas. Retinal angiomas are characterized by small masses of thin-walled capillaries that are fed by large and tortuous arterioles and venules. They are usually located in the peripheral retina so that vision is unaffected. Exudation in the region of the angiomas may lead to retinal detachment and visual loss. Retinal angiomas are treated with photocoagulation and cryocoagulation, and both have produced good results.

Cystic lesions of the kidneys, pancreas, liver, and epididymis as well as pheochromocytoma are frequently associated with von Hippel-Lindau disease. Renal carcinoma is the most common cause of death. Regular follow-up and appropriate imaging studies are necessary to identify lesions that may be treated at an early stage.

Bibliography is available at Expert Consult.

596.5 Linear Nevus Syndrome

Mustafa Sahin

This sporadic condition is characterized by a facial nevus and neurodevelopmental abnormalities. The nevus is located on the forehead and nose and tends to be midline in its distribution. It may be quite faint during infancy but later becomes hyperkeratotic, with a yellow-brown appearance. Two thirds of the patients with linear nevus syndrome demonstrate associated neurologic findings, including cortical dysplasia, glial hamartomas, and low-grade gliomas. Cerebral and cranial anomalies, predominantly hemimegalencephaly and enlargement of the lateral ventricles, were reported in 72% of cases. The incidence of epilepsy has been reported as high as 75% and intellectual disability as high as 60%. Focal neurologic signs including hemiparesis and homonymous hemianopia may also be seen.

Bibliography is available at Expert Consult.

596.6 PHACE Syndrome

Mustafa Sahin

See also Chapter 650.

The syndrome denotes *p*osterior fossa malformations, *h*emangiomas, *a*rterial anomalies, *c*oarctation of the aorta and other cardiac defects, and *e*ye abnormalities. It is also referred to as *PHACES syndrome* when ventral developmental defects, including *s*ternal clefting and/or a *s*upraumbilical raphe, are present. Large facial hemangiomas may be associated with a Dandy-Walker malformation, vascular anomalies (coarctation of aorta, aplasia or hypoplastic carotid arteries, aneurysmal carotid dilation, aberrant left subclavian artery), glaucoma, cataracts, microphthalmia, optic nerve hypoplasia, and ventral defects (sternal clefts). The facial hemangioma is typically ipsilateral to the aortic arch. The Dandy-Walker malformation is the most common developmental abnormality of the brain. Other anomalies include hypoplasia or agenesis of the cerebellum, cerebellar vermis, corpus callosum, cerebrum, and septum pellucidum. Cerebrovascular anomalies can result in acquired, progressive vessel stenosis and acute ischemic stroke. According to a case series of 29 children with PHACE syndrome, 44% had language delay, 36% gross motor delay, and 8% fine motor delay; 52% had an abnormal neurologic exam, with speech abnormalities as the most common finding. Overall, there is a female predominance. The underlying pathogenesis of PHACE syndrome remains unknown. Propranolol is starting to be used for treatment of the infantile hemangiomas associated with PHACE syndrome.

Bibliography is available at Expert Consult.

596.7 Incontinentia Pigmenti

Mustafa Sahin

This rare, heritable, multisystem ectodermal disorder features dermatologic, dental, and ocular abnormalities. The phenotype is produced by functional mosaicism caused by random X-inactivation of an X-linked dominant gene that is lethal in males (*IKBKG [inhibitor of kappa B kinase gamma,* previously *NEMO]* gene). The paucity of affected males, the occurrence of female-to-female transmission, and an increased frequency of spontaneous abortions in carrier females support this supposition.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

This disease has 4 phases, not all of which may occur in a given patient. The **1st phase** is evident at birth or in the 1st few wk of life and consists of erythematous linear streaks and plaques of vesicles (Fig. 596-12) that are most pronounced on the limbs and circumferentially

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Figure 596-12 Whorled vesicular phase of incontinentia pigmenti.

on the trunk. The lesions may be confused with those of herpes simplex, bullous impetigo, or mastocytosis, but the linear configuration is unique. Histopathologically, epidermal edema and eosinophil-filled intraepidermal vesicles are present. Eosinophils also infiltrate the adjacent epidermis and dermis. Blood eosinophilia as high as 65% of the white blood cell count is common. The **1st stage** generally resolves by 4 mo of age, but mild, short-lived recurrences of blisters may develop during febrile illnesses. In the **2nd phase**, as blisters on the distal limbs resolve, they become dry and hyperkeratotic, forming verrucous plaques. The verrucous plaques rarely affect the trunk or face and generally involute within 6 mo. Epidermal hyperplasia, hyperkeratosis, and papillomatosis are characteristic. The **3rd or pigmentary stage** is the hallmark of incontinentia pigmenti. It generally develops over weeks to months and may overlap the earlier phases, be evident at birth, or, more commonly, begin to appear in the 1st few wk of life. Hyperpigmentation is more often apparent on the trunk than the limbs and is distributed in macular whorls, reticulated patches, flecks, and linear streaks that follow Blaschko lines. The axillae and groin are invariably affected. The sites of involvement are not necessarily those of the preceding vesicular and warty lesions. The pigmented lesions, once present, persist throughout childhood. They generally begin to fade by early adolescence and often disappear by age 16 yr. Occasionally, the pigmentation remains permanently, particularly in the groin. The lesion, histopathologically, shows vacuolar degeneration of the epidermal basal cells and melanin in melanophages of the upper dermis as a result of incontinence of pigment. In the **4th stage**, hairless, anhidrotic, hypopigmented patches or streaks occur as a late manifestation of incontinentia pigmenti; they may develop, however, before the hyperpigmentation of stage 3 has resolved. The lesions develop mainly on the flexor aspect of the lower legs and less often on the arms and trunk.

Approximately 80% of affected children have other defects. Alopecia, which may be scarring and patchy or diffuse, is most common on the vertex and occurs in up to 40% of patients. Hair may be lusterless, wiry, and coarse. Dental anomalies, which are present in up to 80% of patients and are persistent throughout life, consist of late dentition, hypodontia, conical teeth, and impaction. Central nervous system manifestations, including seizures, intellectual disability, hemiplegia, hemiparesis, spasticity, microcephaly, and cerebellar ataxia, are found in up to 30% of affected children. Ocular anomalies, such as neovascularization, microphthalmos, strabismus, optic nerve atrophy, cataracts, and retrolenticular masses, occur in >30% of children. Nonetheless, >90% of patients have normal vision. Less common abnormalities include dystrophy of nails (ridging, pitting) and skeletal defects.

Diagnosis of incontinentia pigmenti is made on clinical grounds, although major and minor criteria have been established to aid in diagnosis. Wood's lamp examination may be useful in older children and adolescents to highlight pigmentary abnormalities. Clinical molecular testing is available, and in 80% of the affected patients a deletion that removes exons 4 through 10 of *IKBKG* gene can be detected. Differential diagnosis includes hypomelanosis of Ito, which presents with similar skin manifestations and is often associated with chromosomal mosaicism.

MANAGEMENT

The choice of investigative studies and the plan of management depend on the occurrence of particular noncutaneous abnormalities since the skin lesions are benign. The high incidence of associated major anomalies warrants genetic counseling.

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Chapter 597

Movement Disorders

Jonathan W. Mink

Movement disorders are characterized by abnormal or excessive involuntary movements that may result in abnormalities in posture, tone, balance, or fine motor control. Most movement disorders in children are characterized by involuntary movements. These involuntary movements can represent the sole disease manifestation, or they may be one of many signs and symptoms.

Evaluation of movement disorders begins with a comprehensive history and careful neurologic examination. It is often difficult for children and caregivers to describe abnormal movements, which makes observation of the movements by the clinician an essential component of the evaluation. If the movements are not apparent at the time of the examination, video examples from home or school can be invaluable. With the increasing availability of high quality video capability on cellular phones, obtaining a short video is feasible for most families. Resources are available to guide families in gathering useful video data.

There is no specific diagnostic test to differentiate among movement disorders. The category of movement assists in localizing the pathologic process, whereas the onset, age, and degree of abnormal motor activity and associated neurologic findings help organize the investigation.

When considering the type of movement disorder, the following questions concerning the history and examination of the movement are helpful.

- What is the distribution of the movements across body parts?
- Are the movements symmetric?
- What is the speed of the involuntary movements? Are they rapid and fast or slow and sustained?
- When do the movements occur? Are they present at rest? Are they present with maintained posture or with voluntary actions?
- Are the movements seen in relation to certain postures or boy positions?
- Do the abnormal movements occur only with specific tasks?
- Can the child voluntarily suppress the movements, even for a short time?
- Are the movements stereotyped?
- Are the movements rhythmic?
- What is the temporal pattern of the movements? Are they continuous or intermittent? Do they occur in discrete episodes?
- Are the involuntary movements preceded by an urge to make the movement?
- Do the movements persist during sleep?
- Are the movements associated with impairment of motor function?
- What factors aggravated or alleviate the movements?

Table 597-1 Selected Types of Involuntary Movement in Childhood

TYPE	CHARACTERISTICS
Stereotypies (see Chapter 24)	Involuntary, patterned, coordinated, repetitive, rhythmic movements that occur in the same fashion with each repetition
Tics (see Chapter 24)	Involuntary, sudden, rapid, abrupt, repetitive, nonrhythmic, simple or complex motor movements or vocalizations (phonic productions). Tics are usually preceded by an urge that is relieved by carrying out the movement
Tremor	Oscillating, rhythmic movements about a fixed point, axis, or plane
Dystonia (see Chapter 597.3)	Intermittent and sustained involuntary muscles contractions that produce abnormal postures and movements of different parts of the body, often with a twisting quality
Chorea (see Chapter 597.2)	Involuntary, continual, irregular movements or movement fragments with variable rate and direction that occur unpredictably and randomly
Ballism	Involuntary, high amplitude, flinging movements typically occurring proximally. Ballism is essentially a large amplitude chorea
Athetosis	Slow, writhing, continuous, involuntary movements
Myoclonus	Sudden, quick, involuntary muscle jerks

The first decision to be made is whether the movement disorder is "hyperkinetic"(characterized by excessive and involuntary movements) or "hypokinetic" (characterized by slow voluntary movements and a general paucity of movement). Hyperkinetic movement disorders are much more common than hypokinetic disorders in children. Once the category of movement disorder is recognized, etiology can be considered. Clinical history, including birth history, medication/toxin exposure, trauma, infections, family history, progression of the involuntary movements, developmental progress, and behavior should be explored as the underlying cause is established. Table 597-1 lists types and clinical characteristics of selected hyperkinetic movement disorders.

597.1 Ataxias

Denia Ramirez-Montealegre and Jonathan W. Mink

Ataxia is the inability to make smooth, accurate, and coordinated movements, usually because of a dysfunction of the cerebellum, its inputs or outputs, sensory pathways in the posterior columns of the spinal cord, or a combination of these. Ataxias may be generalized or primarily affect gait or the hands and arms or trunk; they may be acute or chronic; acquired or genetic (Tables 597-2 to 597-5).

Signs and symptoms of ataxia include clumsiness, difficulty walking or sitting, falling to 1 side, slurred speech, hypotonia, intention tremor, dizziness, and delayed motor development. Genetic or chronic causes of cerebellar ataxia are often characterized by a long duration of symptoms, a positive family history, muscle weakness and abnormal gait, abnormal tone and strength, abnormal deep tendon reflexes, pes cavus, and sensory defects. Distinguishing ataxia from vestibular dysfunction may be difficult; however, labyrinth disorders are often characterized by severe vertigo, nausea and vomiting, position-induced vertigo, and a severe sense of unsteadiness.

Congenital anomalies of the posterior fossa, including the Dandy-Walker malformation, Chiari malformation, and encephalocele, are prominently associated with ataxia because of their destruction or replacement of the cerebellum (see Chapter 591.9). *MRI is the method of choice for investigating congenital abnormalities of the cerebellum, vermis, and related structures.* **Agenesis of the cerebellar vermis** presents in infancy with generalized hypotonia and decreased deep-tendon reflexes. Delayed motor milestones and truncal ataxia are typical. **Joubert syndrome and related disorders** are autosomal recessive disorders marked by developmental delay, hypotonia, abnormal eye movements, abnormal respirations, and a distinctive malformation of the cerebellum and brainstem that manifests as the "molar tooth sign" on MRI. Mutations in more than 21 different genes are associated with Joubert syndrome, but only approximately 50% of cases have a demonstrated causal mutation (see Chapter 591).

The major **infectious causes of ataxia** include cerebellar abscess, acute labyrinthitis, and acute cerebellar ataxia. **Acute cerebellar ataxia** occurs primarily in children 1-3 yr of age and is a diagnosis of exclusion. The condition often follows a viral illness, such as varicella virus, coxsackievirus, or echovirus infection by 2-3 wk and is thought to represent an autoimmune response to the viral agent affecting the cerebellum (see Chapters 250, 253, and 603). The onset is sudden, and the truncal ataxia can be so severe that the child is unable to stand or sit. Vomiting may occur initially, but fever and nuchal rigidity are absent. Horizontal nystagmus is evident in approximately 50% of cases and, if the child is able to speak, dysarthria may be impressive. Examination of the cerebrospinal fluid is typically normal at the onset of ataxia but a mild lymphocytic pleocytosis (10-30/mm^3) is not unusual. Later in the course, the cerebrospinal fluid protein undergoes a moderate elevation. The ataxia begins to improve in a few weeks but may persist for as long as 3 mo and rarely longer than that. The incidence of acute cerebellar ataxia appears to have declined with increased rates of vaccination against varicella. The prognosis for complete recovery is excellent; a small number have long-term sequelae, including behavioral and speech disorders as well as ataxia and incoordination. **Acute cerebellitis** in contrast is a more severe form of cerebellar ataxia demonstrating abnormal MRI scans, more severe symptoms, and a poorer long-term prognosis. Infectious agents include Epstein-Barr virus, mycoplasma, mumps, and influenza virus, although in many the etiology is unknown; autoimmune cerebellitis may represent some of these unknown cases. Patients may present with ataxia, increased intracranial pressure from obstructive hydrocephalus, headache and fever. **Acute labyrinthitis** may be difficult to differentiate from acute cerebellar ataxia in a toddler. The condition is associated with middle-ear infections and presents with intense vertigo, vomiting, and abnormalities in labyrinthine function.

Toxic causes of ataxia include alcohol, thallium (which is used occasionally in homes as a pesticide), and the anticonvulsants, particularly phenytoin and carbamazepine when serum levels exceed the usual therapeutic range.

Brain tumors (see Chapter 497), including tumors of the cerebellum and frontal lobe, as well as peripheral nervous system neuroblastoma, may present with ataxia. Cerebellar tumors cause ataxia because of direct disruption of cerebellar function or indirectly because of increased intracranial pressure from compression of the fourth ventricle. Frontal lobe tumors may cause ataxia as a consequence of destruction of the association fibers connecting the frontal lobe with the cerebellum or because of increased intracranial pressure. Neuroblastoma (see Chapter 498) may be associated with a paraneoplastic encephalopathy characterized by progressive ataxia, myoclonic jerks,

Table 597-2 Selected Causes of Ataxia in Childhood

CONGENITAL
- Agenesis of vermis of the cerebellum
- Aplasia or dysplasia of the cerebellum
- Basilar impression
- Cerebellar dysplasia with microgyria, macrogyria, or agyria
- Cervical spinal bifida with herniation of the cerebellum (Chiari malformation type 3)
- Chiari malformation
- Dandy-Walker syndrome
- Encephalocele
- Hydrocephalus (progressive)
- Hypoplasia of the cerebellum

DEGENERATIVE AND/OR GENETIC
- Acute intermittent cerebellar ataxia
- Ataxia, retinitis pigmentosa, deafness, vestibular abnormality, and intellectual deterioration
- Ataxia-telangiectasia
- Biemond posterior column ataxia
- Cerebellar ataxia with deafness, anosmia, absent caloric responses, nonreactive pupils, and hyporeflexia
- Cockayne syndrome
- Dentate cerebellar ataxia (dyssynergia cerebellaris progressiva)
- Familial ataxia with macular degeneration
- Friedreich ataxia
- Hereditary cerebellar ataxia, intellectual retardation, choreoathetosis, and eunuchoidism
- Hereditary cerebellar ataxia with myotonia and cataracts
- Hypertrophic interstitial neuritis
- Marie ataxia
- Marinesco-Sjögren syndrome
- Multiple-system atrophy
- Pelizaeus-Merzbacher disease
- Periodic attacks of vertigo, diplopia, and ataxia–autosomal-dominant inheritance
- Posterior and lateral column difficulties, nystagmus, and muscle atrophy
- Progressive cerebellar ataxia and epilepsy
- Ramsay Hunt syndrome (myoclonic seizures and ataxia)
- Roussy-Lévy disease
- Spinocerebellar ataxia (SCA); olivopontocerebellar ataxias
- Vanishing white matter syndrome

ENDOCRINOLOGIC
- Acquired hypothyroidism
- Cretinism

INFECTIOUS, POSTINFECTIOUS, INFLAMMATORY
- Acute cerebellar ataxia
- Acute disseminated encephalomyelitis
- Autoimmune (anti-glutamic acid decarboxylase, anti–γ-aminobutyric $acid_B$ receptor antibodies)
- Cerebellar abscess
- Cerebellitis
- Coxsackievirus
- Diphtheria
- Echovirus
- Fisher syndrome
- Infectious mononucleosis (Epstein-Barr virus infection)
- Infectious polyneuropathy
- Japanese B encephalitis
- Mumps encephalitis
- *Mycoplasma* pneumonia
- Paraneoplastic (opsoclonus-myoclonus-ataxia syndrome)
- Pertussis
- Polio
- Postbacterial meningitis
- Rubeola
- Tuberculosis
- Typhoid
- Varicella

METABOLIC
- Abetalipoproteinemia
- Argininosuccinic aciduria
- Ataxia with vitamin E deficiency (AVED)
- Congenital disorders of glycosylation
- GM_2 gangliosidosis (late)
- Hartnup disease
- Hyperalaninemia
- Hyperammonemia I and II (urea cycle defects)
- Hypoglycemia
- Kearns-Sayre syndrome
- Leigh disease
- Maple syrup urine disease (intermittent)
- Myoclonic epilepsy with ragged red fibers (MERRF)
- Metachromatic leukodystrophy
- Mitochondrial complex defects (I, III, IV)
- Multiple carboxylase deficiency (biotinidase deficiency)
- Neuronal ceroid-lipofuscinosis
- Neuropathy, ataxia, retinitis pigmentosa (NARP)
- Niemann-Pick disease (late infantile)
- 5-Oxoprolinuria
- Pyruvate decarboxylase deficiency
- Refsum disease
- Sialidosis
- Triose-phosphate isomerase deficiency
- Tryptophanuria
- Wernicke encephalopathy

NEOPLASTIC
- Frontal lobe tumors
- Hemispheric cerebellar tumors
- Midline cerebellar tumors
- Neuroblastoma
- Pontine tumors (primarily gliomas)
- Spinal cord tumors

PRIMARY PSYCHOGENIC
- Conversion reaction

TOXIC
- Alcohol
- Benzodiazepines
- Carbamazepine
- Clonazepam
- Lead encephalopathy
- Neuroblastoma
- Phenobarbital
- Phenytoin
- Primidone
- Tic paralysis poisoning

TRAUMATIC
- Acute cerebellar edema
- Acute frontal lobe edema

VASCULAR
- Angioblastoma of cerebellum
- Basilar migraine
- Cerebellar embolism
- Cerebellar hemorrhage
- Cerebellar thrombosis
- Posterior cerebellar artery disease
- Vasculitis
- von Hippel-Lindau disease

Modified from Jafar-Nejad P, Maricich SM, Zoghbi HY: The cerebellum and the hereditary ataxias. In Swaiman KF, Ashwal S, Ferriero DM, Schor NF, editors: Swaiman's pediatric neurology, *ed 5, Philadelphia, 2012, WB Saunders, Box 67-1.*

Table 597-3 Treatable Causes of Inherited Ataxia

DISORDER	METABOLIC ABNORMALITY	DISTINGUISHING CLINICAL FEATURES	TREATMENT
Acute disseminated encephalomyelitis	Demyelination	Positive MRI findings	Steroids, IVIG, rituximab
Ataxia with vitamin E deficiency	Mutation in α-tocopherol transfer protein	Ataxia, areflexia, retinopathy	Vitamin E
Bassen-Kornzweig syndrome	Abetalipoproteinemia	Acanthocytosis, retinitis pigmentosa, fat malabsorption	Vitamin E
Hartnup disease	Tryptophan malabsorption	Pellagra rash, intermittent ataxia	Niacin
Familial episodic ataxia type 1 and type 2	Mutations in potassium channel (KCNA1) and α_{1A} voltage-gated calcium channel, respectively	Episodic attacks, worse with pregnancy or birth control pills	Acetazolamide
Multiple carboxylase deficiency	Biotinidase deficiency	Alopecia, recurrent infections, variable organic aciduria	Biotin
Mitochondrial complex defects	Complexes I, III, IV	Encephalomyelopathy	Possibly riboflavin, CoQ10, dichloroacetate
Opsoclonus-myoclonus-ataxia syndrome	Paraneoplastic or spontaneous autoimmune	Underlying neuroblastoma or autoantibodies	Steroids, IVIG, rituximab
Pyruvate dehydrogenase deficiency	Block in E-M and Krebs cycle interface	Lactic acidosis, ataxia	Ketogenic diet, possibly dichloroacetate
Refsum disease	Phytanic acid, α-hydroxylase	Retinitis pigmentosa, cardiomyopathy, hypertrophic neuropathy, ichthyosis	Dietary restriction of phytanic acid
Urea cycle defects	Urea cycle enzymes	Hyperammonemia	Protein restriction, arginine, benzoate, α-ketoacids

CoQ10, Coenzyme Q10; E-M, mitochondrial electron transport; IVIG, intravenous immunoglobulin.
Modified from Stumpf DA: The inherited ataxias. Pediatr Neurol *1:129-133, 1985, Table 1; and from Jafar-Nejad P, Maricich SM, Zoghbi HY: The cerebellum and the hereditary ataxias. In Swaiman KF, Ashwal S, Ferriero DM, Schor NF, editors:* Swaiman's pediatric neurology, *ed 5, Philadelphia, 2012, WB Saunders, Table 67-1.*

Table 597-4 Autosomal-Recessive Cerebellar Ataxias

ATAXIA	CHROMOSOME	GENE	GENE PRODUCT	MECHANISM	AGE OF ONSET (yr)
Friedreich ataxia	9q13	*X25*	Frataxin	GAA repeat	2-51
Friedreich ataxia 2	9p23–p11	Unknown	Unknown	Unknown	5-20
AVED	8q13	*TTP1*	TTPA	Missense mutation, deletion, insertion	2-52
Ataxia-telangiectasia	11q22.3	*ATM*	ATM	Missense and deletion mutations	Infancy
ATLD	11q21	*hMRE11*	MRE11A	Missense and deletion mutations	9-48 mo
Ataxia-ocular apraxia 1	9p13.3	*APTX*	Aprataxin	Frameshift, missense, nonsense mutations	2-18
SCAR1	9q34	*SETX*	Senataxin	Frameshift, missense, nonsense mutations	9-22
SCAR2	9q34–qter	Unknown	Unknown	Unknown	Congenital
SCAR3	6p23–p21	Unknown	Unknown	Unknown	3-52
SCAR4	1p36	Unknown	Unknown	Unknown	23-39
SCAR5	15q24–q26	Unknown	Unknown	Unknown	1-10
SCAR6	20q11–q13	Unknown	Unknown	Unknown	Infancy
SCAR7	11p15	Unknown	Unknown	Unknown	Childhood
SCAR8	11p15	*SYNE1*	SYNE1	Splice site mutation, nonsense mutations	17-46

Continued

Table 597-4 Autosomal-Recessive Cerebellar Ataxias—cont'd

ATAXIA	CHROMOSOME	GENE	GENE PRODUCT	MECHANISM	AGE OF ONSET (yr)
SCAR9	1q41	*ADCK3*	ADCK3	Splice site mutation, missense, nonsense mutations	3-11
Ataxia, Cayman type	19q13.3	*ATCAY*	Caytaxin	Missense mutation	Birth
IOSCA	10q24	*C10orf2*	Twinkle	Missense, silent mutations	9-24 mo
Progressive myoclonic epilepsy	21q22.3	*CST6*	Cystatin B	5′ dodecamer repeat	6–13
ARSACS	13q12	*SACS*	Sacsin	Frameshift and nonsense mutations	1–20
Congenital disorders of glycosylation	Multiple	Multiple	Multiple		Birth

ARSACS, autosomal-recessive spastic ataxia of Charlevoix-Saguenay; ATLD, ataxia-telangiectasia-like disorder; AVED, ataxia with vitamin E deficiency; IOSCA, infantile-onset spinocerebellar ataxia; SCAR, spinocerebellar ataxia, autosomal-recessive.

From Jafar-Nejad P, Maricich SM, Zoghbi HY: The cerebellum and the hereditary ataxias. In Swaiman KF, Ashwal S, Ferriero DM, Schor NF, editors: Swaiman's pediatric neurology, *ed 5, Philadelphia, 2012, WB Saunders, Table 67-2.*

Table 597-5 Autosomal-Dominant Cerebellar Ataxias

ATAXIA	CHROMOSOME	GENE	GENE PRODUCT	MECHANISM	AGE OF ONSET (yr)	NORMAL REPEAT	EXPANDED REPEAT	DURATION OF EPISODES
POLYGLUTAMINE EXPANSION								
SCA1	6p23	*SCA1*	Ataxin-1	CAG repeat	6-60	6-44*	39-82*	
SCA2	12q24	*SCA2*	Ataxin-2	CAG repeat	2-65	15-24	35-59	
SCA3/MJD	14q24.3-q31	*MJD1*	Ataxin-3	CAG repeat	11-70	13-47*	45-84*	
SCA6	19q13	*CACNA1A*	CACNA1A	CAG repeat	16-v73	4-20	21-33	
SCA7	3p21.1-p12	*SCA7*	Ataxin-7	CAG repeat	Birth-53	4-35	37-460	
SCA17	6q27	*SCA17*	TBP	CAG repeat	3-48	25-42	45-66	
DRPLA	12p13.31	*DRPLA*	Atrophin-1	CAG repeat	4-55 mo	7-34	53-93	
NONCODING EXPANSION								
SCA8	13q21	*SCA8*	SCA8 RNA	CTG repeat in 3′ UTR	18-72	2-91*	110-155*	
SCA10	22q13	*SCA10*	Ataxin-10	ATTCT repeat in intron 9	14-45	10-29	750-4500	
SCA12	5q31-q33	*SCA12*	P2R2B	CAG repeat in 5′ UTR	8-55	7-32	55-78	
SCA31	16q22.1	*BEAN/TK2*	BEAN/TK2	TGGAA repeat insertion in intron of BEAN and TK	45-72	Rarely (0.23%) 1.5-2.0 kb	2.5-3.8 kb	
OTHER MUTATIONS								
SCA14	19q13.4	*PKC-γ*	PKC-γ	Missense mutation	10-69			
SCA27	13q34	*FGF14*	FGF14	Fibroblast growth factor deficiency	15-20			
SCA5	11p11-q11	*SPTBN2*	β-3 spectrin	Deletion, missense mutations	10-68			
SCA11	15q14-q21.3	*TTBK2*	TTBK2	Truncation mutation	15-43			
SCA13	19q13.3-q13.4	*KCNC3*	KCNC3	Missense mutations	<1-60			
SCA15	3p24.2-3pter	*ITPR1*	ITPR1	Deletion, missense mutation	Child–adult			
SCA28	18p11.22-q11.2.	*AFG3L2*	AFG3L2	Missense mutations	12-36			

Table 597-5 Autosomal-Dominant Cerebellar Ataxias—cont'd

ATAXIA	CHROMOSOME	GENE	GENE PRODUCT	MECHANISM	AGE OF ONSET (yr)	NORMAL REPEAT	EXPANDED REPEAT	DURATION OF EPISODES
MUTATION UNKNOWN								
SCA4	16q22	Unknown	Unknown	Unknown	19-59			
SCA18/SMNA	7q31-q32	Unknown	Unknown	Unknown	12-25			
SCA19	1p21-q21	Unknown	Unknown	Unknown	10-45			
SCA20	11	Unknown	Unknown	Unknown	19-64			
SCA21	7p21.3–p15.1	Unknown	Unknown	Unknown	6-30			
SCA22	1p21-q23	Unknown	Unknown	Unknown	10-46			
SCA23	20p13-p12.2	Unknown	Unknown	Unknown	43-56			
SCA25	2p	Unknown	Unknown	Unknown	1.5-39			
SCA26	19p13.3	Unknown	Unknown	Unknown	26-60			
SCA30	4q34.3-q35.1	Unknown	Unknown	Unknown	45-76			
SAX1	12p13	Unknown	Unknown	Unknown	Early childhood to early 20s			
SPAR	Unknown	Unknown	Unknown	Unknown	15-35			
EPISODIC ATAXIA								
EA1	12p13	*EA1*	KCNA1	Channelopathy	Early childhood			Secs to mins
EA2/FHM	19p13	*CACNA1A*	CACNA1A	Channelopathy: missense and nonsense mutations	4-30			Hours
EA3	1q42	Unknown	Unknown	Unknown	1-42			1 min to 6 h
EA4	Unknown	Unknown	Unknown	Unknown	23-42			Short to constant
EA5	2q22-q23	*CACNB4*	CACNB4	Channelopathy: missense and nonsense mutations	Juvenile			Hours
EA6	5p13	*SLC1A3*	EAAT1	Missense mutation	5			Hours to days
EA7	19q13	Unknown	Unknown	Unknown	<20			Hours to days

*Some overlap of pathogenic and nonpathogenic repeat length.

DRPLA, dentatorubral-pallidoluysian atrophy; EA, episodic ataxia; FHM, familial hemiplegic migraine; MJD, Machado-Joseph disease; SAX, spastic ataxia; SCA, spinocerebellar ataxia; SMNA, sensorimotor neuropathy with ataxia; SPAR, spastic paraplegia, ataxia, and mental retardation; TBP, TATA-binding protein, UTR, untranslated region.

From Jafar-Nejad P, Maricich SM, Zoghbi HY: The cerebellum and the hereditary ataxias. In Swaiman KF, Ashwal S, Ferriero DM, Schor NF, editors: Swaiman's pediatric neurology, *ed 5, Philadelphia, 2012, WB Saunders, Table 67-3.*

and opsoclonus (nonrhythmic, conjugate horizontal and vertical oscillations of the eyes).

Several **metabolic disorders** are characterized by ataxia, including abetalipoproteinemia, arginosuccinic aciduria, and Hartnup disease. **Abetalipoproteinemia** (Bassen-Kornzweig disease) begins in childhood with steatorrhea and failure to thrive (see Chapters 86.3 and 600). A blood smear shows acanthocytosis. Serum chemistries reveal decreased levels of cholesterol and triglycerides; serum β-lipoproteins are absent. Neurologic signs become evident by late childhood and consist of ataxia, retinitis pigmentosa, peripheral neuritis, abnormalities of position and vibration sense, muscle weakness, and intellectual disability. Vitamin E is undetectable in the serum of patients with neurologic symptoms.

Degenerative diseases of the central nervous system represent an important group of ataxic disorders of childhood because of the genetic consequences and poor prognosis. **Ataxia-telangiectasia,** an autosomal recessive condition, is the most common of the degenerative ataxias and is heralded by ataxia beginning at approximately age 2 yr and progressing to loss of ambulation by adolescence. Ataxia-telangiectasia is caused by mutations in the *ATM* gene located at 11q22-q23. ATM is a phosphytidylinositol-3 kinase that phosphorylates proteins involved in DNA repair and cell-cycle control. Oculomotor apraxia of horizontal gaze, defined as difficulty shifting gaze from one object to another and overshooting the target with lateral movement of the head, followed by refixating the eyes, is a frequent finding, as is strabismus, hypometric saccade pursuit abnormalities, and nystagmus. Ataxia-telangiectasia may present with chorea (see Chapter 597.2) rather than ataxia. The telangiectasia becomes evident by mid-childhood and is found on the bulbar conjunctiva, over the bridge of the nose, and on the ears and exposed surfaces of the extremities. Examination of the skin shows a loss of elasticity. Abnormalities of immunologic function that lead to frequent sinopulmonary infections include decreased serum and secretory immunoglobulin (Ig) A as well as diminished IgG_2, IgG_4, and IgE levels in more than 50% of patients. Children with ataxia-telangiectasia have a 50-100–fold increased risk of developing lymphoreticular tumors (lymphoma, leukemia, and Hodgkin disease) as well as brain tumors. Additional laboratory abnormalities include an increased incidence of chromosome breaks, particularly of chromosome 14, and elevated levels of α-fetoprotein. Death results from infection or tumor dissemination.

Friedreich ataxia is inherited as an autosomal-recessive disorder involving the spinocerebellar tracts, dorsal columns in the spinal cord, the pyramidal tracts, and the cerebellum and medulla. The majority of patients are homozygous for a GAA repeat expansion in the noncoding region of the gene coding for the mitochondrial protein frataxin. Mutations cause oxidative injury associated with excessive iron deposits in mitochondria. The onset of ataxia is somewhat later than in ataxia-telangiectasia, but usually occurs before age 10 yr. The ataxia is slowly progressive and involves the lower extremities to a greater degree than the upper extremities. The Romberg test result is positive; the deep-tendon reflexes are absent (particularly at the ankle), and the plantar response is typically extensor (Babinski sign). Patients develop

a characteristic explosive, dysarthric speech, and nystagmus is present in most children. Although patients may appear apathetic, their intelligence is preserved. They may have significant weakness of the distal musculature of the hands and feet. Marked loss of vibration and joint position sense is common and is caused by degeneration of the posterior columns. Friedreich ataxia is also characterized by skeletal abnormalities, including high-arched feet (pes cavus) and hammertoes, as well as progressive kyphoscoliosis. Results of electrophysiologic studies, including visual, auditory brainstem, and somatosensory-evoked potentials, are often abnormal. Hypertrophic cardiomyopathy with progression to intractable congestive heart failure is the cause of death for most patients.

Several forms of **spinocerebellar ataxia** are similar to Friedreich ataxia but are less common. **Roussy-Levy disease** has, in addition to ataxia, atrophy of the muscles of the lower extremity with a pattern of wasting similar to that observed in Charcot-Marie-Tooth disease; **Ramsay Hunt syndrome** has an associated myoclonic epilepsy.

There are more than 20 dominantly inherited spinocerebellar ataxias, some of which present in childhood. These include those associated with CAG (polyglutamine) repeats and noncoding microsatellite expansions. Dominantly inherited episodic ataxias caused by potassium or calcium channel dysfunction present as episodes of ataxia and muscle weakness. Some of these disorders may respond to acetazolamide. The dominantly inherited **olivopontocerebellar atrophies** include ataxia, cranial nerve palsies, and abnormal sensory findings in the 2nd or 3rd decade, but can present in children with rapidly progressive ataxia, nystagmus, dysarthria, and seizures.

Additional degenerative ataxias include **Pelizaeus-Merzbacher disease, neuronal ceroid lipofuscinoses,** and late-onset **GM_2 gangliosidosis** (see Chapters 86.4 and 600). Rare forms of progressive cerebellar ataxia have been described in association with **vitamin E deficiency.** A number of autosomal-dominant progressive spinocerebellar ataxias have been defined at the molecular level, including those caused by unstable trinucleotide repeat expansions.

597.2 Chorea, Athetosis, Tremor

Rebecca K. Lehman and Jonathan W. Mink

Chorea, meaning "dance-like" in Greek, refers to rapid, chaotic movements that seem to flow from 1 body part to another. Affected individuals exhibit motor impersistence, with difficulty keeping the tongue protruded ("darting tongue") or maintaining grip ("milkmaid grip"). Chorea tends to occur both at rest and with action. Patients often attempt to incorporate the involuntary movements into more purposeful movements, making them appear fidgety. *Chorea increases with stress and disappears in sleep.* Chorea can be divided into primary (i.e., disorders in which chorea is the dominant symptom and the etiology is presumed to be genetic) and secondary forms, with the vast majority of pediatric cases falling into the latter category (Tables 597-6 and 597-7).

Sydenham chorea (St. Vitus dance) is the most common acquired chorea of childhood. It occurs in 10-20% of patients with **acute rheumatic fever,** typically weeks to months after a group A β-hemolytic streptococcal infection (see Chapter 183.1). Peak incidence is at age 8-9 yr, with a female predominance of 2:1. There is evidence that group A β-hemolytic streptococci promote the generation of cross-reactive or polyreactive antibodies through molecular mimicry between streptococcal and host antigens. Specifically, antibodies against the *N*-acetyl-β-D-glucosamine epitope (GlcNAc) of streptococcal group A carbohydrate target intracellular β-tubulin and extracellular lysoganglioside GM_1 in human caudate-putamen preparations. These antibodies are also capable of directing calcium/calmodulin–dependent protein kinase II activation, which may cause the neurologic manifestations of Sydenham chorea by increasing dopamine release into the synapse.

The clinical hallmarks of Sydenham chorea are chorea, hypotonia, and emotional lability. Onset of the chorea is usually insidious but may be abrupt. Most patients have generalized chorea but the majority have asymmetric manifestations and up to 20% have hemichorea. Hypotonia manifests with the "pronator sign" (arms and palms turn outward when held overhead) and the "choreic hand" (spooning of the extended hand by flexion of the wrist and extension of the fingers). When chorea and hypotonia are severe, the child may be incapable of feeding, dressing, or walking without assistance. Speech is often involved, sometimes to the point of being unintelligible. Periods of uncontrollable crying and extreme mood swings are characteristic and may precede the onset of the movement disorder.

Table 597-6 Etiologic Classification of Choreic Syndromes

GENETIC CHOREAS
Huntington disease (rarely presents with chorea in childhood)
Huntington disease–like 2 and other Huntington disease –like syndromes
Dentatorubropallidoluysian atrophy
Neuroacanthocytosis
Leigh syndrome and other mitochondrial disorders
Ataxia telangiectasia
Benign hereditary chorea
Wilson disease
Spinocerebellar ataxia (types 2, 3, or 17)
Pantothene kinase–associated neurodegeneration (PKAN)
Paroxysmal kinesigenic choreoathetosis
Paroxysmal nonkinesigenic choreoathetosis
Fahr syndrome
Rett syndrome
STRUCTURAL BASAL-GANGLIA LESIONS
Vascular chorea in stroke, vasculitis, Moyamoya disease
Mass lesions (e.g., central nervous system lymphoma, metastatic brain tumors)
Joubert syndrome and related disorders
Multiple sclerosis plaques
Extrapontine myelinolysis
Trauma
PARAINFECTIOUS AND AUTOIMMUNE DISORDERS
Sydenham chorea
Systemic lupus erythematosus
Chorea gravidarum
Antiphospholipid antibody syndrome
Postinfectious or postvaccinal encephalitis
Anti–N-methyl-D-aspartate (NMDA)–receptor antibody syndrome (Limbic encephalitis)
Paraneoplastic choreas
INFECTIOUS CHOREA
HIV encephalopathy
Toxoplasmosis
Cysticercosis
Diphtheria
Bacterial endocarditis
Neurosyphilis
Scarlet fever
Viral encephalitis (mumps, measles, varicella)
METABOLIC DRUG OR TOXIC ENCEPHALOPATHIES
Acute intermittent porphyria
Hypo-/hypernatremia
Hypocalcemia
Hyperthyroidism
Hypoparathyroidism
Hepatic/renal failure
Carbon monoxide poisoning
Manganese poisoning
Mercury poisoning
Organophosphate poisoning
Pheochromocytoma
DRUG-INDUCED CHOREA (see Table 597-8)

Modified from Cardoso F, Seppi K, Mair KJ, et al: Seminar on choreas, Lancet Neurol *5:589–602, 2006.*

Table 597-7 Genetic Choreas

	MODE OF INHERITANCE	GENE, LOCATION	PROTEIN PRODUCT	USUAL AGE AT ONSET (yr)	CLINICAL SIGNS
HDL2*	AD†	*JPH3*, 16q	Junctophilin-3	20-40	Huntington disease phenotype, sometimes acanthocytosis; almost exclusively African ethnicity
SCA17	AD†	*TBP*, 6q	TBP	10-30	Cerebellar ataxia, chorea, dystonia, hyperreflexia, cognitive decline
DRPLA	AD†	*DRPLA*, 12p	Atrophin-1	About 20	Variable phenotypic picture including chorea, ataxia, seizures, psychiatric disturbances, dementia; more common in Japan than in Europe or United States
SCA3/MJD	AD†	*MJD*, 14q	Ataxin-3	35-40	Wide phenotypic variability with cerebellar ataxia, protruded eyes, chorea, dystonia, parkinsonian features, neuropathy, pyramidal tract features
SCA2	AD†	*Ataxin-2*, 12q	Ataxin-2	30-35	Cerebellar ataxia, chorea, markedly reduced velocity of saccadic eye movements, hyporeflexia
Chorea-acanthocytosis	AR	*VPS13A* (formerly *CHAC*), 9q	Chorein	20-50	Orofacial self-mutilation, dystonia, neuropathy, myopathy, seizures, acanthocytosis
McLeod syndrome	X-linked, recessive	*XK*, Xp	XK-protein	40-70	Dystonia, neuropathy, myopathy, cardiomyopathy, seizures, acanthocytosis, raised creatine kinase, weak expression of Kell antigen
Neuroferritinopathy	AD	*FTL*, 19q	FTL	20-55	Chorea, dystonia, parkinsonian features; usually reduced serum ferritin; MR abnormalities with cyst formation and increased T2 signal in globus pallidus and putamen
AT and ATLD	AR	*ATM*, 11q (*AT*) *MRE11*, 11q (*ATLD*)	ATM (AT) MRE11 (ATLD)	Childhood	Ataxia, neuropathy, oculomotor apraxia, other extrapyramidal manifestations including chorea, dystonia, and myoclonus In AT: oculocutaneous telangiectasias; predisposition to malignancies, IgA and IgG deficiency, high α-fetoprotein in serum and high concentrations of carcinoembryonic antigen
AOA 1 and 2	AR	*APTX*, 9p (*AOA 1*) *SETX*, 9q (*AOA 2*)	Aprataxin (AOA 1) Senataxin (AOA 2)	Childhood or adolescence (later onset in AOA 2)	Ataxia, neuropathy, oculomotor apraxia, other extrapyramidal manifestations including chorea and dystonia; ataxia with oculomotor apraxia type 1: hypoalbuminemia and hypercholesterolemia; ataxia with oculomotor apraxia type 2: raised α-fetoprotein in serum
Pantothenate kinase associated neurodegeneration (formerly Hallervorden-Spatz syndrome)	AR	*PANK2*, 20p	Pantothenate kinase 2	Childhood, but also adult-onset subtype	Chorea, dystonia, parkinsonian features, pyramidal tract features; MR abnormalities with decreased T2 signal in the globus pallidus and substantia nigra, "eye of the tiger" sign (hyperintense area within the hypointense area); sometimes acanthocytosis, abnormal cytosomes in lymphocytes

Continued

Table 597-7 Genetic Choreas—cont'd

	MODE OF INHERITANCE	GENE, LOCATION	PROTEIN PRODUCT	USUAL AGE AT ONSET (yr)	CLINICAL SIGNS
Lesch-Nyhan syndrome	X-linked, recessive	*HPRT*, Xq	Hypoxanthine-guanine phosphoribosyl-transferase	Childhood	Chorea, dystonia, hypotonia, self-injurious behavior with biting of fingers and lips, mental retardation; short stature, renal calculi, hyperuricemia
Wilson disease	AR	*ATP7B*, 13q	Copper transporting P-type adenosine triphosphatase (ATPase)	<40	Parkinsonian features, dystonia, tremor, rarely chorea, behavioral and cognitive change, corneal Kayser-Fleischer rings, liver disease
PKC syndrome and ICCA syndrome	AD	Unknown, 16p	Unknown	<1-40	Paroxysmal movement disorders presenting with recurrent brief episodes of abnormal involuntary movements with dramatic response to low-dose carbamazepine (PKC); recurrent brief episodes of abnormal involuntary movements in association with infantile convulsions (ICCA)
Benign hereditary chorea	AD	*TITF-1*, 14q; other	Thyroid transcription factor 1	Childhood	Chorea, mild ataxia; genetically heterogeneous

*HDL1, HDL3, and HDL4 are very rare conditions (only 1 family known) and therefore not included in the table.
†Disorders based on expanded CAG repeats (HDL2 based on CAG/CTG repeats; SCA 17 based on CAG/CAA repeats); age of symptom onset inversely related to repeat size.
AD, autosomal dominant; AOA, ataxia with oculomotor apraxia (types 1 or 2); AR, autosomal recessive; AT, ataxia telangiectasia; ATLD, ataxia telangiectasia–like disorder; DRPLA, dentatorubropallidoluysian atrophy; ICCA, infantile convulsions and paroxysmal choreoathetosis syndrome; MJD, Machado-Joseph disease; PKC, paroxysmal kinesigenic choreoathetosis; SCA, spinocerebellar ataxia (types 2, 3, or 17).
Modified from Cardoso F, Seppi K, Mair KJ, et al: Seminar on choreas, Lancet Neurol *5:589–602, 2006.*

Sydenham chorea is a clinical diagnosis; a combination of acute *and* convalescent serum antistreptolysin O titers may help to confirm an acute streptococcal infection. Negative titers do not exclude the diagnosis. All patients with Sydenham chorea should be evaluated for carditis and started on long-term antibiotic prophylaxis (e.g., penicillin G benzathine 1.2 million units IM every 4 wk or penicillin V 250 mg PO twice daily) to decrease the risk of rheumatic heart disease with recurrence. For patients with chorea that is impairing, treatment options include valproate, carbamazepine, and dopamine receptor antagonists. Historically, there have been conflicting data regarding the efficacy of prednisone, intravenous immunoglobulin, and other immunomodulatory agents in Sydenham chorea, making it difficult to recommend their routine use. A more recent randomized, double-blinded study of 37 children with Sydenham chorea compared high-dose prednisone (2 mg/kg/day, max: 60 mg) for 4 wk vs a placebo and found that steroids significantly reduced time to remission (54.3 days vs 119.9 days in controls). There is no evidence that treatment with prednisone alters recurrence rate or long-term outcome.

Sydenham chorea usually resolves spontaneously within 6-9 mo, although it can persist for up to 2 yr and, in rare cases, can remain a lifelong condition. Relapse in the 1st few yr is relatively common, occurring in 37.9% of patients in 1 series. Remote recurrence of chorea is rare, but may be provoked by streptococcal infections, pregnancy **(chorea gravidarum),** or oral contraceptive use.

Although much rarer than Sydenham chorea, **systemic lupus erythematosus** (see Chapter 158) is a well-known cause of chorea in children. In some cases, chorea may be the presenting sign of systemic lupus erythematosus. A recent retrospective study of a large pediatric lupus cohort examined the prevalence of antiphospholipid antibodies and evaluated their association with neuropsychiatric symptoms. There was a significant association between a persistently positive lupus anticoagulant and chorea ($p = 0.02$); however, only 2 of the 137 patients in the cohort had chorea. Regardless, a child with chorea of unknown cause should be investigated for the presence of antiphospholipid antibodies.

Table 597-8 Drugs That Can Induce Chorea

DOPAMINE RECEPTOR BLOCKING AGENTS (UPON WITHDRAWAL OR AS A TARDIVE SYNDROME) Phenothiazines Butyrophenones Benzamides	CALCIUM CHANNEL BLOCKERS Cinnarizine Flunarizine Verapamil
ANTIPARKINSONIAN DRUGS L-DOPA Dopamine agonists Anticholinergics	OTHERS Lithium Baclofen Digoxin Tricyclic antidepressants Cyclosporine Steroids/oral contraceptives Theophylline Propofol
ANTIEPILEPTIC DRUGS Phenytoin Carbamazepine Valproic acid	
PSYCHOSTIMULANTS Amphetamines Methylphenidate Cocaine	

Modified from Cardoso F, Seppi K, Mair KJ, et al: Seminar on choreas, Lancet Neurol *5:589–602, 2006.*

Additional causes of secondary chorea include metabolic (hyperthyroidism, hypoparathyroidism), infectious (Lyme disease), immune-mediated (systemic lupus erythematosus; anti–*N*-methyl-D-aspartate receptor antibody syndrome), vascular (stroke, moyamoya disease), heredodegenerative disorders (Wilson disease), and drugs (Table 597-8). Although chorea is a hallmark of Huntington disease in adults, children who develop Huntington disease tend to present with rigidity and bradykinesia **(Westphal variant)** or dystonia rather than chorea.

Athetosis is characterized by slow, continuous, writhing movements that repeatedly involve the same body part(s), usually the distal

extremities, face, neck, or trunk. Like chorea, athetosis may occur at rest and is often worsened by voluntary movement. Because athetosis tends to co-occur with other movement disorders, such as chorea **(choreoathetosis)** and dystonia, it is often difficult to distinguish as a discrete entity. Choreoathetosis is associated with cerebral palsy, kernicterus, and other forms of basal ganglia injury; therefore, it is often seen in conjunction with **rigidity**—increased muscle tone that is equal in the flexors and extensors in all directions of passive movement regardless of the velocity of the movement. This is to be differentiated from **spasticity,** a velocity-dependent ("clasp-knife") form of hypertonia that is seen with upper motor neuron dysfunction. As with chorea, athetosis/choreoathetosis can also be seen with hypoxic-ischemic injury and dopamine-blocking drugs.

Tremor is a rhythmic, oscillatory movement around a central point or plane that results from the action of antagonist muscles. Tremor can affect the extremities, head, trunk, or voice and can be classified by both its frequency (slow [4 Hz], intermediate [4-7 Hz], and fast [>7 Hz]) and by the context in which it is most pronounced. **Rest tremor** is maximal when the affected body part is inactive and supported against gravity, whereas **postural tremor** is most notable when the patient sustains a position against gravity. **Action tremor** occurs with performance of a voluntary activity and can be subclassified into **simple kinetic tremor**, which occurs with limb movement, and **intention tremor**, which occurs as the patient's limb approaches a target and is a feature of cerebellar disease.

Essential tremor (ET) is the most common movement disorder in adults, and 50% of persons diagnosed with ET report an onset in childhood; thus ET may be the most common tremor disorder in children as well. Clinical experience in pediatric movement disorders clinic suggests that ET is more common in the pediatric population than the literature would suggest. ET is an autosomal-dominant condition with variable expressivity but complete penetrance by the age of 60 yr. Although the genetics of ET are not fully understood, at least 3 different genes—*EMT1* on chromosome 3q13, *EMT2* on chromosome 2p22-25, and *LINGO1* on chromosome 15q24—are linked to the condition. Based on functional imaging studies, the defect is thought to localize to cerebellar circuits.

ET is characterized by a slowly progressive, bilateral, 4-9 Hz postural tremor that involves the upper extremities and occurs in the absence of other known causes of tremor. Mild asymmetry is common, but ET is rarely unilateral. ET may be worsened by actions, such as trying to pour water from cup to cup. Affected adults may report a history of ethanol responsiveness. Most young children present for evaluation because a parent, teacher, or therapist has noticed the tremor, rather than because the tremor causes impairment. Most children with ET do not require pharmacologic intervention. If they are having difficulty with their handwriting or self-feeding, an occupational therapy evaluation and/or assistive devices, such as wrist weights and weighted silverware, may be helpful. Teenagers tend to report more impairment from ET. Teenagers who do require pharmacotherapy usually respond to the same medications that are used in adults—propranolol and primidone. Propranolol, which is generally considered the first-line treatment, can be started at 20–40 mg daily and titrated to effect, with most patients responding to doses of 60-80 mg/day. Propranolol should not be used in patients with reactive airway disease. Primidone can be started at 12.5-25 mg at bedtime and increased gradually in a twice daily schedule. Most patients respond to doses of 50-200 mg/day. Other treatments options for ET reported in the adult literature include atenolol, gabapentin, topiramate, and alprazolam. Surgical treatments, which include deep brain stimulation of the thalamus and unilateral thalamotomy, are generally reserved for adults with medically refractory disabling tremor.

In addition to ET, there are numerous secondary etiologies of tremor in children (Table 597-9). **Holmes tremor,** previously referred to as midbrain or rubral tremor, is characterized by a slow frequency, high-amplitude tremor that is present at rest and with intention. It is a symptomatic tremor, which usually results from lesions of the brainstem, cerebellum, or thalamus. **Psychogenic tremor** is distinguished by its variable appearance, abrupt onset and remission, nonprogressive course, and association with selective but not task-specific disabilities. In some cases, tremor may even occur as a manifestation of another movement disorder, as is seen with position- or task-specific tremor (e.g., writing tremor), dystonic tremor, and myoclonic tremor.

When evaluating a child with tremor, it is important to screen for common metabolic disturbances, including electrolyte abnormalities and thyroid disease, assess the child's caffeine intake, and review the child's medication list for known tremor-inducing agents. It is also critical to exclude Wilson disease in teenagers with characteristic "wing-beating" tremor, as this is a treatable condition.

Table 597-9 Selected Causes of Tremor in Children

BENIGN
Enhanced physiologic tremor
Shuddering attacks
Jitteriness
Spasmus nutans
STATIC INJURY/STRUCTURAL
Cerebellar malformation
Stroke (particularly in the midbrain or cerebellum)
Multiple sclerosis
HEREDITARY/DEGENERATIVE
Familial essential tremor
Fragile X premutation
Wilson disease
Huntington disease
Juvenile parkinsonism (tremor is rare)
Pallidonigral degeneration
METABOLIC
Hyperthyroidism
Hyperadrenergic state (including pheochromocytoma and neuroblastoma)
Hypomagnesemia
Hypocalcemia
Hypoglycemia
Hepatic encephalopathy
Vitamin B_{12} deficiency
Inborn errors of metabolism
Mitochondrial disorders
DRUGS/TOXINS
Valproate, phenytoin, carbamazepine, lamotrigine, gabapentin, lithium, tricyclic antidepressants, stimulants (cocaine, amphetamine, caffeine, thyroxine, bronchodilators), neuroleptics, cyclosporine, toluene, mercury, thallium, amiodarone, nicotine, lead, manganese, arsenic, cyanide, naphthalene, ethanol, lindane, serotonin reuptake inhibitors
PERIPHERAL NEUROPATHIES
PSYCHOGENIC

597.3 Dystonia

Erika F. Augustine and Jonathan W. Mink

Dystonia is a disorder of movement characterized by sustained muscle contraction, frequently causing twisting and repetitive movements or abnormal postures. Major causes of dystonia include primary generalized dystonia, medications, metabolic disorders, and perinatal asphyxia (Tables 597-10 and 597-11).

INHERITED PRIMARY DYSTONIAS

Primary generalized dystonia, also referred to as primary torsion dystonia or *dystonia musculorum deformans*, is caused by a group of genetic disorders with onset in childhood. One form, which occurs more commonly in the Ashkenazi Jewish population, is caused by a dominant mutation in the ***DYT1*** gene coding for the adenosine

Table 597-10 Causes of Dystonia in Childhood

STATIC INJURY/STRUCTURAL DISORDERS
Cerebral palsy
Hypoxic–ischemic injury
Kernicterus
Head trauma
Encephalitis
Tumors
Stroke in the basal ganglia (which may be a result of vascular abnormalities or varicella)
Congenital malformations

HEREDITARY/DEGENERATIVE DISORDERS
DYT1 (9q34, encodes torsinA)
DYT2 (autosomal-recessive)
DYT3 (X-linked dystonia-parkinsonism syndrome of Lubag–Xq13)
DYT4
DYT5 (14q22.1-2, encodes GTP cyclohydrolase I, leading to dopa-responsive dystonia or Segawa disease)
DYT6 (8p21-q22)
DYT7 (18p)
DYT8 (2q33-q35, causing paroxysmal nonkinesigenic choreoathetosis [PNKC])
DYT9 (1p, causing paroxysmal nonkinesigenic dyskinesia [PNKD] and spasticity)
DYT10 (16p11.2-q12.1, causing paroxysmal kinesigenic choreoathetosis [PKC])
DYT11 (heterogeneous, causing familial myoclonus-dystonia)
Rapid-onset dystonia-parkinsonism (DYT12)
Fahr disease (often caused by hypoparathyroid disease)
Pantothenate kinase-associated neurodegeneration (PKAN; neuronal brain iron accumulation type 1, formerly Hallervorden-Spatz disease, caused by mutations in PANK2)
Huntington disease (particularly the Westphal variant, IT15-4p16.3)
Spinocerebellar ataxias (SCAs, including SCA3/Machado-Joseph disease)
Neuronal ceroid-lipofuscinoses (NCL)
Rett syndrome
Striatal necrosis
Leigh disease
Neuroacanthocytosis
HARP syndrome (hypoprebetalipoproteinemia, acanthocytosis, retinitis pigmentosa, and pallidal degeneration)
Ataxia-telangiectasia
Tay-Sachs disease
Sandhoff's disease
Niemann-Pick type C
GM_1 gangliosidosis
Metachromatic leukodystrophy (MLD)
Lesch-Nyhan disease

METABOLIC DISEASE
Glutaric aciduria types 1 and 2
Acyl-coenzyme A (CoA) dehydrogenase deficiencies
Dopa-responsive dystonia (tyrosine hydroxylase deficiency, guanosine triphosphate [GTP] cyclohydrolase 1 deficiency, DYT5)
Dopamine agonist-responsive dystonia (aromatic l-amino acid decarboxylase deficiency, aminolevulinic acid dehydrase [ALAD])
Biotin responsive basal ganglia disease
Mitochondrial disorders
Wilson disease
Vitamin E deficiency
Homocystinuria
Methylmalonic aciduria
Tyrosinemia

DRUGS/TOXINS
Neuroleptic and antiemetic medications (haloperidol, chlorpromazine, olanzapine, risperidone, prochlorperazine)
Calcium channel blockers
Stimulants (amphetamine, cocaine, ergot alkaloids)
Anticonvulsants (carbamazepine, phenytoin)
Thallium
Manganese
Carbon monoxide
Ethylene glycol
Cyanide
Methanol
Wasp sting

PAROXYSMAL DISORDERS
Paroxysmal kinesigenic choreoathetosis (PKC)
Paroxysmal nonkinesigenic choreoathetosis (PNKC)
Exercise-induced dystonia
Complex migraine
Alternating hemiplegia of childhood (AHC)
Paroxysmal torticollis of infancy

DISORDERS THAT MIMIC DYSTONIA
Tonic seizures (including paroxysmal nocturnal dystonia caused by nocturnal frontal lobe seizures)
Arnold-Chiari malformation type II
Atlantoaxial subluxation
Syringomyelia
Posterior fossa mass
Cervical spine malformation (including Klippel-Feil syndrome)
Skew deviation with vertical diplopia causing neck twisting
Juvenile rheumatoid arthritis
Sandifer syndrome (associated with hiatal hernia in infants)
Spasmus nutans
Tics
Infant masturbation
Spasticity
Myotonia
Rigidity
Stiff-person syndrome
Isaac syndrome (neuromyotonia)
Startle disease (hyperekplexia)
Neuroleptic malignant syndrome
Central herniation with posturing
Psychogenic dystonia

From Sanger TD, Mink JW: Movement disorders. In Swaiman KF, Ashwal S, Ferriero DM, Schor NF, editors: Swaiman's pediatric neurology: principles and practice, *ed 5, Philadelphia, 2012, WB Saunders, Box 68-2.*

Table 597-11 Examples of Primary and Secondary Dystonia in Childhood

DIAGNOSIS	ADDITIONAL CLINICAL FEATURES
Aicardi-Goutières syndrome	Encephalopathy, developmental regression Acquired microcephaly Sterile pyrexias Lesions on the digits, ears (chilblain) Epilepsy CT: calcification of the basal ganglia
Alternating hemiplegia of childhood	Episodic hemiplegia/quadriplegia Abnormal ocular movements Autonomic symptoms Epilepsy Global developmental impairment Environmental triggers for spells
Aromatic amino acid decarboxylase deficiency (AADC)	Developmental delay Oculogyric crises Autonomic dysfunction Hypotonia
ARX gene mutation (X-linked)	Male Cognitive impairment Infantile spasms, epilepsy Brain malformation
Benign paroxysmal torticollis of infancy	Episodic Cervical dystonia only Family history of migraine
Complex regional pain syndrome	Lower limb involvement Prominent pain
Dopa-responsive dystonia (DRD)	Diurnal variation
Drug-induced dystonia	
Dystonia-deafness optic neuropathy syndrome	Sensorineural hearing loss in early childhood Psychosis Optic atrophy in adolescence
DYT1 dystonia	Lower limb onset followed by generalization
Glutaric aciduria type 1	Macrocephaly Encephalopathic crises MRI: striatal necrosis
GM_1 gangliosidosis type 3	Short stature, skeletal dysplasia Orofacial dystonia Speech/swallowing disturbance Parkinsonism MRI: putaminal hyperintensity
Huntington disease	Parkinsonism Epilepsy Family history of Huntington disease
Kernicterus	Jaundice in infancy Hearing loss Impaired upgaze Enamel dysplasia MRI: hyperintense lesions in the globus pallidus
Leigh syndrome	Motor delays, weakness, hypotonia Ataxia, tremor Elevated lactate MRI: bilateral symmetric hyperintense lesions in the basal ganglia or thalamus
Lesch-Nyhan syndrome (X-linked)	Male Self-injurious behavior Hypotonia Oromandibular dystonia, inspiratory stridor Oculomotor apraxia Cognitive impairment Elevated uric acid
Myoclonus dystonia	Myoclonus Head, upper limb involvement
Niemann-Pick type C	Hepatosplenomegaly Hypotonia Supranuclear gaze palsy Ataxia, dysarthria Epilepsy Psychiatric symptoms
Neuroacanthocytosis	Oromandibular and lingual dystonia
Neurodegeneration with brain iron accumulation	Cognitive impairment Retinal pigmentary degeneration, optic atrophy
Rapid onset dystonia parkinsonism (DYT12)	Acute onset Distribution face > arm > leg Prominent bulbar signs
Rett syndrome	Female Developmental regression following a period of normal development Stereotypic hand movements Acquired microcephaly Epilepsy
Spinocerebellar ataxia 17 (SCA17)	Ataxia Dementia, psychiatric symptoms Parkinsonism
Tics	Stereotyped movements Premonitory urge, suppressible
Tyrosine hydroxylase deficiency	Infantile encephalopathy, hypotonia Oculogyric crises, ptosis Autonomic symptoms Less diurnal fluctuation than DRD

triphosphate (ATP) binding protein torsinA. The initial manifestation of *DYT1* dystonia is often intermittent unilateral posturing of a lower extremity, which assumes an extended and rotated position. Ultimately, all 4 extremities and the axial musculature can be affected, but the dystonia may also remain localized to one limb. Cranial involvement can occur in *DYT1* dystonia, but it is uncommon compared to non-*DYT1* dystonias. There is a wide clinical spectrum, varying even within families. If a family history of dystonia is absent, the diagnosis should still be considered, given the intrafamilial variability in clinical expression.

More than a dozen loci for genes for torsion dystonia have been identified (*DYT1-DYT24*). One is the autosomal dominant disorder **dopa-responsive dystonia (DRD, *DYT5a*),** also called Segawa syndrome. The gene for DRD codes for guanosine triphosphate cyclohydrolase 1, the rate-limiting enzyme for tetrahydrobiopterin synthesis, which is a cofactor for synthesis of the neurotransmitters dopamine

and serotonin. Thus, the genetic mutation results in dopamine deficiency. The hallmark of the disorder, particularly in adolescents and adults, is diurnal variation: symptoms worsen as the day progresses and may transiently improve with sleep. Early-onset patients, who tend to present with delayed or abnormal gait from dystonia of a lower extremity, can easily be confused with patients with dystonic cerebral palsy. It should be noted that in the presence of a progressive dystonia, diurnal fluctuation, or if loss of previously achieved motor skills occurs, a prior diagnosis of cerebral palsy should be reexamined. DRD responds dramatically to small daily doses of levodopa. The responsiveness to levodopa is a sustained benefit, even if the diagnosis is delayed several years, as long as contractures have not developed.

Myoclonus dystonia (DYT11), caused by mutations in the epsilon-sarcoglycan *(SCGE)* gene, is characterized by dystonia involving the upper extremities, head, and/or neck, as well as myoclonic movements in these regions. Although a combination of myoclonus and dystonia typically occurs, each manifestation can present in isolation. When repetitive, the myoclonus may take on a tremor-like appearance, termed *dystonic tremor*. Improvement in symptoms following alcohol ingestion, reported by affected adult family members, may be a helpful clue to this diagnosis.

Common to the inherited dystonias, there is considerable intrafamilial variability in clinical manifestations, distribution, and severity of dystonia. In primary dystonias, although the main clinical features are motor, there may be an increased risk for major depression. Anxiety, obsessive-compulsive disorder, and depression have all been reported in the myoclonus–dystonia syndrome. Screening for psychiatric comorbidities cannot be overlooked in this population.

DRUG-INDUCED DYSTONIAS

A number of medications are capable of inducing involuntary movements, drug-induced movement disorders, in children and adults. Dopamine-blocking agents, including antipsychotics (e.g., haloperidol) and antiemetics (e.g., metoclopramide, prochlorperazine), as well as atypical antipsychotics (e.g., risperidone) can produce acute dystonic reactions or delayed (tardive) drug-induced movement disorders. **Acute dystonic reactions,** occurring in the 1st days of exposure, typically involve the face and neck, manifesting as torticollis, retrocollis, oculogyric crisis, or tongue protrusion. Life-threatening presentations with laryngospasm and airway compromise can also occur, requiring prompt recognition and treatment of this entity. Intravenous diphenhydramine, 1-2 mg/kg/dose, may rapidly reverse the drug-related dystonia. The high potency of the dopamine blocker, young age, and prior dystonic reactions may be predisposing factors. Acute dystonic reactions have also been described with cetirizine.

Severe rigidity combined with high fever, autonomic symptoms (tachycardia, diaphoresis), delirium, and dystonia are signs of **neuroleptic malignant syndrome**, which typically occurs a few days after starting or increasing the dose of a neuroleptic drug, or in the setting of withdrawal from a dopaminergic agent. In contrast to acute dystonic reactions, which take place within days, neuroleptic malignant syndrome occurs within a month of medication initiation or dose increase.

Delayed onset involuntary movements, **tardive dyskinesias,** develop in the setting of chronic (>3 mo duration) neuroleptic use. Involvement of the face, particularly the mouth, lips, and/or jaw with chewing or tongue thrusting is characteristic. The risk of tardive dyskinesia, which is much less frequent in children compared to adults, increases as medication dose and duration of treatment increase. There are data to suggest that children with autism spectrum disorders may also be at increased risk for this drug-induced movement disorders. Unlike acute dystonic reactions and neuroleptic malignant syndrome, discontinuation of the offending agent may not result in clinical improvement. In these patients, use of dopamine-depletors, such as reserpine or tetrabenazine, may prove helpful.

Therapeutic doses of phenytoin or carbamazepine rarely cause progressive dystonia in children with epilepsy, particularly in those who have an underlying structural abnormality of the brain.

During evaluation of new onset dystonia, a careful history of prescriptions and potential medication exposures is critical.

CEREBRAL PALSY

See Chapter 598.

METABOLIC DISORDERS

Disorders of monamine neurotransmitter metabolism, of which DRD is one, present in infancy and early childhood with dystonia, hypotonia, oculogyric crises, and/or autonomic symptoms. The more common disorders among this group of rare diseases include DRD, tyrosine hydroxylase deficiency, and aromatic amino acid decarboxylase deficiency. Abnormalities of the dopamine transporter (DAT) can also present in infancy with dystonia. Detailed discussion is beyond the scope of this chapter; reviews, however, are available for reference.

Wilson disease is an autosomal recessive inborn error of copper transport characterized by cirrhosis of the liver and degenerative changes in the central nervous system, particularly the basal ganglia (see Chapter 357.2). It has been determined that there are multiple mutations in the Wilson disease gene (*WND*), accounting for the variability in presentation of the condition. The neurologic manifestations of Wilson disease rarely appear before age 10 yr, and the initial sign is often progressive dystonia. Tremors of the extremities develop, unilaterally at first, but they eventually become coarse, generalized, and incapacitating. Other neurologic signs of Wilson disease relate to progressive basal ganglia disease, such as parkinsonism, dysarthria, dysphonia, and choreoathetosis. Less frequent are ataxia and pyramidal signs. The MRI or CT scan shows ventricular dilation in advanced cases with atrophy of the cerebrum, cerebellum, and/or brainstem, along with signal intensity change in the basal ganglia, thalamus, and/or brainstem, particularly the midbrain.

Pantothenate kinase–associated neurodegeneration (formerly known as *Hallervorden-Spatz disease*) is a rare autosomal recessive neurodegenerative disorder. Many patients have mutations in pantothenate kinase 2 *(PANK2)* localized to mitochondria in neurons. The condition usually begins before 6 yr of age and is characterized by rapidly progressive dystonia, rigidity, and choreoathetosis. Spasticity, extensor plantar responses, dysarthria, and intellectual deterioration become evident during adolescence, and death usually occurs by early adulthood. MRI shows lesions of the globus pallidus, including low signal intensity in T2-weighted images (corresponding to iron pigments) and an anteromedial area of high signal intensity (tissue necrosis and edema), or "eye-of-the-tiger" sign (Fig. 597-1). Neuropathologic examination indicates excessive accumulation of iron-containing pigments in the globus pallidus and substantia nigra. More recently, similar disorders of high brain iron content without *PANK2* mutations, including infantile neuroaxonal dystrophy, neuroferritinopathy, and aceruloplasminemia, have been grouped as disorders of neurodegeneration with brain iron accumulation. Patterns of iron deposition visualized by brain MRI have shown utility in differentiating these disorders.

Biotin-responsive basal ganglia disease manifests with episodes of acute dystonia, external ophthalmoplegia and encephalopathy. *SLC19A3* is the responsible mutated gene. MRI demonstrates involvement of the basal ganglia, with vasogenic edema and the "bat-wing" sign (Fig. 597-2). Treatment with biotin and thiamine results in improvement in 2-4 days.

Although dystonia may present in isolation as the first sign of a metabolic or neurodegenerative disorder, this group of diseases should be considered mainly in those who demonstrate signs of systemic disease, (e.g., organomegaly, short stature, hearing loss, vision impairment, epilepsy), those with episodes of severe illness, evidence of regression, or cognitive impairment. Table 597-11 outlines additional features suggestive of specific disorders.

OTHER DISORDERS

Although uncommon, movement disorders, including dystonia, may be part of the presenting symptoms of **complex regional pain syndrome**. Onset of involuntary movements within 1 yr of the traumatic event, affected lower limb, pain disproportionate to inciting event, and changes in the overlying skin and blood flow to the affected area suggest complex regional pain syndrome. Although sustained dystonia

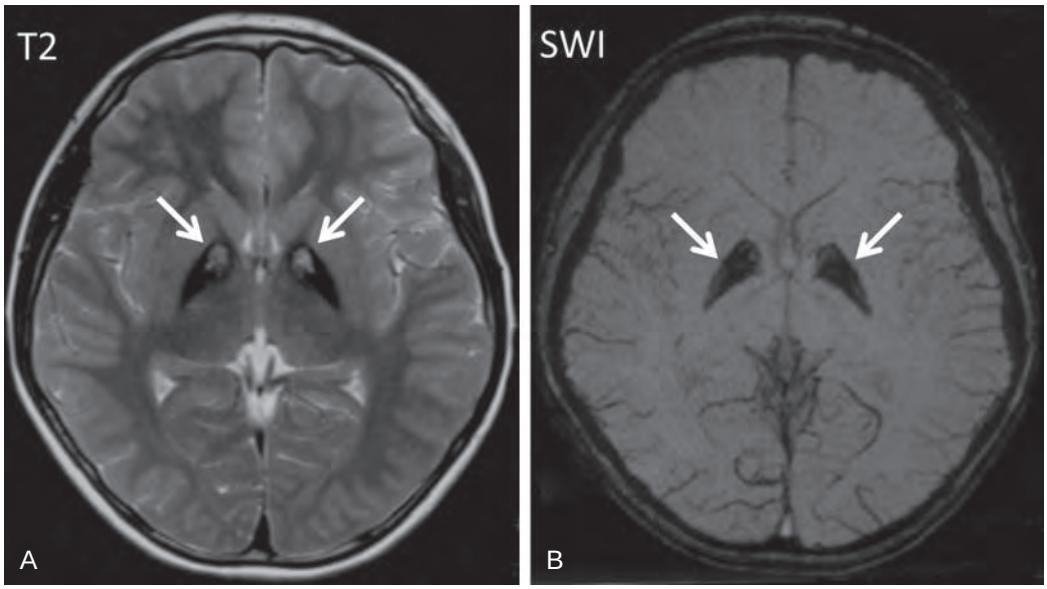


Figure 597-1 Pantothenate kinase–associated neurodegeneration (PKAN). **A,** Axial T2-weighted image showing symmetric hypointensity in the bilateral globi pallidi with central hyperintensity ("eye-of-the-tiger sign," *arrows*). **B,** Axial susceptibility-weighted image (SWI) image showing hypointensity in the globi pallidi representing increased iron accumulation *(arrows). (From From Bosemani T, Meoded A, Poretti A: Susceptibility-weighted imaging in pantothenate kinase-associated neurodegeneration.* J Pediatr *164:212, 2014.)*

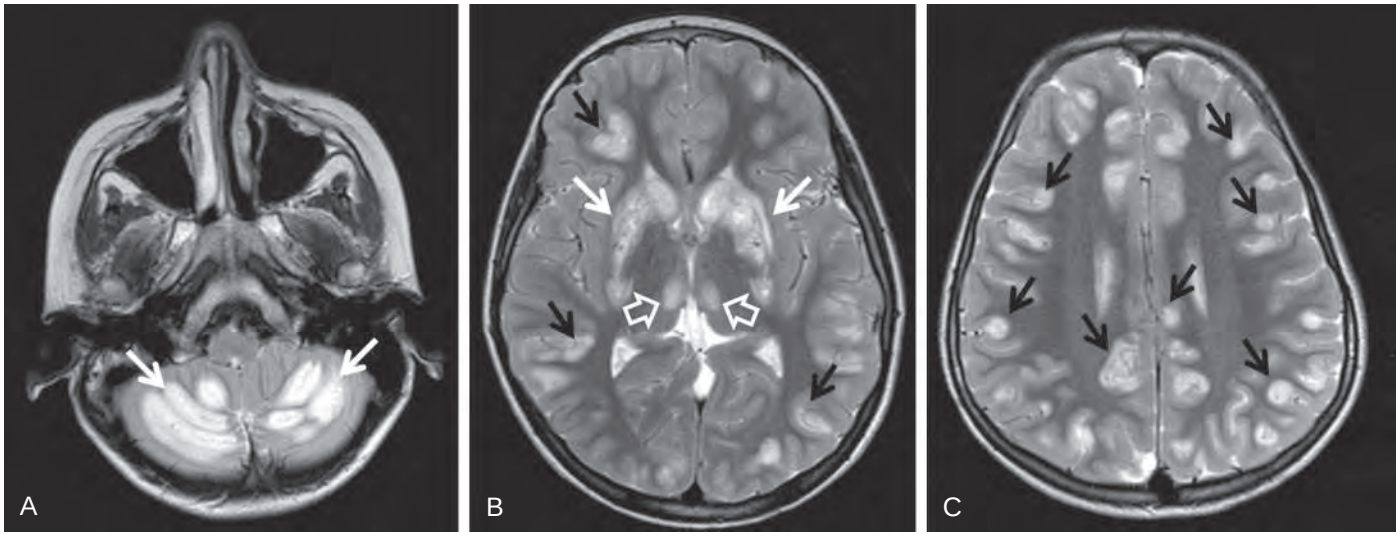


Figure 597-2 Biotin-responsive basal ganglia disease. An initial brain MRI showed high-signal intensity alterations on T2-weighted images bilaterally involving the **(A)** cerebellum *(arrows),* **(B)** basal ganglia *(white arrows),* and medial nucleus of the thalamus *(open arrows),* and **(B, C)** cerebral cortex *(black arrows). (Modified from Tabarki B, Al-Sheikh F, Al-Shahwan S, Zuccoli G: Bilateral external ophthalmoplegia in biotin-responsive basal ganglia disease.* J Pediatr *162:1291–1292, 2013.)*

can produce pain or discomfort, complex regional pain syndrome should be considered in those who have a prominent component of pain and recent history of trauma to the affected limb.

There are disorders unique to childhood that warrant exploration in this section. **Benign paroxysmal torticollis of infancy** is characterized by recurrent episodes of cervical dystonia beginning in the 1st few mo of life. The torticollis may alternate sides from 1 episode to the next and may also persist during sleep. Associated signs and symptoms include irritability, pallor, vomiting, vertigo, ataxia, and occasionally limb dystonia. Family history is often notable for migraine and/or motion sickness in 1st-degree relatives. Despite the high frequency of spells, imaging studies are normal, and the outcome is uniformly benign with resolution by 3 yr of age.

In **alternating hemiplegia of childhood**, episodic hemiplegia affecting either side of the body is the hallmark of the disorder. However, patients are also affected by episodes of dystonia, ranging from minutes to days in duration. On average, both features of the disorder commence at approximately 6 mo of age. Episodic abnormal eye movements are observed in a large proportion of patients (93%) with onset as early as the 1st wk of life. Alternating hemiplegia of childhood is associated with mutations in the *ATP1A2* and *ATP1A3* genes. Alternating hemiplegia of childhood can similarly be triggered by fluctuations in temperature, certain foods, or water exposure. Over time, epilepsy and cognitive impairment emerge, and the involuntary movements change from episodic to constant. Infantile onset and the paroxysmal nature of symptoms early in the disease course are key features to this diagnosis.

Finally, although a diagnosis of exclusion, the presence of odd movements or selective disability may indicate a psychogenic dystonia in older children. There is considerable overlap in features of organic and

psychogenic movement disorders, making the diagnosis difficult to establish. For instance, both organic and psychogenic movement disorders have the potential to worsen in the setting of stress and may dissipate with relaxation or sleep. History should include review of recent stressors, psychiatric symptoms, and exposure to others with similar disorders. On examination, a changing movement disorder, inconsistent motor or sensory exam, or response to suggestion, are supportive of a possible psychogenic movement disorder. Early recognition of this disorder may lessen morbidity caused by unnecessary diagnostic and interventional procedures.

TREATMENT

Children with generalized dystonia, including those with involvement of the muscles of swallowing, may respond to the anticholinergic agent trihexyphenidyl (Artane). Titration occurs slowly over the course of months in an effort to limit untoward side effects, such as urinary retention, mental confusion, or blurred vision. Additional drugs that have been effective include levodopa and diazepam. Segmental dystonia, such as torticollis, often responds well to botulinum toxin injections. Intrathecal baclofen delivered through implantable constant infusion pump may be helpful in some patients. Deep brain stimulation with leads implanted in the globus pallidus is most helpful for children with severe primary generalized dystonia. Recent data suggest, however, that deep brain stimulation may also be of benefit in children with secondary dystonias, such as cerebral palsy.

In the case of drug-induced dystonias, removal of the offending agent and treatment with intravenous diphenhydramine typically suffices. For neuroleptic malignant syndrome, dantrolene may be indicated.

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Chapter 598

Encephalopathies

Michael V. Johnston

Encephalopathy is a generalized disorder of cerebral function that may be acute or chronic, progressive, or static. The etiologies of the encephalopathies in children include infectious, toxic (carbon monoxide, drugs, lead), metabolic, genetic, and ischemic causes. Hypoxic–ischemic encephalopathy is discussed in Chapter 99.5.

598.1 Cerebral Palsy

Michael V. Johnston

See Chapters 36, 97.2, and 597.3.

Cerebral palsy (CP) is a diagnostic term used to describe a group of permanent disorders of movement and posture causing activity limitation, that are attributed to nonprogressive disturbances in the in the developing fetal or infant brain. The motor disorders are often accompanied by disturbances of sensation, perception, cognition, communication, and behavior as well as by epilepsy and secondary musculoskeletal problems. CP is caused by a broad group of developmental, genetic, metabolic, ischemic, infectious, and other acquired etiologies that produce a common group of neurologic phenotypes. CP has historically been considered a static encephalopathy, but some of the neurologic features of CP, such as movement disorders and orthopedic complications, including scoliosis and hip dislocation, can change or progress over time. Many children and adults with CP function at a high educational and vocational level, without any sign of cognitive dysfunction.

EPIDEMIOLOGY AND ETIOLOGY

CP is the most common and costly form of chronic motor disability that begins in childhood; data from the Centers for Disease Control and Prevention indicate that the incidence is 3.6 per 1,000 children with a male : female ratio of 1.4 : 1. The Collaborative Perinatal Project, in which approximately 45,000 children were regularly monitored from in utero to the age of 7 yr, found that most children with CP had been born at term with uncomplicated labors and deliveries. In 80% of cases, features were identified pointing to antenatal factors causing abnormal brain development. A substantial number of children with CP had congenital anomalies external to the central nervous system (CNS). Fewer than 10% of children with CP had evidence of intrapartum asphyxia. Intrauterine exposure to maternal infection (chorioamnionitis, inflammation of placental membranes, umbilical cord inflammation, foul-smelling amniotic fluid, maternal sepsis, temperature >38°C [100.4°F] during labor, urinary tract infection) was associated with a significant increase in the risk of CP in normal birthweight infants. Elevated levels of inflammatory cytokines have been reported in heelstick blood collected at birth from children who later were identified with CP. Genetic factors may contribute to the inflammatory cytokine response, and a functional polymorphism in the interleukin-6 gene is associated with a higher rate of CP in term infants.

The prevalence of CP has increased somewhat as a result of the enhanced survival of very premature infants weighing <1,000 g, who go on to develop CP at a rate of approximately 15 per 100. However, the gestational age at birth-adjusted prevalence of CP among 2 yr old former premature infants born at 20-27 wk of gestation has decreased over the past decade. The major lesions that contribute to CP in preterm infants are **intracerebral hemorrhage** and **periventricular leukomalacia** (PVL). Although the incidence of intracerebral hemorrhage has declined significantly, PVL remains a major problem. PVL reflects the enhanced vulnerability of immature oligodendroglia in premature infants to oxidative stress caused by ischemia or infectious/inflammatory insults. White matter abnormalities (loss of volume of periventricular white matter, extent of cystic changes, ventricular dilation, thinning of the corpus callosum) present on MRI at 40 wk of gestational age among former preterm infants are a predictor of later CP.

In 2006, the European Cerebral Palsy Study examined prenatal and perinatal factors as well as clinical findings and results of MRI in a contemporary cohort of more than 400 children with CP. In agreement with the Collaborative Perinatal Project study, more than half the children with CP in this study were born at term, and less than 20% had clinical or brain imaging indicators of possible intrapartum factors such as asphyxia. The contribution of intrapartum factors to CP is higher in some underdeveloped regions of the world. Also in agreement with earlier data, antenatal infection was strongly associated with CP and 39.5% of mothers of children with CP reported having an infection during the pregnancy, with 19% having evidence of a urinary tract infection and 11.5% reporting taking antibiotics. Multiple pregnancy was also associated with a higher incidence of CP and 12% of the cases in the European CP study resulted from a multiple pregnancy, in contrast to a 1.5% incidence of multiple pregnancy in the study. Other studies have also documented a relationship between multiple births and CP, with a rate in twins that is 5-8 times greater than in singleton pregnancies and a rate in triplets that is 20-47 times greater. Death of a twin in utero carries an even greater risk of CP that is 8 times that of a pregnancy in which both twins survive and approximately 60 times the risk in a singleton pregnancy. Infertility treatments are also associated with a higher rate of CP, probably because these treatments are often associated with multiple pregnancies. Among children from multiple pregnancies, 24% were from pregnancies after infertility treatment compared with 3.4% of the singleton pregnancies in the study. CP is more common and more severe in boys compared to girls and this effect is enhanced at the extremes of body weight. Male infants with intrauterine growth retardation and a birthweight less than the 3rd percentile are 16 times more likely to have CP than males with optimal growth, and infants with weights above the 97th percentile are 4 times more likely to have CP.

Table 598-1 Classification of Cerebral Palsy and Major Causes

MOTOR SYNDROME (APPROX. % OF CP)	NEUROPATHOLOGY/MRI	MAJOR CAUSES
Spastic diplegia (35%)	Periventricular leukomalacia Periventricular cysts or scars in white matter, enlargement of ventricles, squared off posterior ventricles	Prematurity Ischemia Infection Endocrine/metabolic (e.g., thyroid)
Spastic quadriplegia (20%)	Periventricular leukomalacia Multicystic encephalomalacia Cortical malformations	Ischemia, infection Endocrine/metabolic, genetic/developmental
Hemiplegia (25%)	Stroke: in utero or neonatal Focal infarct or cortical, subcortical damage Cortical malformations	Thrombophilic disorders Infection Genetic/developmental Periventricular hemorrhagic infarction
Extrapyramidal (athetoid, dyskinetic) (15%)	Asphyxia: symmetric scars in putamen and thalamus Kernicterus: scars in globus pallidus, hippocampus Mitochondrial: scaring globus pallidus, caudate, putamen, brainstem No lesions: ? dopa-responsive dystonia	Asphyxia Kernicterus Mitochondrial Genetic/metabolic

CLINICAL MANIFESTATIONS

CP is generally divided into several major motor syndromes that differ according to the pattern of neurologic involvement, neuropathology, and etiology (Table 598-1). The physiologic classification identifies the major motor abnormality, whereas the topographic taxonomy indicates the involved extremities. CP is also commonly associated with a spectrum of developmental disabilities, including intellectual impairment, epilepsy, and visual, hearing, speech, cognitive, and behavioral abnormalities. The motor handicap may be the least of the child's problems.

Infants with **spastic hemiplegia** have decreased spontaneous movements on the affected side and show hand preference at a very early age. The arm is often more involved than the leg and difficulty in hand manipulation is obvious by 1 yr of age. Walking is usually delayed until 18-24 mo, and a circumductive gait is apparent. Examination of the extremities may show growth arrest, particularly in the hand and thumbnail, especially if the contralateral parietal lobe is abnormal, because extremity growth is influenced by this area of the brain. Spasticity refers to the quality of increased muscle tone, which increases with the speed of passive muscle stretching and is greatest in antigravity muscles. It is apparent in the affected extremities, particularly at the ankle, causing an equinovarus deformity of the foot. An affected child often walks on tiptoe because of the increased tone in the antigravity gastrocnemius muscles, and the affected upper extremity assumes a flexed posture when the child runs. Ankle clonus and a Babinski sign may be present, the deep tendon reflexes are increased, and weakness of the hand and foot dorsiflexors is evident. About one-third of patients with spastic hemiplegia have a seizure disorder that usually develops in the 1st yr or 2; approximately 25% have cognitive abnormalities including mental retardation. MRI is far more sensitive than CT for most lesions seen with CP, although a CT scan may be useful for detecting calcifications associated with congenital infections. In the European CP study, 34% of children with hemiplegia had injury to the white matter that probably dated to the in utero period and 27% had a focal lesion that may have resulted from a stroke. Other children with hemiplegic CP had had malformations from multiple causes including infections (e.g., cytomegalovirus), lissencephaly, polymicrogyria, schizencephaly, or cortical dysplasia. Focal cerebral infarction (stroke) secondary to intrauterine or perinatal thromboembolism related to thrombophilic disorders, like the presence of anticardiolipin antibodies, is an important cause of hemiplegic CP (see Chapter 601). Family histories suggestive of thrombosis and inherited clotting disorders, such as factor V Leiden mutation, may be present and evaluation of the mother may provide information valuable for future pregnancies and other family members.

Spastic diplegia is bilateral spasticity of the legs that is greater than in the arms. Spastic diplegia is strongly associated with damage to the immature white matter during the vulnerable period of immature oligodendroglia between 20-34 wk of gestation. However, approximately 15% of cases of spastic diplegia result from in utero lesions in infants who go on to delivery at term. The first clinical indication of spastic diplegia is often noted when an affected infant begins to crawl. The child uses the arms in a normal reciprocal fashion but tends to drag the legs behind more as a rudder (commando crawl) rather than using the normal 4-limbed crawling movement. If the spasticity is severe, application of a diaper is difficult because of the excessive adduction of the hips. If there is paraspinal muscle involvement, the child may be unable to sit. Examination of the child reveals spasticity in the legs with brisk reflexes, ankle clonus, and a bilateral Babinski sign. When the child is suspended by the axillae, a scissoring posture of the lower extremities is maintained. Walking is significantly delayed, the feet are held in a position of equinovarus, and the child walks on tiptoe. Severe spastic diplegia is characterized by disuse atrophy and impaired growth of the lower extremities and by disproportionate growth with normal development of the upper torso. The prognosis for normal intellectual development for these patients is good, and the likelihood of seizures is minimal. Such children often have learning disabilities and deficits in other abilities, such as vision, because of disruption of multiple white matter pathways that carry sensory as well as motor information.

The most common neuropathologic finding in children with spastic diplegia is PVL, which is visualized on MRI in more than 70% of cases. MRI typically shows scarring and shrinkage in the periventricular white matter with compensatory enlargement of the cerebral ventricles. However, neuropathology has also demonstrated a reduction in oligodendroglia in more widespread subcortical regions beyond the periventricular zones, and these subcortical lesions may contribute to the learning problems these patients can have. MRI with diffusion tensor imaging is being used to map white matter tracks more precisely in patients with spastic diplegia, and this technique has shown that thalamocortical sensory pathways are often injured as severely as motor corticospinal pathways (Fig. 598-1). These observations have led to greater interest in the importance of sensory deficits in these patients, which may be important for designing rehabilitative techniques.

Spastic quadriplegia is the most severe form of CP because of marked motor impairment of all extremities and the high association with intellectual disability and seizures. Swallowing difficulties are common as a result of supranuclear bulbar palsies, often leading to aspiration pneumonia. The most common lesions seen on pathologic examination or on MRI scanning are severe PVL and multicystic cortical encephalomalacia. Neurologic examination shows increased tone and spasticity in all extremities, decreased spontaneous movements, brisk reflexes, and plantar extensor responses. Flexion contractures of the knees and elbows are often present by late childhood. Associated

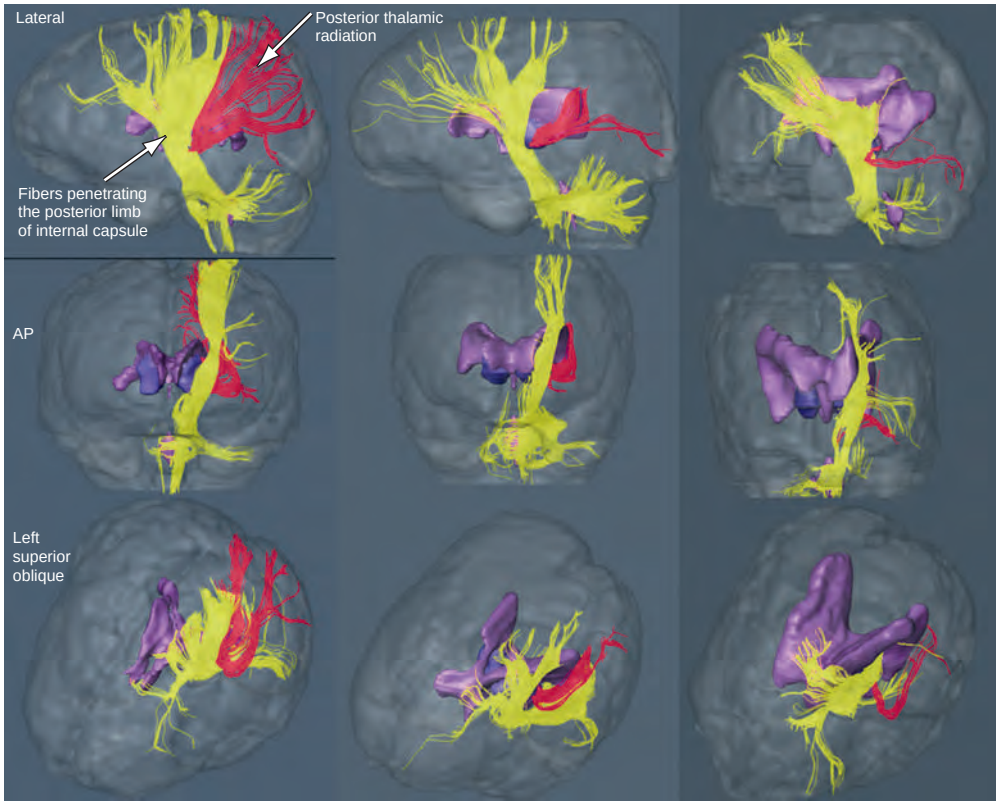


Figure 598-1 Diffusion tensor image of white matter pathways in the brains of 2 patients with spastic diplegia on the right compared to a normal child on the far left. Yellow fibers are corticospinal pathways projected from the motor cerebral cortex at the top downward into the brainstem, whereas the red fibers are thalamocortical sensory fibers projected from the thalamus upward to the cortex. In the children with spastic diplegia, both the corticospinal and thalamocortical pathways are reduced in size, but the ascending thalamocortical pathways are more affected. *(From Nagae LM, Hoon AH Jr, Stashinko E, et al: Diffusion tensor imaging in children with periventricular leukomalacia: variability of injuries to white matter tracts,* AJNR Am J Neuroradiol *28:1213–1222, 2007.)*

developmental disabilities, including speech and visual abnormalities, are particularly prevalent in this group of children. Children with spastic quadriparesis often have evidence of athetosis and may be classified as having mixed CP.

Athetoid CP, also called **choreoathetoid, extrapyramidal,** or **dyskinetic** CP, is less common than spastic CP and makes up approximately 15-20% of patients with CP. Affected infants are characteristically hypotonic with poor head control and marked head lag and develop variably increased tone with rigidity and dystonia over several years. The term *dystonia* refers to the abnormality in tone in which muscles are rigid throughout their range of motion and involuntary contractions can occur in both flexors and extensors leading to limb positioning in fixed postures. Unlike spastic diplegia, the upper extremities are generally more affected than the lower extremities in extrapyramidal CP. Feeding may be difficult, and tongue thrust and drooling may be prominent. Speech is typically affected because the oropharyngeal muscles are involved. Speech may be absent or sentences are slurred, and voice modulation is impaired. Generally, upper motor neuron signs are not present, seizures are uncommon, and intellect is preserved in many patients. This form of CP is also referred to in Europe as dyskinetic CP and is the type most likely to be associated with **birth asphyxia.** In the European CP study, 76% of patients with this form of CP had lesions in the basal ganglia and thalamus. Extrapyramidal CP secondary to acute intrapartum near-total asphyxia is associated with bilaterally symmetric lesions in the posterior putamen and ventrolateral thalamus. These lesions appear to be the correlate of the neuropathologic lesion called *status marmoratus* in the basal ganglia. Athetoid CP can also be caused by **kernicterus** secondary to high levels of bilirubin, and in this case the MRI scan shows lesions in the globus pallidus bilaterally. Extrapyramidal CP can also be associated with lesions in the basal ganglia and thalamus caused by metabolic genetic disorders such as mitochondrial disorders and glutaric aciduria. MRI scanning and possibly metabolic testing are important in the evaluation of children with extrapyramidal CP to make a correct etiologic diagnosis. In patients with dystonia who have a normal MRI, it is important to have a high level of suspicion for dihydroxyphenylalanine (DOPA)-responsive dystonia (Segawa disease), which causes prominent dystonia that can resemble CP. These patients typically have diurnal variation in their signs with worsening dystonia in the legs during the day; however, this may not be prominent. These patients can be tested for a response to small doses of L-dopa and/or cerebrospinal fluid can be sent for neurotransmitter analysis.

Associated comorbidities are common and include pain (in 75%), cognitive disability (50%), hip displacement (30%), seizures (25%), behavioral disorders (25%), sleep disturbances (20%), visual impairment (19%), and hearing impairment (4%).

DIAGNOSIS

A thorough history and physical examination should preclude a **progressive disorder** of the CNS, including degenerative diseases, metabolic disorders, spinal cord tumor, or muscular dystrophy. The possibility of anomalies at the base of the skull or other disorders affecting the cervical spinal cord needs to be considered in patients with little involvement of the arms or cranial nerves. An MRI scan of the brain is indicated to determine the location and extent of structural lesions or associated congenital malformations; an MRI scan of the spinal cord is indicated if there is any question about spinal cord pathology. Additional studies may include tests of hearing and visual function. Genetic evaluation should be considered in patients with congenital malformations (chromosomes) or evidence of metabolic disorders (e.g., amino acids, organic acids, MR spectroscopy). In addition to the genetic disorders mentioned earlier that can present as CP,

the urea cycle disorder arginase deficiency is a rare cause of spastic diplegia and a deficiency of sulfite oxidase or molybdenum cofactor can present as CP caused by perinatal asphyxia. Tests to detect inherited thrombophilic disorders may be indicated in patients in whom an in utero or neonatal stroke is suspected as the cause of CP.

Because CP is usually associated with a wide spectrum of developmental disorders, a multidisciplinary approach is most helpful in the assessment and treatment of such children.

TREATMENT

Some progress has been made in both prevention of CP before it occurs and treatment of children with the disorder. Preliminary results from controlled trials of magnesium sulfate given intravenously to mothers in premature labor with birth imminent before 32 wk gestation showed significant reduction in the risk of CP at 2 yr of age. Nonetheless, one study that followed preterm infants whose mothers received magnesium sulfate demonstrated no benefit in terms of the incidence of CP and abnormal motor, cognitive, or behavioral function at school age. Furthermore, several large trials have shown that cooling term infants with hypoxic–ischemic encephalopathy to 33.3°C (91.9°F) for 3 days, starting within 6 hr of birth, reduces the risk of dyskinetic or spastic quadriplegia form of CP.

For children who have a diagnosis of CP, a team of physicians, including neurodevelopmental pediatricians, pediatric neurologists, and physical medicine and rehabilitation specialists, as well as occupational and physical therapists, speech pathologists, social workers, educators, and developmental psychologists, is important to reduce abnormalities of movement and tone and to optimize normal psychomotor development. Parents should be taught how to work with their child in daily activities such as feeding, carrying, dressing, bathing, and playing in ways that limit the effects of abnormal muscle tone. They also need to be instructed in the supervision of a series of exercises designed to prevent the development of contractures, especially a tight Achilles tendon. Physical and occupational therapies are useful for promoting mobility and the use of the upper extremities for activities of daily living. Speech language pathologists promote acquisition of a functional means of communications. These therapists help children to achieve their potential and often recommend further evaluations and adaptive equipment.

Children with spastic diplegia are treated initially with the assistance of adaptive equipment, such as walkers, poles, and standing frames. If a patient has marked spasticity of the lower extremities or evidence of hip dislocation, consideration should be given to performing surgical soft-tissue procedures that reduce muscle spasm around the hip girdle, including an adductor tenotomy or psoas transfer and release. A rhizotomy procedure in which the roots of the spinal nerves are divided produces considerable improvement in selected patients with severe spastic diplegia (Fig. 598-2). A tight heel cord in a child with spastic hemiplegia may be treated surgically by tenotomy of the Achilles tendon. Quadriplegia is managed with motorized wheelchairs, special feeding devices, modified typewriters, and customized seating arrangements. The function of the affected extremities in children with **hemiplegic CP** can often be improved by therapy in which movement of the good side is constrained with casts while the impaired extremities perform exercises which induce improved hand and arm functioning. This constraint-induced movement therapy is effective in patients of all ages.

Several drugs have been used to **treat spasticity,** including the benzodiazepines and baclofen. These medications have beneficial effects in some patients but can also cause side effects such as sedation for benzodiazepines and lowered seizure threshold for baclofen. Several drugs can be used to **treat spasticity,** including oral diazepam (0.01-0.3 mg/kg/day, divided bid or qid), baclofen (0.2-2 mg/kg/day, divided bid or tid) or dantrolene (0.5-10 mg/kg/day, bid). Small doses of levodopa (0.5-2 mg/kg/day) can be used to treat dystonia or DOPA-responsive dystonia. Artane (trihexyphenidyl, 0.25 mg/day, divided bid or tid and titrated upward) is sometimes useful for treating dystonia and can increase use of the upper extremities and vocalizations. Reserpine (0.01-0.02 mg/kg/day, divided bid to a maximum of 0.25 mg daily) or tetrabenazine (12.5-25.0 mg, divided bid or tid) can be useful for hyperkinetic movement disorders including athetosis or chorea.

Intrathecal baclofen delivered with an implanted pump has been used successfully in many children with severe spasticity, and can be useful because it delivers the drug directly around the spinal cord where it reduces neurotransmission of afferent nerve fibers. Direct delivery to the spinal cord overcomes the problem of CNS side effects caused by the large oral doses needed to penetrate the blood–brain barrier. This therapy requires a team approach and constant follow-up for complications of the infusion pumping mechanism and infection. **Botulinum toxin** injected into specific muscle groups for the management of spasticity shows a very positive response in many patients. Botulinum toxin injected into salivary glands may also help reduce the severity of drooling, which is seen in 10-30% of patients with CP and has been traditionally treated with anticholinergic agents. Patients with rigidity, dystonia, and spastic quadriparesis sometimes respond to levodopa, and children with dystonia may benefit from carbamazepine or trihexyphenidyl. Hyperbaric oxygen has not been shown to improve the condition of children with CP.

Communication skills may be enhanced by the use of Bliss symbols, talking typewriters, electronic speech generating devices, and specially adapted computers including artificial intelligence computers to augment motor and language function. Significant behavior problems may substantially interfere with the development of a child with CP; their early identification and management are important, and the assistance of a psychologist or psychiatrist may be necessary. Learning and attention deficit disorders and mental retardation are assessed and managed by a psychologist and educator. Strabismus, nystagmus, and optic atrophy are common in children with CP; an ophthalmologist should be included in the initial assessment. Lower urinary tract dysfunction should receive prompt assessment and treatment.

Bibliography is available at Expert Consult.

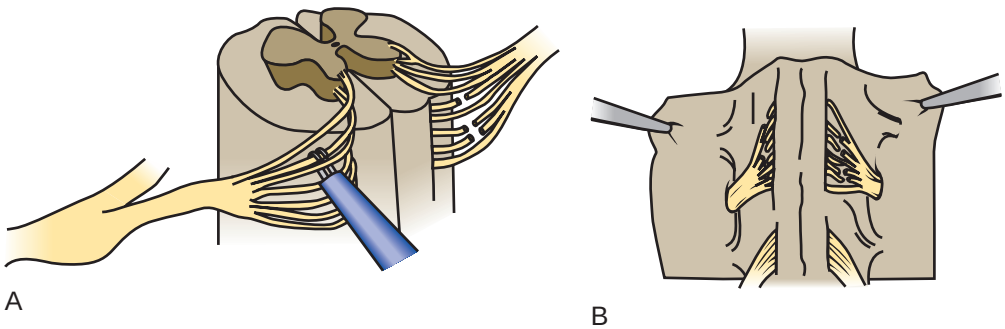


Figure 598-2 Schematic of the technique of selected dorsal rhizotomy. **A,** After laminectomy, the dura is opened and the dorsal spinal rootlets are exposed. The rootlets are stimulated so that abnormal rootlet activity can be identified. **B,** A proportion of rootlets are transected. *(From Koman LA, Smith BP, Shilt JS: Cerebral palsy,* Lancet *363:1619–1631, 2004. Reproduced with permission from Wake Forest University Orthopaedic Press.)*

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598.2 Mitochondrial Encephalomyopathies

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See Chapters 87.4 and 611.4.

Mitochondrial encephalomyopathies are a heterogeneous group of clinical syndromes caused by genetic lesions that impair energy production through oxidative phosphorylation. The signs and symptoms of these disorders reflect the vulnerability of the nervous system, muscles, and other organs to energy deficiency. Signs of brain and muscle dysfunction (seizures, weakness, ptosis, external ophthalmoplegia, psychomotor regression, hearing loss, movement disorders, and ataxia) in association with lactic acidosis are prominent features of mitochondrial disorders. Cardiomyopathy and diabetes mellitus can also result from mitochondrial disorders.

Children with mitochondrial disorders often have multifocal signs that are intermittent or relapsing–remitting, often in association with intercurrent illness. Many of these disorders were described as clinical syndromes before their genetics were understood. Children with mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes (MELAS) present with developmental delay, weakness, and headaches, as well as focal signs that suggest a stroke. Brain imaging indicates that injury does not fit within the usual vascular territories. Children with myoclonic epilepsy with ragged red fibers (MERRF) present with myoclonus and myoclonic seizures as well as intermittent muscle weakness. The ragged red fibers referred to in the name of this disorder are clumps of abnormal mitochondria seen within muscle fibers in sections from a muscle biopsy stained with Gomori trichrome stain. NARP syndrome (neuropathy, ataxia, and retinitis pigmentosa), Kearns-Sayre syndrome (KSS; ptosis, ophthalmoplegia, heart block), Leigh disease (subacute necrotizing encephalomyelopathy), and Leber hereditary optic neuropathy (LHON) are also defined as relatively homogeneous clinical subgroups (Table 598-2). It is important to keep in mind that mitochondrial disorders can be difficult to diagnose. They often present with novel combinations of signs and symptoms as a consequence of high mutation rates for mitochondrial DNA (mtDNA), and the severity of disease varies from person to person.

Mitochondrial diseases can be caused by mutations of nuclear DNA (nDNA) or mtDNA (see Chapters 80, 86, and 87). Oxidative phosphorylation in the respiratory chain is mediated by 4 intramitochondrial enzyme complexes (complexes I-IV) and 2 mobile electron carriers (coenzyme Q and cytochrome c) that create an electrochemical proton gradient utilized by complex V (adenosine triphosphate [ATP] synthase) to create the ATP required for normal cellular function. The maintenance of oxidative phosphorylation requires coordinated regulation of nuclear DNA and mtDNA genes. Human mtDNA is a small (16.6 kb), circular, double-stranded molecule that has been completely sequenced and encodes 37 genes including 13 structural proteins, all of which are subunits of the respiratory chain complexes, as well as 2 ribosomal RNAs and 22 transfer RNAs (tRNAs) needed for translation. The nuclear DNA is responsible for synthesizing approximately 70 subunits, transporting them to the mitochondria via chaperone proteins, ensuring their passage across the inner mitochondrial membrane, and coordinating their correct processing and assembly. Diseases of mitochondrial oxidative phosphorylation can be divided into 3 groups: (1) defects of mtDNA, (2) defects of nDNA, and (3) defects of communication between the nuclear and mitochondrial genome. mtDNA is distinct from nDNA for the following 4 reasons: (1) its genetic code differs from nDNA, (2) it is tightly packed with information because it contains no introns, (3) it is subject to spontaneous mutations at a higher rate than nDNA, (4) it has less efficient repair mechanisms.

Inheritance of mutations present on mtDNA is nonmendelian and can be complex. At fertilization, mtDNA is present in hundreds or thousands of copies per cell and is transmitted by maternal inheritance from her oocyte to all her children, but only her daughters can pass it on to their children. Through the process called heteroplasmy or threshold effect, mtDNA containing mutations can be distributed unequally between cells in specific tissues. Some cells receive few or no mutant genomes (**normal** or **wild-type homoplasmy**), whereas

Table 598-2 Clinical Manifestations of Mitochondrial Encephalomyopathies

TISSUE	SYMPTOMS/SIGNS	MELAS	MERRF	NARP	KSS	LEIGH	LHON
CNS	Regression	+	+		+	+	
	Seizures	+	+				
	Ataxia	+	+	+	+		
	Cortical blindness	+					
	Deafness	+		+			
	Migraine	+					
	Hemiparesis	+					
	Myoclonus	+	+				
	Movement disorder	+					+
Nerve	Peripheral neuropathy	+	+	+	+		
Muscle	Ophthalmoplegia				+		
	Weakness	+	+	+	+	+	
	RRF on muscle biopsy	+	+		+		
	Ptosis				+		
Eye	Pigmentary retinopathy			+	+		
	Optic atrophy				+	+	+
	Cataracts						
Heart	Conduction block				+		+
	Cardiomyopathy				+		
Blood	Anemia	+					
	Lactic acidosis		+		+	+	
Endocrine	Diabetes mellitus				+		
	Short stature	+	+		+		
Kidney	Fanconi syndrome	+	+		+		

KSS, Kearns-Sayre syndrome; LHON, Leber hereditary optic neuropathy; MELAS, mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes; MERRF, myoclonic epilepsy with ragged red fibers; NARP, neuropathy, ataxia and retinitis pigmentosa; RRF, ragged red fibers.

others receive a mixed population of **mutant** and **wild-type** mtDNAs **(heteroplasmy),** and still others receive primarily or exclusively **mutant** genomes **(mutant homoplasmy).** The important implications of maternal inheritance and heteroplasmy are as follows: (1) inheritance of the disease is maternal, but both sexes are equally affected; (2) phenotypic expression of an mtDNA mutation depends on the relative proportions of mutant and wild-type genomes, with a minimum critical number of mutant genomes being necessary for expression **(threshold effect);** (3) at cell division, the proportional distribution may shift between daughter cells (mitotic segregation), leading to a corresponding phenotypic change; and (4) subsequent generations are affected at a higher rate than in autosomal dominant diseases. The critical number of mutant mtDNAs required for the threshold effect may vary, depending on the vulnerability of the tissue to impairments of oxidative metabolism as well as on the vulnerability of the same tissue over time that may increase with aging. In contrast to maternally inherited disorders caused by mutations in mtDNA, diseases resulting from defects in nDNA follow mendelian inheritance. Mitochondrial diseases caused by defects in nDNA include defects in substrate transport (plasmalemmal carnitine transporter, carnitine palmitoyltransferases I and II, carnitine acylcarnitine translocase defects), defects in substrate oxidation (pyruvate dehydrogenase complex, pyruvate carboxylase, intramitochondrial fatty acid oxidation defects), defects in the Krebs cycle (α-ketoglutarate dehydrogenase, fumarase, aconitase defects), and defects in the respiratory chain (complexes I-V), including defects of oxidation/phosphorylation coupling (Luft syndrome), and defects in mitochondrial protein transport.

Diseases caused by defects in mtDNA can be divided into those associated with point mutations that are maternally inherited (e.g., LHON, MELAS, MERRF, and NARP syndromes) and those caused by deletions or duplications of mtDNA that reflect altered communication between the nucleus and the mitochondria (KSS; Pearson syndrome, a rare severe encephalopathy with anemia and pancreatic dysfunction; and progressive external ophthalmoplegia). These disorders can be inherited by sporadic, autosomal dominant or recessive mechanisms and mutations in multiple genes, including mitochondrial mtDNA polymerase γ catalytic subunit (POLG), have been identified. **POLG mutations** have also been identified in patients with Alpers-Huttenlocher syndrome, which causes a refractory seizure disorder and hepatic failure as well as autosomal dominant and recessive progressive external ophthalmoplegia, childhood myocerebrohepatopathy spectrum disorders, myoclonic epilepsy myopathy sensory ataxia syndrome, and *POLG*-related ataxia neuropathy spectrum disorders. Other genes that regulate the supply of nucleotides for mtDNA synthesis are associated with severe encephalopathy and liver disease, and new disorders are being identified that result from defects in the interactions between mitochondria and their milieu in the cell.

MITOCHONDRIAL MYOPATHY, ENCEPHALOPATHY, LACTIC ACIDOSIS, AND STROKELIKE EPISODES

Children with MELAS may be normal for the 1st several yr, but they gradually display delayed motor and cognitive development and short stature. The clinical syndrome is characterized by (1) recurrent stroke-like episodes of hemiparesis or other focal neurologic signs with lesions most commonly seen in the posterior temporal, parietal, and occipital lobes (CT or MRI evidence of focal brain abnormalities); (2) lactic acidosis, ragged red fibers (RRF), or both; and (3) at least 2 of the following: focal or generalized seizures, dementia, recurrent migraine headaches, and vomiting. In 1 series, onset was before age 15 yr in 62% of patients, and hemianopia or cortical blindness was the most common manifestation. Cerebrospinal fluid protein is often increased. The MELAS 3243 mutation on mtDNA is the most common mutation to produce MELAS and can also be associated with different combinations of exercise intolerance, myopathy, ophthalmoplegia, pigmentary retinopathy, hypertrophic or dilated cardiomyopathy, cardiac conduction defects, deafness, endocrinopathy (diabetes mellitus), and proximal renal tubular dysfunction. A number of other mutations have been reported, and 2 patients have been described with bilateral rolandic lesions and epilepsia partialis continua associated with mtDNA mutations at 10158T>C and 10191T>C. MELAS is a progressive disorder that has been reported in siblings. However, most maternal relatives of MELAS patients are mildly affected or unaffected. MELAS is punctuated with episodes of stroke leading to dementia (see Chapter 611.4).

Regional cerebral hypoperfusion can be detected by single-photon emission CT studies and MR spectroscopy can detect focal areas of lactic acidosis in the brain. Neuropathology may show cortical atrophy with infarct-like lesions in both cortical and subcortical structures, basal ganglia calcifications, and ventricular dilation. Muscle biopsy specimens usually show RRF. Mitochondrial accumulations and abnormalities have been shown in smooth muscle cells of intramuscular vessels and of brain arterioles and in the epithelial cells and blood vessels of the choroid plexus, producing a mitochondrial angiopathy. Muscle biochemistry shows complex I deficiency in many cases; however, multiple defects have also been documented involving complexes I, III, and IV. Targeted molecular testing for specific mutations or sequence analysis and mutation scanning are generally used to make a diagnosis of MELAS when clinical evaluation suggests the diagnosis. Because the number of mutant genomes is lower in blood than in muscle, muscle is the preferable tissue for examination. Inheritance is maternal, and there is a highly specific, although not exclusive, point mutation at nt 3243 in the $tRNA^{Leu(UUR)}$ gene of mtDNA in approximately 80% of patients. An additional 7.5% have a point mutation at nt 3271 in the $tRNA^{Leu(UUR)}$ gene. A third mutation has been identified at nt 3252 in the $tRNA^{Leu(UUR)}$ gene. The prognosis in patients with the full syndrome is poor. Therapeutic trials reporting some benefit have included corticosteroids, coenzyme Q10, nicotinamide, carnitine, creatine, riboflavin and various combinations of these; L-arginine and preclinical studies reported some success with resveratrol.

MYOCLONUS EPILEPSY AND RAGGED RED FIBERS

MERRF syndrome is characterized by progressive myoclonic epilepsy, mitochondrial myopathy, and cerebellar ataxia with dysarthria and nystagmus. Onset may be in childhood or in adult life, and the course may be slowly progressive or rapidly downhill. Other features include dementia, sensorineural hearing loss, optic atrophy, peripheral neuropathy, and spasticity. Because some patients have abnormalities of deep sensation and pes cavus, the condition may be confused with Friedreich ataxia. A significant number of patients have a positive family history and short stature. This condition is maternally inherited.

Pathologic findings include elevated serum lactate concentrations, RRF on muscle biopsy, and marked neuronal loss and gliosis affecting, in particular, the dentate nucleus and inferior olivary complex with some dropout of Purkinje cells and neurons of the red nucleus. Pallor of the posterior columns of the spinal cord and degeneration of the gracile and cuneate nuclei occur. Muscle biochemistry has shown variable defects of complex III, complexes II and IV, complexes I and IV, or complex IV alone. More than 80% of cases are caused by a heteroplasmic G to A point mutation at nt 8344 of the $tRNA^{Lys}$ gene of mtDNA. Additional patients have been reported with a T to C mutation at nt 8356 in the $tRNA^{Lys}$ gene. Targeted mutation analysis or mutation analysis after sequencing of the mitochondrial genome is used to diagnosis MERRF.

There is no specific therapy, although coenzyme Q10 appeared to be beneficial in a mother and daughter with the MERRF mutation. The anticonvulsant levetiracetam is reported to help reduce myoclonus and myoclonic seizures in this disorder.

NEUROPATHY, ATAXIA, AND RETINITIS PIGMENTOSA SYNDROME

This maternally inherited disorder presents with either Leigh syndrome or with neurogenic weakness and NARP syndrome, as well as seizures. It is caused by a point mutation at nt 8993 within the ATPase subunit 6 gene. The severity of the disease presentation appears to have close correlation with the percentage of mutant mtDNA in leukocytes.

Two clinical patterns are seen in patients with NARP syndrome: (1) neuropathy, ataxia, retinitis pigmentosa, dementia, and ataxia, and (2) severe infantile encephalopathy resembling Leigh syndrome with lesions in the basal ganglia on MRI.

LEBER HEREDITARY OPTIC NEUROPATHY

LHON is characterized by onset usually between the ages of 18 and 30 yr of acute or subacute visual loss caused by severe bilateral optic atrophy, although children as young as 5 yr have been reported to have LHON. Three mtDNA mutations account for most cases of LHON and at least 85% of patients are young men. An X-linked factor may modulate the expression of the mtDNA point mutation. The classic ophthalmologic features include circumpapillary telangiectatic microangiopathy and pseudoedema of the optic disc. Variable features may include cerebellar ataxia, hyperreflexia, Babinski sign, psychiatric symptoms, peripheral neuropathy, or cardiac conduction abnormalities (preexcitation syndrome). Some cases are associated with widespread white matter lesions as seen with multiple sclerosis. Lactic acidosis and RRF tend to be conspicuously absent in LHON. More than 11 mtDNA point mutations have been described, including a usually homoplasmic G to A transition at nt 11,778 of the ND4 subunit gene of complex I. The latter leads to replacement of a highly conserved arginine residue by histidine at the 340th amino acid and accounts for 50-70% of cases in Europe and more than 90% of cases in Japan. Certain LHON pedigrees with other point mutations are associated with complex neurologic disorders and may have features in common with MELAS syndrome and with infantile bilateral striatal necrosis. One family has been reported with pediatric onset of progressive generalized dystonia with bilateral striatal necrosis associated with a homoplasmic G14459A mutation in the mtDNA *ND6* gene, which is also associated with LHON alone and LHON with dystonia.

KEARNS-SAYRE SYNDROME

KSS is a characteristic multiorgan disorder involving external ophthalmoplegia, heart block, and retinitis pigmentosa with onset before age 20 yr caused by single deletions in mtDNA. There must also be at least 1 of the following: heart block, cerebellar syndrome, or cerebrospinal fluid protein >100 mg/dL. Other nonspecific but common features include dementia, sensorineural hearing loss, and multiple endocrine abnormalities, including short stature, diabetes mellitus, and hypoparathyroidism. The prognosis is guarded, despite placement of a pacemaker, and progressively downhill, with death resulting by the 3rd or 4th decade. Unusual clinical presentations can include renal tubular acidosis and Lowe syndrome. There are also a few overlap cases of children with KSS and stroke-like episodes. Muscle biopsy shows RRF and variable cytochrome c oxidase (COX)-negative fibers. Most patients have mtDNA deletions, and some have duplications. These may be new mutations accounting for the generally sporadic nature of KSS. A few pedigrees have shown autosomal dominant transmission. Patients should be monitored closely for endocrine abnormalities, which can be treated. Coenzyme Q is reported anecdotally to have some beneficial effect; a positive effect of folinic acid for low folate levels also is reported. A report of positive effects of a cochlear implant for deafness is also reported.

Sporadic progressive external ophthalmoplegia with ragged red fibers is a clinically benign condition characterized by adolescent or young adult–onset ophthalmoplegia, ptosis, and proximal limb girdle weakness. It is slowly progressive and compatible with a relatively normal life. The muscle biopsy material demonstrates RRF and COX-negative fibers. Approximately 50% of patients with progressive external ophthalmoplegia have mtDNA deletions, and there is no family history.

REVERSIBLE INFANTILE CYTOCHROME C OXIDASE DEFICIENCY MYOPATHY

Mutations in mtDNA are also responsible for a reversible form of severe neuromuscular weakness and hypotonia in infants that is the result of a maternally inherited homoplasmic m.14674T>C mt-tRNA^{Glu} mutation associated with a deficiency of COX. Affected children present within the 1st few wk of life with hypotonia, severe muscle weakness, and very elevated serum lactate levels, and they often require mechanical ventilation. However, feeding and psychomotor development are not affected. Muscle biopsies taken from these children in the neonatal period show RRF and deficient COX activity, but these findings disappeared within 5-20 mo when the infants recovered spontaneously. It is difficult to distinguish these infants from those with lethal mitochondrial disorders without waiting for them to improve. The mechanism for this recovery is not established, but it may reflect a developmental switch in mitochondrial RNAs later in infancy. This reversible disorder is observed only in COX deficiency associated with the 14674T>C mt-tRNA^{Glu} mutation, so it is suggested that infants with this type of severe weakness in the neonatal period be tested for this mutation to help with prognosis.

LEIGH DISEASE (SUBACUTE NECROTIZING ENCEPHALOMYOPATHY)

Leigh disease is a progressive degenerative disorder presenting in infancy with feeding and swallowing problems, vomiting, and failure to thrive associated with lactic acidosis and lesions seen in the brainstem and/or basal ganglia on MRI (Table 598-3). There are several genetically determined causes of Leigh disease that result from nuclear DNA mutations in genes that code for components of the respiratory chair: pyruvate dehydrogenase complex deficiency, complex I or II deficiency, complex IV (COX) deficiency, complex V (ATPase) deficiency, and deficiency of coenzyme Q10. These defects may occur sporadically or be inherited by autosomal recessive transmission, as in the case of COX deficiency; by X-linked transmission, as in the case of pyruvate dehydrogenase $E_1\alpha$ deficiency; or by maternal transmission, as in complex V (ATPase 6 nt 8993 mutation) deficiency. Approximately 30% of cases are caused by mutations in mtDNA. Delayed motor and language milestones may be evident, and generalized seizures, weakness, hypotonia, ataxia, tremor, pyramidal signs, and nystagmus are prominent findings. Intermittent respirations with associated sighing or sobbing are characteristic and suggest brainstem dysfunction. Some patients have external ophthalmoplegia, ptosis, retinitis pigmentosa, optic atrophy, and decreased visual acuity. Abnormal results on CT or MRI scan consist of bilaterally symmetric areas of low attenuation in the basal ganglia and brainstem as well as elevated lactic acid on MR spectroscopy (Fig. 598-3). Pathologic changes consist of focal symmetric areas of necrosis in the thalamus, basal ganglia, tegmental gray matter, periventricular and periaqueductal regions of the brainstem, and posterior columns of the spinal cord. Microscopically, these spongiform lesions show cystic cavitation with neuronal loss, demyelination, and vascular proliferation. Elevations in serum lactate levels are characteristic and hypertrophic cardiomyopathy, hepatic failure and rental tubular dysfunction can occur. The overall outlook is poor, but a few patients experience prolonged periods of remission. There is no definitive treatment for the underlying disorder, but a range of vitamins including riboflavin, thiamine, and coenzyme Q are often given to try to improve mitochondrial function. Biotin, creatine, succinate, and idebenone, as well as a high-fat diet have also been used, but phenobarbital and valproic acid should be avoided because of their inhibitory effect on the mitochondrial respiratory chain.

REYE SYNDROME

This encephalopathy, which has become uncommon, is associated with pathologic features characterized by fatty degeneration of the viscera (microvesicular steatosis) and mitochondrial abnormalities and biochemical features consistent with a disturbance of mitochondrial metabolism (see Chapter 361).

Recurrent Reye-like syndrome is encountered in children with genetic defects of fatty acid oxidation, such as deficiencies of the plasmalemmal carnitine transporter, carnitine palmitoyltransferases I and II, carnitine acylcarnitine translocase, medium- and long-chain acyl-coenzyme A dehydrogenase, multiple acyl-coenzyme A dehydrogenase, and long-chain L-3 hydroxyacyl-coenzyme A dehydrogenase or trifunctional protein. These disorders are manifested by recurrent hypoglycemic and hypoketotic encephalopathy, and they are inherited

Table 598-3 Clinical Features of Congenital Leigh Syndrome or Leigh-Like Syndrome

NEUROLOGIC MANIFESTATIONS	NONNEUROLOGIC MANIFESTATIONS
Brainstem	***Dysmorphic Features***
Bradypnea, hypopnea, episodes of apnea	Lip cleft
Bradycardia	Short distal phalanges
Tetraparesis	Single palmar crease
Hypotonia (floppy infant)	Rostral vertebrae
Failure to thrive, poor sucking	Round face
Swallowing difficulties, dysphagia, poor feeding, poor sucking	Frontal bossing
Vomiting	Flat nasal root
Spasticity, brisk tendon reflexes	Microcephaly
Dysphasia, dysarthria	Thin lips
Squint	Small chin
Absence of optic or acoustic blink	Long, featureless philtrum
Other Cerebral Manifestations	Hypospadia
Stroke-like episodes	***Others***
Delay of developmental milestones	Inguinal hernia
Paralysis of vertical gaze	Stiff neck
Myoclonic jerks of limbs or eyelids	Retinal dystrophy, retinopathy
Hypothermia	Deafness, hypoacusis
Drowsiness, dizziness	Hypertrophic, dilated cardiomyopathy
Psychomotor (mental) retardation	Pancreatitis
Ataxia, tremor	Diarrhea
Seizures, convulsions	Urinary excretion of Krebs-cycle intermediates
Growth retardation	Intrauterine growth retardation
Dystonia	Hypertrichosis
Clumsiness, dullness	Villous atrophy
Nystagmus, uncoordinated eye movement, slow saccades	Nephrotic syndrome
Optic atrophy	Nephropathy
Visual loss	Hyperhidrosis
Facial dyskinesia	Scoliosis
Ocular apraxia	
Drooling	
Gaze fixation difficulty	
Peripheral Nervous System Manifestations	
Cranial nerve palsies	
Generalized wasting	
Bilateral ptoses	
Chronic progressive external ophthalmoplegia, strabismus	
Reduced tendon reflexes	
Polyneuropathy	
Muscle weakness	
Myopathy	

From Finsterer J: Leigh and Leigh-like syndrome in children and adults. Pediatr Neurol *39:223–235, 2008, Table 1.*

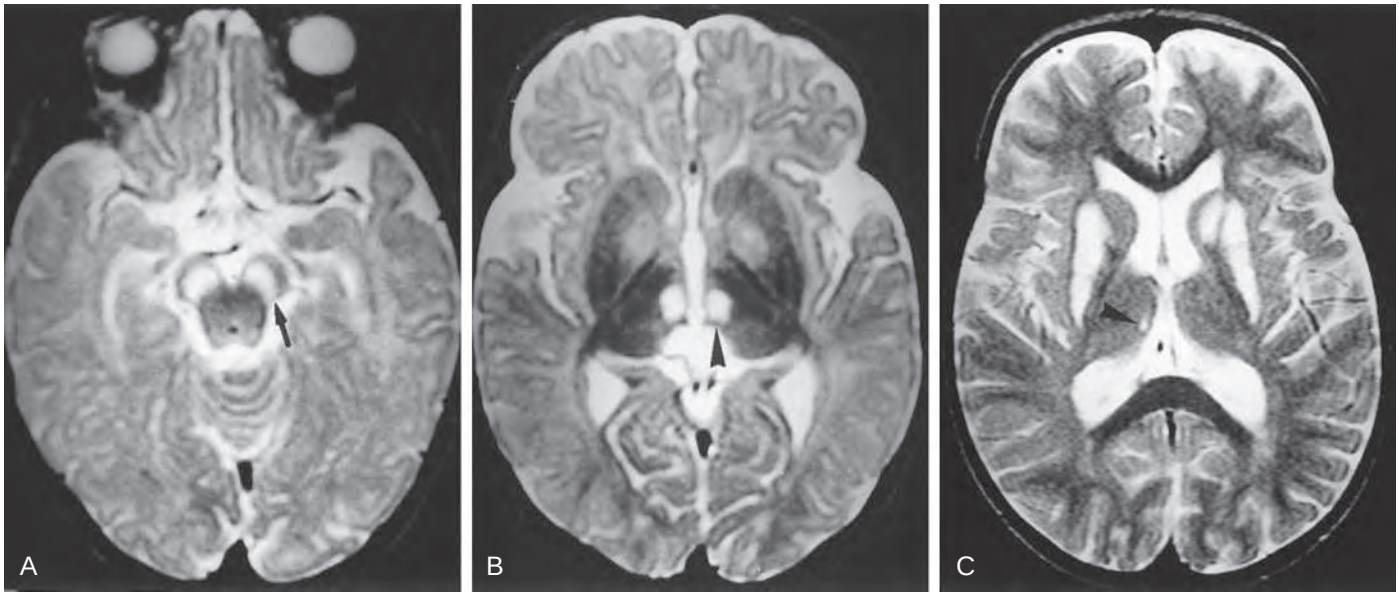


Figure 598-3 Leigh syndrome. Axial T2-weighted magnetic resonance images (TR/TE/NEX = 3,000/120/1 msec) of 8 mo old girl with Leigh syndrome because of a *SURF1* mutation indicate hyperintense lesions in substantia nigra and medial thalamic nuclei **(A, B).** Follow-up images (TR/TE/NEX = 2,028/120/2 msec) at age 26 mo **(C)** indicate hyperintense putamina and hyperintense left caudate nucleus. *(From Farina L, Chiapparini L, Uziel G, et al: MR findings in Leigh syndrome with COX deficiency and* SURF-1 *mutations,* AJNR Am J Neuroradiol *23:1095–1100, 2002, Fig. 2.)*

in an autosomal recessive pattern. Other potential inborn errors of metabolism presenting with Reye syndrome include urea cycle defects (ornithine transcarbamylase, carbamyl phosphate synthetase) and certain of the organic acidurias (glutaric aciduria type I), respiratory chain defects, and defects of carbohydrate metabolism (fructose intolerance).

Bibliography is available at Expert Consult.

598.3 Other Encephalopathies

Michael V. Johnston

HIV ENCEPHALOPATHY

Encephalopathy is an unfortunate and common manifestation in infants and children with HIV infection (see Chapter 276).

LEAD ENCEPHALOPATHY

See Chapter 721.

BURN ENCEPHALOPATHY

An encephalopathy develops in approximately 5% of children with significant burns in the 1st several wk of hospitalization (see Chapter 75). There is no single cause of burn encephalopathy but rather a combination of factors that include anoxia (smoke inhalation, carbon monoxide poisoning, laryngospasm), electrolyte abnormalities, bacteremia and sepsis, cortical vein thrombosis, a concomitant head injury, cerebral edema, drug reactions, and emotional distress. Seizures are the most common clinical manifestation of burn encephalopathy, but altered states of consciousness, hallucinations, and coma may also occur. Management of burn encephalopathy is directed to a search for the underlying cause and treatment of hypoxemia, seizures, specific electrolyte abnormalities, or cerebral edema. The prognosis for complete neurologic recovery is generally excellent, particularly if seizures are the primary abnormality.

HYPERTENSIVE ENCEPHALOPATHY

Hypertensive encephalopathy is most commonly associated with renal disease in children, including acute glomerulonephritis, chronic pyelonephritis, and end-stage renal disease (see Chapters 445 and 535). In some cases, hypertensive encephalopathy is the initial manifestation of underlying renal disease. Marked systemic hypertension produces vasoconstriction of the cerebral vessels, which leads to vascular permeability, causing areas of focal cerebral edema and hemorrhage. The onset may be acute, with seizures and coma, or more indolent, with headache, drowsiness and lethargy, nausea and vomiting, blurred vision, transient cortical blindness, and hemiparesis. Examination of the eyegrounds may be nondiagnostic in children, but papilledema and retinal hemorrhages may occur. MRI often shows increased signal intensity in the occipital lobes on T2-weighted images, which is known as **posterior reversible leukoencephalopathy (PRES)** and may be confused with cerebral infarctions. These high signal areas may appear in other regions of the brain as well. PRES may also be seen in children without hypertension. In all circumstances, PRES manifests with generalized motor seizures, headache, mental status changes, and visual disturbances. CT may be normal in PRES; MRI is the study of choice. Treatment is directed at restoration of a normotensive state and control of seizures with appropriate anticonvulsants.

RADIATION ENCEPHALOPATHY

Acute radiation encephalopathy is most likely to develop in young patients who have received large daily doses of radiation. Excessive radiation injures vessel endothelium, resulting in enhanced vascular permeability, cerebral edema, and numerous hemorrhages. The child may suddenly become irritable and lethargic, complain of headache, or present with focal neurologic signs and seizures. Patients occasionally develop hemiparesis as the result of an infarct secondary to vascular occlusion of the cerebral vessels. Steroids are often beneficial in reducing the cerebral edema and reversing the neurologic signs. Late-radiation encephalopathy is characterized by headaches and slowly progressive focal neurologic signs, including hemiparesis and seizures. Exposure of the brain to radiation for treatment of childhood cancer increases the risk of later cerebrovascular disease, including stroke, moyamoya disease, aneurysm, vascular malformations, mineralizing microangiopathy, and stroke-like migraines. Some children with acute lymphocytic leukemia treated with a combination of intrathecal methotrexate and cranial irradiation develop neurologic signs months or years later; signs consist of increasing lethargy, loss of cognitive abilities, dementia, and focal neurologic signs and seizures (see Chapter 494). The CT scan shows calcifications in the white matter, and the postmortem examination demonstrates a necrotizing encephalopathy. This devastating complication of the treatment of leukemia has prompted re-evaluation and reduction in the use of cranial radiation in the treatment of these children.

Table 598-4 Diagnostic Criteria for Acute Necrotizing Encephalopathy of Childhood

1. Acute encephalopathy following (1-3 days) a febrile disease. Rapid deterioration in the level of consciousness. Seizures.
2. No cerebrospinal fluid pleocytosis. Increase in cerebrospinal fluid protein.
3. CT or MRI evidence of symmetric, multifocal brain lesions. Involvement of the bilateral thalami. Lesions also common in the cerebral periventricular white matter, internal capsule, putamen, upper brainstem tegmentum and cerebellar medulla. No involvement of other central nervous system regions.
4. Elevation of serum aminotransferases of variable degrees. No increase in blood ammonia.
5. Exclusion of resembling diseases.
   A. Differential diagnosis from clinical viewpoints.
   Overwhelming bacterial and viral infections, and fulminant hepatitis; toxic shock, hemolytic uremic syndrome, and other toxin-induced diseases; Reye syndrome, hemorrhagic shock and encephalopathy syndrome, and heat stroke.
   B. Differential diagnosis from radiologic viewpoints.
   Leigh encephalopathy and related mitochondrial cytopathies; glutaric acidemia, methylmalonic acidemia, and infantile bilateral striatal necrosis; Wernicke encephalopathy and carbon monoxide poisoning; acute disseminated encephalomyelitis, acute hemorrhagic leukoencephalitis, other types of encephalitis, and vasculitis; arterial or venous infection, and the effects of severe hypoxia or head trauma

Modified from Hoshino A, Saitoh M, Oka, et al: Epidemiology of acute encephalopathy in Japan, with emphasis on the association of viruses and syndromes. Brain Dev *34:337–343, 2012, Table 1.*

ACUTE NECROTIZING ENCEPHALOPATHY

Acute necrotizing encephalopathy is a rare, severe encephalopathy seen more commonly in Asian countries. It is thought to be triggered by a viral infection (influenza, HHV-6) in a genetically susceptible host. Table 598-4 lists the diagnostic criteria. The elevation of hepatic enzymes without hyperammonemia is a unique feature. A familial or recurrent form is associated with mutations in the *RANBP2* gene and is designated ANE1. MRI finding are characterized by symmetric lesions that must be present in the thalami (Fig. 598-4). The prognosis is usually poor, however some patients have responded to steroids and intravenous immunoglobulin (IVIG).

CYSTIC LEUKOENCEPHALOPATHY

An autosomal recessive disorder caused by mutations of RNASET2 proteins produces a brain MRI study that closely resembles congenital cytomegalovirus infection. Cystic leukoencephalopathy is manifest as a static encephalopathy without megalencephaly.

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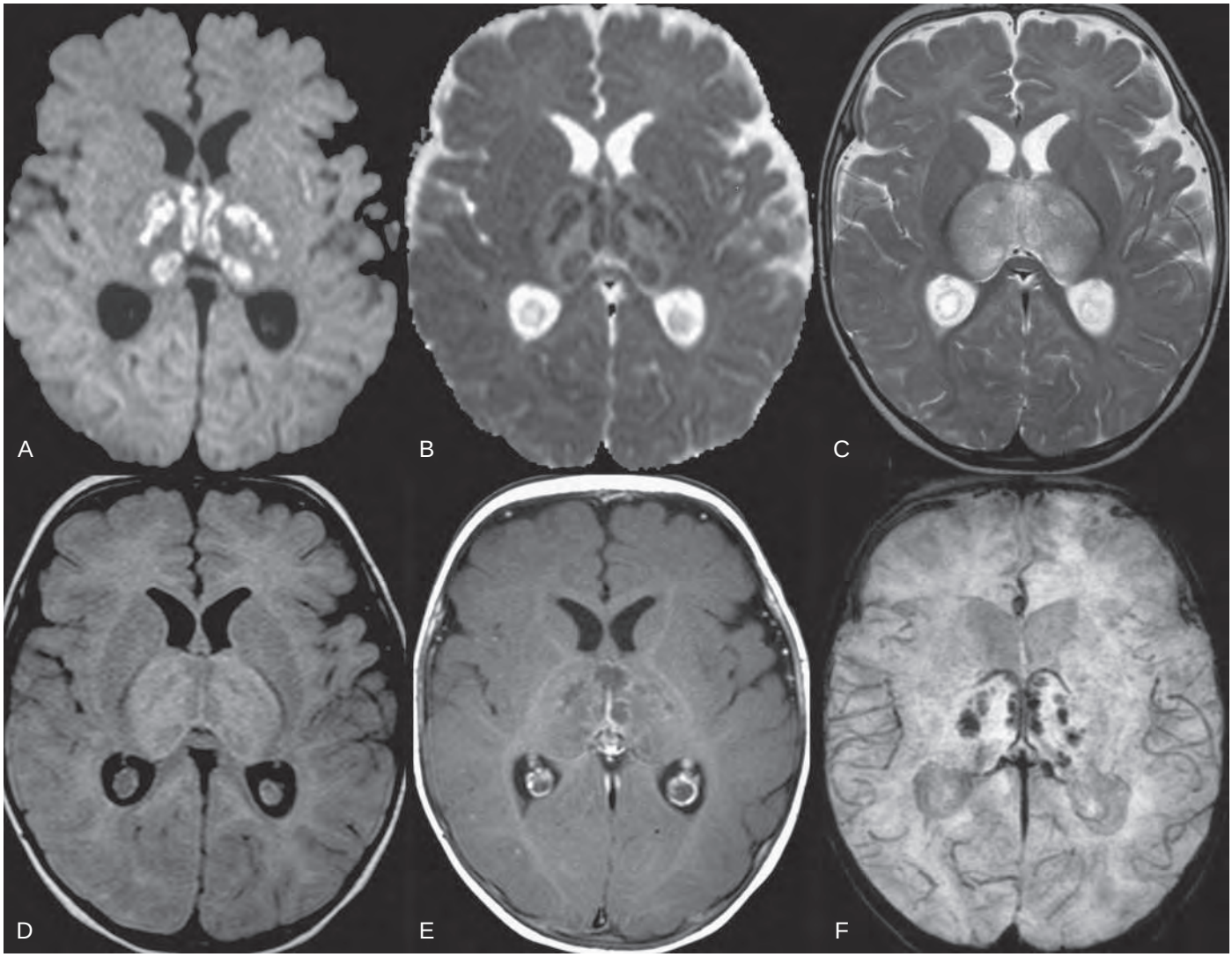


Figure 598-4 Acute necrotizing encephalopathy. MRI at presentation. **A,** Axial diffusion-weighted image; **B,** axial apparent diffusion coefficient (ADC) map; **C,** axial T2-weighted image; **D,** axial fluid-attenuated inversion recovery (FLAIR) image; **E,** contrast-enhanced axial T1-weighted image; **F,** axial susceptibility weighted image. Diffusion-weighted images **(A)** and corresponding ADC map **(B)** clearly show multiple areas of restricted diffusion against a background of increased diffusion involving both thalami, which are swollen. On T2-weighted **(C)** and FLAIR **(D)** images, the thalami are markedly swollen and hyperintense. On T1-weighted images obtained after intravenous gadolinium chelate injection **(E),** multiple necrotic portions are well delineated by peripheral faint, linear enhancement. Incidental choroid plexus cysts are detected. Susceptibility weighted image **(F)** shows multiple hypointense spots, consistent with petechial hemorrhage. *(From Bergamino L, Capra V, Biancheri R, et al: Immunomodulatory therapy in recurrent acute necrotizing encephalopathy ANE1: is it useful?* Brain Dev *34:384–391, 2012, Fig. 1.)*

598.4 Autoimmune Encephalitis

Thaís Armangué and Josep O. Dalmau

Autoimmune encephalitis comprises an expanding group of clinical syndromes that can occur at all ages (<1 yr to adult) but preferentially affect younger adults and children (Table 598-5). These disorders associate with antibodies against neuronal cell surface proteins and synaptic receptors involved in synaptic transmission, plasticity, or neuronal excitability. The syndromes vary according to the associated antibody with phenotypes that resemble those in which the function of the target antigen is pharmacologically or genetically modified.

Most of these disorders are severe and potentially fatal but patients frequently respond to immunotherapy with good outcomes. Moreover, because of the broad spectrum of symptoms—including alterations of behavior, psychosis, catatonia, memory deficits, seizures, abnormal movements, and autonomic dysregulation—patients usually require a multidisciplinary treatment approach often in an intensive care unit.

The identification of these disorders provides a definitive diagnosis to many cases of encephalitis previously considered idiopathic, infectious, or postinfectious, although no causative agents were found. Because the etiology and pathogenic mechanisms were unknown, some of these disorders were previously defined with descriptive terms. More than half of cases under the ill-defined term "encephalitis lethargica" and some cases of "choreoathetosis post–herpes simplex encephalitis" are known to be anti–*N*-methyl-D-aspartate receptor (NMDAR) encephalitis.

The mechanisms that trigger the production of the antibodies are unknown. In a small subgroup of adolescent or young adult patients, the presence of a tumor that expresses the target neuronal antigen likely contributes in triggering the immune response. In addition, the high prevalence of prodromal viral-like symptoms has suggested that nonspecific viral infections may contribute to breaking immune tolerance and increase the permeability of the blood–brain barrier to antibodies. Nonetheless in many of these disorders the blood–brain barrier appears intact and there is evidence that the autoantibodies are

Table 598-5 Autoimmune Encephalitis in Children

	MECHANISMS	TUMOR ASSOCIATION	SYNDROME	ANCILLARY TEST	TREATMENT/ PROGNOSIS
DEMONSTRATED IMMUNE MECHANISMS					
Anti-NMDAR encephalitis	Antibodies against NR1 subunit of NMDAR, disrupt function by crosslinking and internalization of receptors	Age and gender related: 41% in females older than 12 yr; <6% in girls younger than 12 yr. No tumors identified in young boys	Psychiatric symptoms, seizures, orofacial dyskinesias and other abnormal movements, autonomic dysfunction	EEG: almost always abnormal; it may show "extreme delta brush" pattern Brain MRI: nonspecific findings in ~35% CSF: pleocytosis and/or increased protein in >80%	80% complete recovery after immunotherapy and tumor removal (if appropriate). Frequently second-line drug* immunotherapy is required. Relapses in ~15% of patients
Limbic encephalitis	**Antibodies against intraneuronal antigens:** Hu, Ma2, amphiphysin, GAD **Antibodies against synaptic antigens:** $GABA_BR$, mGluR5	Extremely rare in children (see text)	Severe short-term memory loss, seizures	EEG: temporal lobe epileptic activity; focal or generalized slowing MRI: increased T2 and FLAIR signal in limbic region CSF: pleocytosis and increased proteins	If autoantigens are intracellular, poor response to immunotherapy If autoantigens are on the cell surface, ~80% are responsive to immunotherapy
STRONGLY SUSPECTED IMMUNE MECHANISMS					
Opsoclonus-myoclonus and other cerebellar-brainstem encephalitis	Most patients do not have detectable antibodies (a few patients have Hu antibodies)	Neuroblastoma occurs in 50% of children <2 year old; teratoma in teenagers and young adults	Opsoclonus often accompanied by irritability, ataxia, falling, myoclonus, tremor, and drooling	CSF abnormalities suggesting B-cell activation MRI: in some cases cerebellar atrophy	Partial response to immunotherapy in neuroblastoma-related opsoclonus High response to immunotherapy in teratoma-associated opsoclonus
Bickerstaff encephalitis	GQ1b antibodies	No tumor association	Ophthalmoplegia, ataxia, hyperreflexia. May overlap with Miller-Fisher syndrome	MRI: abnormal in ~30% (T2-signal abnormalities in the brainstem, thalamus, and cerebellum) Nerve conduction studies: abnormal in ~44% (predominant axonal degeneration, less frequent demyelination)	Often good outcome with steroids, IVIG and/or plasma exchange
Hashimoto encephalitis	TPO antibodies	No tumor association	Stroke-like symptoms, tremor, myoclonus, aphasia, sleep and behavioral problems seizures, ataxia	48% hypothyroidism, MRI often normal EEG: slow activity CSF: elevated protein	Steroid-responsive. Partial responses are frequent
Rasmussen encephalitis	Most likely immune mediated (unclear mechanism)	No tumor association	Progressive refractory partial seizures, cognitive decline, focal deficits, and brain hemiatrophy	MRI: progressive unilateral hemispheric atrophy	Limited response to immunotherapy. Patients may need functional hemispherectomy
Basal ganglia encephalitis	Antibodies to D2R in some cases	No tumor association	Abnormal movement and behavior disorder	Variable basal ganglia T2/FLAIR abnormalities	Mostly monophasic, can relapse
POSSIBLE IMMUNE MECHANISMS					
CLIPPERS	No antibodies	No tumor association	Episodic diplopia or facial paresthesias with subsequent development of symptoms of brainstem and occasionally spinal cord dysfunction	MRI: symmetric curvilinear gadolinium enhancement peppering the pons and extending variably into the medulla, brachium pontis, cerebellum, midbrain, and, occasionally, spinal cord	Steroid-responsive but may require chronic steroid or other immunosuppressive therapy
ROHHAD	Unknown. Autoimmune and genetic origin postulated.	Neural crest tumor in ~50% of cases†	Rapid onset obesity, hyperphagia, abnormal behavior, autonomic dysfunction, and central hypoventilation	Brain MRI, usually normal	Symptomatic; in some patients limited response to immunotherapy

*Includes rituximab and cyclophosphamide.

†Exact frequency is unknown.

CLIPPERS, Chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids; CSF, cerebrospinal fluid; D2R, dopamine 2 receptor; EEG, electroencephalography; FLAIR, fluid-attenuated inversion recovery; $GABA_BR$, γ-aminobutyric acid-B receptor, GAD, glutamic acid decarboxylase; IVIG, intravenous immunoglobulin; mGluR5, metabotropic glutamate receptor 5; MRI, magnetic resonance imaging; NMDAR, *N*-methyl-D-aspartate receptor; ROHHAD, rapid onset obesity with hypothalamic dysfunction, hypoventilation, and autonomic dysregulation; TPO, thyroid peroxidase.

synthesized within the CNS by plasma cells that form part of local brain and meningeal inflammatory infiltrates.

ANTI-*N*-METHYL-D-ASPARTATE RECEPTOR ENCEPHALITIS

In this disorder, the antibodies target the NR1 subunit of the NMDA receptor. The exact frequency of this syndrome is unknown but it is considered the second most common cause of autoimmune encephalitis after acute disseminated encephalomyelitis in children and adolescents. Overall, the disorder predominates in females (80%), although in patients younger than 12 yr the frequency of males is higher (40%). The resulting syndrome is highly predictable and usually evolves in stages. In teenagers and young adults, the disorder usually presents with prominent psychiatric manifestations that may include rapidly progressive anxiety, agitation, delusional thoughts, bizarre behavior, labile affect, mood disturbances (mania), catatonic features, memory deficit, language disintegration, aggression, and insomnia or other sleep disturbances. In many cases, these symptoms had been preceded by a few days of prodromal headache, fever or viral-like symptoms. As a result of this symptom presentation, patients are often misdiagnosed with new-onset psychosis or a primary psychiatric disorder. However, in a few days or weeks, additional symptoms occur, including a decreased level of consciousness, seizures (including status epilepticus), limb or oral dyskinesias, choreoathetoid movements, and autonomic instability which usually includes tachycardia, bradycardia, fluctuations of blood pressure, hypoventilation, hyperthermia and sialorrhea. In rare instances, bradycardia and cardiac pauses occur, at times requiring the transient use of a pacemaker. The disorder also occurs in toddlers and infants (the youngest patient identified to date was 6 mo old), and although the evolution of the syndrome is similar to that of adults, young patients more frequently present with motor or complex seizures and movement disorders. Because of their age, the psychiatric–behavioral features may be missed. In this young age group, behavior changes include irritability, new-onset temper tantrums, agitation, aggression, reduced speech, mutism, and autistic-like regression. Moreover, compared with adults some children also develop cerebellar ataxia and hemiparesis; in contrast, autonomic dysfunction is usually milder and less severe in children. There is often an abrupt on–off phenomenon in alterations of responsiveness or level of consciousness.

Brain MRI is abnormal in approximately 35% of cases, usually showing nonspecific cortical and subcortical T2–fluid-attenuated inversion recovery (FLAIR) signal abnormalities, sometimes with transient cortical or meningeal enhancement; nonspecific white matter abnormalities are common. Lesions may also involve the spinal cord producing symptoms of myelitis. The cerebrospinal fluid (CSF) is initially abnormal in approximately 80% of cases, showing moderate lymphocytic pleocytosis and less frequently increased protein synthesis and oligoclonal bands. The electroencephalogram (EEG) is abnormal in virtually all patients, and usually shows focal or diffuse slow activity in the delta and theta range, which does not correlate with abnormal movements. In addition, many patients develop epileptic activity, requiring video-monitoring for adequate clinical management. A characteristic EEG pattern called "extreme delta brush" characterized by beta-delta complexes occurs in 30% of adults and has been described in children (Fig. 598-5).

The diagnosis of the disorder is established by demonstrating NMDAR antibodies in CSF or serum. The sensitivity is higher in CSF compared with serum (100% vs 85%), and the levels of antibodies in CSF appear to correlate better with outcome. Antibodies may remain detectable, albeit at lower titers, after patients recover.

The presence of an underlying tumor, mostly teratomas, is age and sex dependent. Whereas 40% of females older than 12 yr have an underlying teratoma of the ovary, less than 6% of females younger than 12 yr have a tumor. In young boys with anti-NMDAR encephalitis, the presence of an underlying tumor is exceptional; in young adults, the presence of a testicular teratoma is also rare (<15% of cases). In children, MRI of abdomen and pelvis and abdominal and testicular ultrasound are the preferred tumor screening tests.

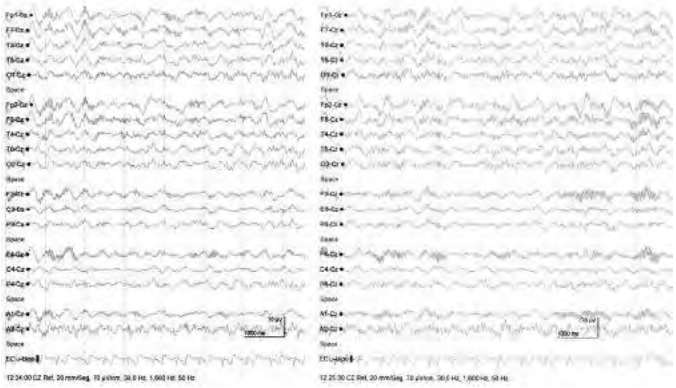


Figure 598-5 Electroencephalogram showing a pattern named "extreme delta brush" in a 14 yr old girl with anti–*N*-methyl-D-aspartate receptor (NMDAR) encephalitis. This pattern has been found to be characteristic of anti-NMDAR encephalitis. It consists of a nearly continuous combination of delta activity with superimposed fast activity, usually in the beta range, symmetrically involving all head regions, with a frontal preference in patients who are not under effects of sedation or anesthetics. *(From Armangue T, Titulaer MJ, Málaga I, et al: Pediatric anti-N-methyl-D-aspartate receptor encephalitis—clinical analysis and novel findings in a series of 20 patients.* J Pediatr *162:850–856, 2012, Fig. 2.)*

In a small number of patients, anti-NMDAR encephalitis occurs simultaneously or after infections with a variety of pathogens, including *Mycoplasma pneumoniae*, human herpes simplex viruses 1 and 6 (HSV), enterovirus, and influenza. A pathogenic link with most of these infections has not established; there is evidence that some patients with HSV encephalitis develop antibodies against the NR1 subunit of the NMDAR. These patients may progress to develop relapsing neurologic symptoms post-HSV encephalitis. In a subgroup of patients with noninfectious relapsing neurologic symptoms post-HSV encephalitis, or "choreoathetosis post-HSV encephalitis," the disorder is in fact anti-NMDAR encephalitis (see Videos 598-1, 598-2, and 598-3).

Although no prospective clinical trials have been done, there is evidence that tumor removal, when appropriate, and prompt immunotherapy improve outcome. Most children receive first-line immunotherapies, including corticosteroids, IVIG, or plasma exchange. However, because these treatments fail in almost 50% of patients, and with an increasing number of reports showing that rituximab can be effective, this treatment is increasingly being used in combination with IVIG and steroids, or after first-line immunotherapies. Cyclophosphamide can be effective when there has been no response to these treatments.

Although anti-NMDAR encephalitis has a mortality rate of 7%, approximately 80% of patients have substantial or full recovery. Recovery is usually slow and can take as long as 2 yr after symptom onset. The last symptoms to improve are social interactions, and language and executive functions. Relapses occur in approximately 15% of patients; they can develop as partial syndromes, are usually milder than the initial episode and respond equally to immunotherapy. Initial comprehensive immunotherapy appears to prevent or reduce the number of relapses. The efficacy of chronic immunosuppression with drugs such as azathioprine or mycophenolate mofetil in preventing relapses is unknown.

The differential diagnosis of anti-NMDAR encephalitis is extensive and varies according to the stage of the disease (Table 598-6). The most frequently considered disorders are viral encephalitis, neuroleptic malignant syndrome, acute psychosis, and drug abuse.

LIMBIC ENCEPHALITIS

This disorder refers to an inflammatory process of the limbic system including, the medial temporal lobes, amygdala, and cingulate gyri. In adults, the most frequent immune-mediated limbic encephalitis occurs

Table 598-6 Differential Diagnosis of Anti-NMDAR Encephalitis in Children

DISORDER	COMMENTS
Viral encephalitis	Viral encephalitis is often suggested by the acute onset of symptoms, CSF pleocytosis, and hyperthermia. Most viral encephalitides (except rabies) occur with higher levels of CSF pleocytosis and protein concentration. Psychosis and dyskinesias are significantly less frequent in viral encephalitis than in anti-NMDAR encephalitis.
Relapsing post–herpes simplex virus encephalitis	Occurs ~4-6 wk after successful treatment of herpes simplex encephalitis. This may represent a true viral relapse of encephalitis (CSF PCR-positive, progression of necrotic MRI changes, response to acyclovir), or an autoimmune disorder (CSF PCR-negative, no new necrotic lesions on MRI, lack of response to acyclovir). In a proportion of the latter patients, the disorder is anti-NMDAR encephalitis.
New-onset psychosis	Because most patients with anti-NMDAR encephalitis present with psychosis, a primarily psychiatric disorder is frequently considered. As the disease evolves, the development of neurological symptoms usually reveals the diagnosis.
Drugs/toxins	The acute development of personality and behavioral changes, and symptoms suggesting involvement of dopaminergic pathways (rigidity, dystonia, orofacial movements) usually leads to a suspicion of drug abuse (e.g., ketamine, phencyclidine, among others). Carbon monoxide.
Neuroleptic malignant syndrome	The occurrence of altered level of consciousness, episodes of rigidity, hyperthermia, and autonomic instability often suggest NMS. In addition, some patients with anti-NMDAR encephalitis have elevated serum creatine kinase and rhabdomyolysis (in the absence of antipsychotic medication). The frequent use of neuroleptics to control the abnormal behavior adds further confusion between both syndromes. The presence of dyskinesias and catatonia suggest anti-NMDAR encephalitis.
Limbic encephalitis	Criteria of LE are well defined. Patients with LE do not have dyskinesias or central hypoventilation; the MRI usually shows abnormalities restricted to the medial temporal lobes, and the EEG findings (epileptic or slow activity) are largely restricted to the temporal lobes.
Encephalitis lethargica	This is an ill-defined entity, likely representing multiple disorders. Criteria include: acute or subacute encephalitis with at least 3 of the following: signs of basal ganglia involvement; oculogyric crises; ophthalmoplegia; obsessive-compulsive behavior; akinetic mutism; central respiratory irregularities; and somnolence and/or sleep inversion. Approximately, 50% of patients categorized as encephalitis lethargica hyperkinetica have anti-NMDAR encephalitis.
Childhood disintegrative disorder/late-onset autism	Children with anti-NMDAR encephalitis often show cognitive regression, rapid loss of language function, autistic features, and seizures, suggesting a childhood disintegrative disorder. While the prognosis of CDD is poor, most patients with anti-NMDAR encephalitis respond to immunotherapy and have substantial clinical recovery.
Kleine-Levin syndrome	Symptoms of hypersomnia, compulsive hyperphagia, hypersexuality, apathy, and child-like behavior, which are typical components of Kleine-Levin syndrome, may occur transiently during the process of recovery of anti-NMDAR encephalitis, or as permanent sequelae.
Inborn errors of metabolism	Glutaric aciduria type I can present in previously asymptomatic patients as episodes of encephalopathy with dystonia, coinciding with an infection or febrile process. Several inborn errors of metabolism can also occur with acute or subacute encephalopathy with extrapyramidal signs, including 3-methylglutaconic aciduria, creatine transport deficiency, mitochondrial disorders (Leigh syndrome), Wilson, and Lesch-Nyhan syndromes. Pantothenate kinase associated neurodegeneration, porphyria, and urea cycle defects should also be considered.
Monoamine neurotransmitter disorders	Deficiency of dopamine, serotonin or both can result in encephalopathy, epilepsy, and pyramidal and extrapyramidal symptoms. The diagnosis is established by examining the CSF for levels of these neurotransmitters.
Demyelinating disorders	Acute disseminated encephalomyelitis and neuromyelitis optica are immune-mediated inflammatory and demyelinating disorders of the central nervous system. These disorders should be considered in the differential diagnosis of multifocal neurologic abnormalities and encephalopathy in children. As with anti-NMDAR encephalitis these disorders may be preceded by an infection and can show pleocytosis. The diagnosis is suggested by the MRI findings. In NMO the presence of aquaporin 4 antibodies in serum or CSF is associated with relapses and poor prognosis.
CNS vasculitis	CNS vasculitis results in neurologic deficits and psychiatric manifestations. The diagnosis is established by angiography in large vessel angiitis, and brain biopsy in small vessel angiitis. In the latter, serum inflammatory markers (erythrocyte sedimentation rate, C-reactive protein, Complement 3, von Willebrand factor antigen) are usually elevated, and the MRI shows FLAIR/T2 abnormalities in the white and/or gray matter, not restricted to vascular territories with frequent leptomeningeal and/or local enhancement.
Systemic rheumatic disorders	Systemic lupus erythematosus and other rheumatic disorders can result in encephalopathy and multifocal neurologic and psychiatric manifestations. These disorders are usually suggested by the presence of signs and symptoms of involvement of systemic organs: skin, joints, kidneys, blood-forming cells, and blood vessels.

CDD, childhood disintegrative disorder; CNS, central nervous system; CSF, cerebrospinal fluid; EEG, electroencephalography; FLAIR, fluid-attenuated inversion recovery; LE, limbic encephalitis; MRI, magnetic resonance imaging; NMDAR, *N*-methyl-D-aspartate receptor; NMO, neuromyelitis optica; NMS, neuroleptic malignant syndrome; PCR, polymerase chain reaction.

in association with antibodies against proteins that were once thought to be voltage-gated potassium channels (VGKC), but which, in fact, target a secreted neuronal protein called leucine-rich glioma-inactivated 1 (LGI1), and a protein called Caspr2 expressed in brain and juxtaparanodal regions of myelinated nerves. Patients with LGI1 antibody associated limbic encephalitis often develop *hyponatremia*; in some patients the disorder is preceded by short-lasting episodes of distinctive dystonic or myoclonic-like movements, described as *faciobrachial dystonic seizures*, but with EEG features of tonic seizures. Patients with antibodies to Caspr2 usually develop Morvan syndrome, which includes encephalopathy, seizures, autonomic dysfunction, and neuromyotonia. How the clinical significance of antibodies called "VGKC-complex proteins" differs from LGI1 and Caspr2 is unknown.

Other less frequent types of autoimmune limbic encephalitis in adults are paraneoplastic and may occur with antibodies against intracellular antigens (e.g., Hu, CRMP5, Ma2) or neuronal cell surface and synaptic proteins (e.g., AMPA, $GABA_B$ receptor, mGluR5). While the disorders associated with antibodies against intracellular antigens appear to be mediated by cytotoxic T-cell responses and are poorly responsive to treatment, those associated with antibodies to cell surface and synaptic antigens are likely mediated by the antibodies and treatment responsive.

In children, autoimmune or paraneoplastic limbic encephalitis is exceptional. Unfortunately, any type of encephalopathy resulting in seizures and alteration of memory and behavior is frequently labeled as "limbic encephalitis," making data based on literature searches using the term "limbic encephalitis" unreliable. Fewer than 30 children with limbic encephalitis have been described in the English literature, some of them with antibodies against intracellular or cell surface antigens (Hu, Ma2, GAD, amphiphysin, $GABA_B$, and VGKC-complex proteins different from LGI1 and Caspr2). In some cases an underlying tumor was identified and included, leukemia, ganglioneuroblastoma, neuroblastoma, and small-cell carcinoma of the ovary.

The **Ophelia syndrome** is a form of limbic encephalitis that occurs in association with Hodgkin's lymphoma and predominantly affects young adults, teenagers or children. Some patients develop antibodies against mGluR5, a receptor involved in learning and memory; symptoms are usually responsive to chemotherapy.

HASHIMOTO ENCEPHALOPATHY

Hashimoto encephalopathy is defined by the detection of thyroid peroxidase (TPO) antibodies in patients with acute or subacute encephalitis that responds to corticosteroids. Since almost 50% of patients have normal thyroid function and not all patients respond to steroids, the term "encephalopathy associated with autoimmune thyroid disease" is considered more accurate than the previous term "steroid-responsive encephalopathy associated with autoimmune thyroiditis." Clinical features are not specific and may include stroke-like symptoms, tremor, myoclonus, transient aphasia, sleep and behavior abnormalities, hallucinations, seizures, and ataxia. The CSF usually shows elevated protein level with less-frequent pleocytosis. EEG studies almost always are abnormal frequently showing generalized slowing. Brain MRI is usually normal, although it may show diffuse white matter abnormalities and meningeal enhancement that can resolve with steroid therapy. As TPO antibodies occur in approximately 10% of asymptomatic children (nonencephalopathic and most cases euthyroid), as well as in patients who have more relevant antibody-associated disorders, such as $GABA_B$, LGI1, or NMDAR antibodies, TPO antibodies should be viewed as a marker of autoimmunity rather than a neurologic disease-specific or pathogenic antibody. Importantly the presence of TPO antibodies should not prevent testing for more relevant antibodies.

OPSOCLONUS–MYOCLONUS AND OTHER BRAINSTEM–CEREBELLAR ENCEPHALITIDES

Opsoclonus-myoclonus occurs in infants, teenagers and adults, although it probably represents different diseases and pathogenic mechanisms. In infants, the syndrome usually develops in the 1st 2 yr of life (mean: 20 mo), and at least 50% of patients have an underlying neuroblastoma. The child often presents with irritability, ataxia, falling, myoclonus, tremor, and drooling. Additional symptoms may include refusal to walk or sit, speech problems, hypotonia, and the typical features of opsoclonus characterized by rapid, chaotic, multidirectional eye movements without saccadic intervals. Because opsoclonus may be absent at symptom presentation, patients may initially be diagnosed with acute cerebellitis or labyrinthitis. Typically CSF abnormalities suggest B-cell activation, and the presence of antibodies against neuronal proteins has been demonstrated in several studies, although the identification of a specific autoantigen has been elusive.

Immunosuppressive treatment, including corticosteroids, IVIG, rituximab, and cyclophosphamide often improves the abnormal eye movements, but residual behavioral, language, and cognitive problems persist in the majority of patients, often requiring special education. In addition, insomnia and abnormal response to pain are common. Relapses occur in 50% of the patients, usually as a result of an intercurrent infection or drug tapering. Delay in treatment appears to associate with a poorer neurologic outcome; therefore, in cases with neuroblastoma, removal of the tumor should not delay the start of immunotherapy.

In teenagers and young adults, opsoclonus–myoclonus and brainstem–cerebellar encephalitis without opsoclonus are often considered "idiopathic" or "postinfectious"; however, there is evidence that some of these patients have an underlying teratoma, usually in the ovaries. These patients do not harbor NMDAR antibodies, and compared with those with anti-NMDAR encephalitis are less likely to initially present with psychosis and behavioral changes, and rarely develop dyskinesias. Although these patients do not appear to have neuronal antibodies, the CSF often shows pleocytosis and elevated protein concentration. Identification of this subphenotype of opsoclonus–myoclonus is important because patients usually have full recovery after treatment with immunotherapy (corticosteroids, IVIG, and/or plasma exchange) and if present, removal of the ovarian teratoma. The prognosis of this disorder seems better than that of neuroblastoma-associated opsoclonus, or the paraneoplastic opsoclonus of older patients, usually related to breast, ovarian, or lung cancer.

BICKERSTAFF ENCEPHALITIS

This term is used to describe patients with subacute progressive ophthalmoplegia and ataxia in addition to drowsiness or hyperreflexia. Although this entity has been described more frequently in adults, children as young as 3 yr old have been identified. Most patients are treated with steroids, IVIG, and/or plasma exchange, and often have good outcome. Serum GQ1b immunoglobulin G antibodies are found in 66% of patients. Brain MRI abnormalities occur in 30% of the patients and usually include increased T2-signal abnormalities in the brainstem, thalamus, cerebellum, and sometimes cerebral white matter. Some patients develop hyporeflexia and limb weakness, with predominant axonal involvement, overlapping with symptoms of the Miller-Fisher syndrome and the axonal subtype of the Guillain-Barré syndrome.

CHRONIC LYMPHOCYTIC INFLAMMATION WITH PONTINE PERIVASCULAR ENHANCEMENT RESPONSIVE TO STEROIDS

This is a clinically and radiologically distinct pontine-predominant encephalomyelitis. To date fewer than 30 patients have been reported and two of them were children (13 and 16 yr). Patients usually present with episodic diplopia or facial paresthesias with subsequent development of symptoms of brainstem and occasionally spinal cord dysfunction. Brain MRI shows symmetric curvilinear gadolinium enhancement peppering the pons and extending variably into the medulla, brachium pontis, cerebellum, midbrain and occasionally spinal cord. The clinical and radiological findings usually respond to high dose steroids but may worsen after the steroid taper, requiring chronic steroid or other immunosuppressive therapy. The differential diagnosis is extensive and includes infections, granulomatous disease, lymphoma or vasculitis. Biopsy studies may be needed to exclude these and other conditions.

AUTOIMMUNE ENCEPHALOPATHIES ASSOCIATED WITH EPILEPSY AND STATUS EPILEPTICUS

Rasmussen encephalitis is an inflammatory encephalopathy characterized by progressive refractory partial seizures, cognitive deterioration, and focal deficits that occur with gradual atrophy of 1 brain hemisphere. The disorder frequently presents in 6-8 yr old children, although adolescents and adults can be affected. The etiology is unknown and, therefore, multiple theories are proposed, including the presence of antibodies against the GluR3 subunit of the AMPA receptor and T-cell mediated mechanisms triggered by a viral infection. None of these mechanisms satisfactorily explains the unilateral brain involvement characteristic of the disorder. Treatment with high-dose steroids, plasma exchange, or IVIG can ameliorate symptoms in early stages of the disease. Rituximab and intraventricular γ-interferon have been effective in a few isolated cases. In a small series, patients treated with tacrolimus showed better outcomes of neurologic function and slower progression of cerebral hemiatrophy, but not improved seizure control. The only definitive treatment is functional hemispherectomy that consists in surgical disconnection of the affected hemisphere.

The discovery of treatment-responsive encephalitis associated with antibodies against cell surface or synaptic proteins has resumed the interest for a potential autoimmune basis of several devastating encephalopathies with refractory seizures. Some well-defined autoimmune encephalitis such as **anti-NMDAR encephalitis** can present in children with refractory seizures or status epilepticus. In these patients, the development over a short period of time of the characteristic spectrum of symptoms (altered behavior, orofacial dyskinesias, and autonomic dysfunction) and demonstration of NMDAR antibodies leads to the correct diagnosis and initiation of immunotherapy.

A devastating epileptic encephalopathy associated with fever named **fever-induced refractory epileptic encephalopathy syndrome,** among other terms, is suspected to be an infection-triggered autoimmune process because of its biphasic clinical course and the occasional finding of neuronal antibodies in a few patients. However, the lack of response to most treatments including immunotherapy, and the rare and inconsistent association to different types of antibodies cast doubts on an autoimmune pathogenesis. Other investigators suggest a genetic error in metabolism.

Antibodies to VGKC-complex proteins different from LGI1 and Caspr2 have been described in a few children with encephalitis with or without status epilepticus. Given that the target antigens are unknown and the response to immunotherapy is unpredictable, the significance of these antibodies is unclear.

OTHER SUSPECTED AUTOIMMUNE ENCEPHALITIDES

Demyelinating disorders, vasculitis of the CNS, and rheumatic diseases associate with autoimmune mechanisms can result in encephalitis.

Rapid onset obesity with hypothalamic dysfunction, hypoventilation, and autonomic dysregulation (**ROHHAD**) usually affects children who had normal development until 2-4 yr of age and then develop rapid onset of hyperphagia, weight gain, and abnormal behavior (social disinhibition, irascibility, impulsivity, lethargy, outburst of euphoria and laughing, impaired concentration), followed by autonomic dysfunction (abnormal pupillary responses, thermal dysregulation, gastrointestinal dysmotility), and central hypoventilation. An autoimmune or paraneoplastic etiology of ROHHAD syndrome is supported by the frequent association to neural crest tumors, the identification in some patients of genetic factors predisposing to autoimmunity, and the finding of intrathecal oligoclonal bands and infiltrates of lymphocytes and histiocytes in the hypothalamus of some patients. Furthermore, responses to immunotherapy have been described in a few patients. A possible genetic origin is suggested because of the similarities of this syndrome with the congenital central hypoventilation syndrome (Ondine curse) related to a *PHOX2B* mutation, which presents in the neonatal period and also associates with autonomic problems (Hirschsprung disease) and neural crest tumors (see Chapter 418.2). However, no mutations in *PHOX2B* and other candidate genes have been found in patients with ROHHAD.

The term **basal ganglia encephalitis** is used to describe patients with predominant or isolated involvement of the basal ganglia. These patients typically have abnormal movements and neuropsychiatric disease. Although these disorders probably have multiple etiologies, including metabolic, toxic, genetic, and infectious processes, an immune-mediated etiology has been postulated in some patients. There have been no clinical trials, but case reports and small noncontrolled case series describe the potential benefit of immunotherapy. Antibodies against the dopamine-2 receptor have been identified in some of these patients as well as in patients with Sydenham chorea and Tourette syndrome.

Pseudomigraine syndrome with CSF pleocytosis (**PMP**) or **headache with neurologic deficits and CSF lymphocytosis** (**HaNDL**) is an ill-defined entity that predominantly affects young male adults with a family history of migraine, although adolescents can be affected. This syndrome is characterized by repeated episodes of severe headache with transient neurologic deficits, accompanied by aseptic CSF lymphocytosis and normal brain MRI. Patients frequently show high CSF opening pressure, elevated CSF protein concentration, and focal EEG slowing, which normalize after the episodes of headache. Because of the inflammatory characteristics of the CSF and the high prevalence of prodromal viral-like symptoms, an infectious-autoimmune mediated mechanism has been proposed. Other theories include spreading cortical depression and trigeminal-vascular activation.

An immune-mediated mechanism and trigeminal-vascular activation are also considered as possible mechanisms of **ophthalmoplegic migraine,** also named **recurrent cranial neuralgia.** This disorder predominantly affects young children and is characterized by recurrent bouts of head pain in addition to cranial nerves III, IV, and/or VI involvement. In contrast to PMP/HaNDL, CSF studies do not show pleocytosis, and in approximately 75% of cases, the MRI shows focal nerve thickening and contrast enhancement. Observational data suggest that treatment with steroids may be beneficial. In this syndrome, as well as in PMP/HaNDL, the differential diagnosis includes structural, neoplastic, traumatic, metabolic, and infectious disorders.

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Chapter 599

Neurodegenerative Disorders of Childhood

Jennifer M. Kwon

Neurodegenerative disorders of childhood encompass a large, heterogeneous group of diseases that result from specific genetic and biochemical defects, chronic viral infections, and varied unknown causes. Children with suspected neurodegenerative disorders were once subjected to brain and rectal (neural) biopsies, but with modern neuroimaging techniques and specific biochemical and molecular diagnostic tests, these invasive procedures are rarely necessary. The most important component of the diagnostic investigation continues to be a thorough history and physical examination. The hallmark of a neurodegenerative disease is **regression and progressive deterioration** of neurologic function with loss of speech, vision, hearing, or locomotion, often associated with seizures, feeding difficulties, and impairment of intellect. The age of onset, rate of progression, and principal

Table 599-1 Neurometabolic Conditions Associated with Developmental Regression

AGE AT ONSET (yr)	CONDITIONS	COMMENTS
<2 with hepatomegaly	Fructose intolerance	Vomiting, hypoglycemia, poor feeding, failure to thrive (when given fructose)
	Galactosemia	Lethargy, hypotonia, icterus, cataract, hypoglycemia (when given lactose)
	Glycogenosis (glycogen storage disease) types I-IV	Hypoglycemia, cardiomegaly (type II)
	Mucopolysaccharidosis types I and II	Coarse facies, stiff joints
	Niemann-Pick disease, infantile type	Gray matter disease, failure to thrive
	Tay-Sachs disease	Seizures, cherry-red macula, edema, coarse facies
	Zellweger syndrome	Hypotonia, high forehead, flat facies
	Gaucher disease (neuronopathic form)	Extensor posturing, irritability
	Carbohydrate-deficient glycoprotein syndromes	Dysmyelination, cerebellar hypoplasia
<2, without hepatomegaly	Krabbe disease	Irritability, extensor posturing, optic atrophy, and blindness
	Rett syndrome	Girls with deceleration of head growth, loss of hand skills, hand wringing, impaired language skills, gait apraxia
	Maple syrup urine disease	Poor feeding, tremors, myoclonus, opisthotonos
	Phenylketonuria	Light pigmentation, eczema, seizures
	Menkes kinky hair disease	Hypertonia, irritability, seizures, abnormal hair
	Subacute necrotizing encephalopathy of Leigh disease	White matter disease
	Canavan disease	White matter disease, macrocephaly
	Neurodegeneration with brain iron accumulation disease	White matter disease, movement disorder
2-5	Niemann-Pick disease types III and IV	Hepatosplenomegaly, gait difficulty
	Wilson disease	Liver disease, Kayser-Fleischer ring; deterioration of cognition is late
	Gangliosidosis type II	Gray matter disease
	Neuronal ceroid lipofuscinosis	Gray matter disease
	Mitochondrial encephalopathies (e.g., myoclonic epilepsy with ragged red fibers [MERRF])	Gray matter disease
	Ataxia-telangiectasia	Basal ganglia disease
	Huntington disease (chorea)	Basal ganglia disease
	Neurodegeneration with brain iron accumulation syndrome	Basal ganglia disease
	Metachromatic leukodystrophy	White matter disease
	Adrenoleukodystrophy	White matter disease, behavior problems, deteriorating school performance, quadriparesis
5-15	Adrenoleukodystrophy	Same as for adrenoleukodystrophy in 2-5 yr olds
	Multiple sclerosis	White matter disease
	Neuronal ceroid lipofuscinosis, juvenile and adult (Spielmeyer-Vogt and Kufs disease)	Gray matter disease
	Schilder disease	White matter disease, focal neurologic symptoms
	Refsum disease	Peripheral neuropathy, ataxia, retinitis pigmentosa
	Sialidosis II, juvenile form	Cherry-red macula, myoclonus, ataxia, coarse facies
	Subacute sclerosing panencephalitis	Diffuse encephalopathy, myoclonus; may occur years after measles

From Kliegman RM, Greenbaum LA, Lye PS: Practical strategies in pediatric diagnosis and therapy, *ed 2, Philadelphia, 2004, WB Saunders, p. 542.*

neurologic findings determine whether the disease affects primarily the white or the gray matter. Upper motor neuron signs and progressive spasticity are the hallmarks of white matter disorders; convulsions and intellectual and visual impairments that occur early in the disease course are the hallmarks of gray matter disorders. A precise history confirms regression of developmental milestones, and the neurologic examination localizes the process within the nervous system. Although the outcome of a neurodegenerative condition is usually fatal and available therapies are often limited in effect, it is important to make the correct diagnosis so that genetic counseling may be offered and prevention strategies can be implemented. Bone marrow transplantation and other novel therapies may prevent the progression of disease in certain individuals who are either presymptomatic or very early in their disease course. For all conditions in which the specific enzyme defect is known, prevention by prenatal diagnosis (chorionic villus sampling or amniocentesis) is possible. Carrier detection is also often possible by enzyme assay. Table 599-1 summarizes selected inherited neurodegenerative and metabolic disorders by their usual age of onset.

599.1 Sphingolipidoses

Jennifer M. Kwon

The sphingolipidoses are characterized by intracellular storage of lipid substrates resulting from defective catabolism of the sphingolipids comprising cellular membranes (Fig. 599-1). The sphingolipidoses are subclassified into 6 categories: Niemann-Pick disease, Gaucher disease, GM_1 gangliosidosis, GM_2 gangliosidosis, Krabbe disease, and metachromatic leukodystrophy. Niemann-Pick disease and Gaucher disease are discussed in Chapter 86.4.

GANGLIOSIDOSES

See also Chapter 86.4.

Gangliosides are glycosphingolipids, normal constituents of the neuronal and synaptic membranes. The basic structure of GM_1 ganglioside consists of an oligosaccharide chain attached to a hydroxyl group of ceramide and sialic acid bound to galactose. The gangliosides are catabolized by sequential cleavage of the sugar molecules

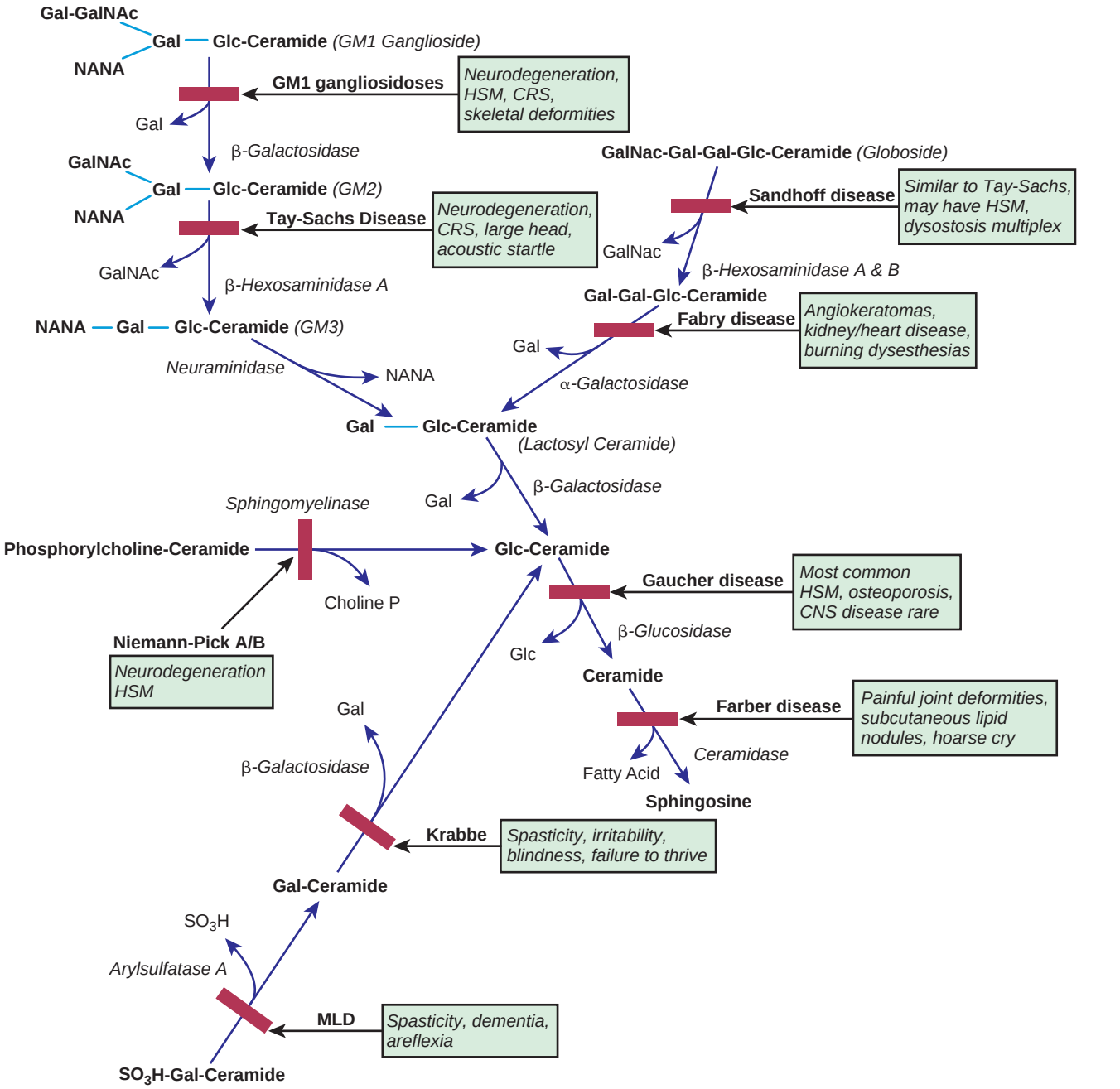


Figure 599-1 Sphingolipid degradation pathway showing the sites of enzyme deficiencies and their associated disorders. Sphingolipids are composed of a ceramide backbone with oligosaccharide side chains. CRS, cherry-red spot (retinal); Gal-, galactosyl-; GalNAc, N-acetyl-galactose; Glc-, glucosyl-; HSM, hepatosplenomegaly; MLD, metachromatic leukodystrophy; NANA, N-acetyl-neuraminic acid.

by specific exoglycosidases. Abnormalities in catabolism result in an accumulation of the ganglioside within the cell. Defects in ganglioside degradation can be classified into 2 groups: the GM_1 gangliosidoses and the GM_2 gangliosidoses.

GM_1 Gangliosidoses

The 3 subtypes of GM_1 gangliosidoses are classified according to age at presentation: infantile (type 1), juvenile (type 2), and adult (type 3). The condition is inherited as an autosomal recessive trait and results from a marked deficiency of acid β-galactosidase. This enzyme may be assayed in leukocytes and cultured fibroblasts. The acid β-galactosidase gene has been mapped to chromosome 3p14.2. Prenatal diagnosis is possible by measurement of acid β-galactosidase in cultured amniotic cells.

Infantile GM_1 gangliosidosis presents at birth or during the neonatal period with anorexia, poor sucking, and inadequate weight gain. Development is globally delayed, and generalized seizures are prominent. The phenotype is striking and shares many characteristics with Hurler syndrome. The facial features are coarse, the forehead is prominent, the nasal bridge is depressed, the tongue is large (macroglossia), and the gums are hypertrophied. Hepatosplenomegaly is present early in the course as a result of accumulation of foamy histiocytes, and kyphoscoliosis is evident because of anterior beaking of the vertebral bodies. The neurologic examination is dominated by apathy, progressive blindness, deafness, spastic quadriplegia, and decerebrate rigidity. A cherry-red spot in the macular region is visualized in approximately 50% of cases. The **cherry-red spot** is characterized by an opaque ring (sphingolipid-laden retinal ganglion cells) encircling the normal red fovea (Fig. 599-2). Children rarely survive beyond age 2-3 yr, and death may be from aspiration pneumonia.

Juvenile GM_1 gangliosidosis has a delayed onset beginning about 1 yr of age. The initial symptoms consist of incoordination, weakness,

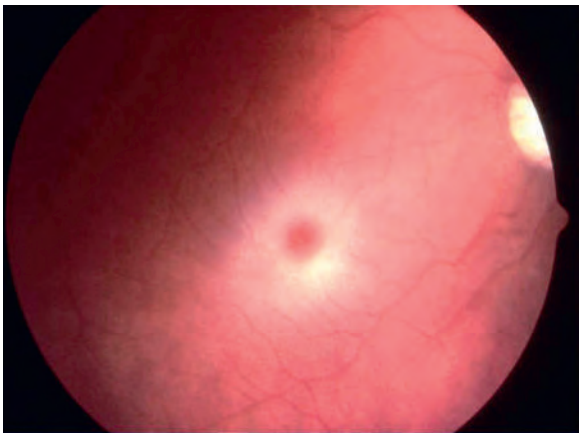


Figure 599-2 A cherry-red spot in a patient with GM_1 gangliosidosis. Note the whitish ring of sphingolipid-laden ganglion cells surrounding the fovea. *(From Leavitt JA, Kotagal S: The "cherry red" spot.* Pediatr Neurol *37(1):74–75, 2007, Fig. 1.)*

ataxia, and regression of language. Thereafter, convulsions, spasticity, decerebrate rigidity, and blindness are the major findings. Unlike the infantile type, this type is not usually marked by coarse facial features and hepatosplenomegaly. Radiographic examination of the lumbar vertebrae may show minor beaking. Children rarely survive beyond 10 yr of age. **Adult GM_1 gangliosidosis** is a slowly progressive disease consisting of spasticity, ataxia, dysarthria, and a gradual loss of cognitive function.

GM_2 Gangliosidoses

The GM_2 gangliosidoses are a heterogeneous group of autosomal recessive inherited disorders that consist of several subtypes, including Tay-Sachs disease (TSD), Sandhoff disease, juvenile GM_2 gangliosidosis, and adult GM_2 gangliosidosis. **TSD** is most prevalent in the Ashkenazi Jewish population and has an approximate carrier rate of 1 in 30 Jews in the United States. TSD is caused by mutations in the *HEXA* gene located on chromosome 15q23-q24. Affected infants appear normal until approximately 6 mo of age, except for a marked startle reaction to noise that is evident soon after birth. Affected children then begin to lag in developmental milestones and, by 1 yr of age, they lose the ability to stand, sit, and vocalize. Early hypotonia develops into progressive spasticity, and relentless deterioration follows, with convulsions, blindness, deafness, and cherry-red spots in almost all patients (see Fig. 599-2). Macrocephaly becomes apparent by 1 yr of age and results from the 200-300–fold normal content of GM_2 ganglioside deposited in the brain. Few children live beyond 3-4 yr of age, and death is usually associated with aspiration or bronchopneumonia. A deficiency of the isoenzyme hexosaminidase A is found in tissues of patients with TSD. Mass screening for prenatal diagnosis of TSD is a reliable and cost-effective method of prevention because the condition occurs most frequently in a defined population (Ashkenazi Jews). Targeted screening is responsible for the fact that currently, the rare children with TSD born in the United States are most commonly born to non-Jewish parents who are not routinely screened. An accurate and inexpensive carrier detection test is available (serum or leukocyte hexosaminidase A), and the disease can be reliably diagnosed by chorionic villus sampling in the 1st trimester of pregnancy in couples at risk (heterozygote parents).

Sandhoff disease is very similar to TSD in the mode of presentation, including progressive loss of motor and language milestones beginning at 6 mo of age. Seizures, cherry-red spots, macrocephaly, and doll-like facies are present in most patients; however, children with Sandhoff disease may also have splenomegaly. The visual evoked potentials (VEPs) are normal early in the course of Sandhoff disease and TSD, but become abnormal or absent as the disease progresses. The auditory brainstem responses show prolonged latencies. The diagnosis of Sandhoff disease is established by finding deficient levels of hexosaminidases A and B in serum and leukocytes. Children usually die by 3 yr of age. Sandhoff disease is caused by mutations in the *HEXB* gene located on chromosome 5q13.

Juvenile GM_2 gangliosidosis develops in mid-childhood, initially with clumsiness followed by ataxia. Signs of spasticity, athetosis, loss of language, and seizures gradually develop. Progressive visual loss is associated with optic atrophy, but cherry-red spots rarely occur in juvenile GM_2 gangliosidosis. A deficiency of hexosaminidase is variable (total deficiency to near normal) in these patients. Death occurs around 15 yr of age.

Adult GM_2 gangliosidosis is characterized by a myriad neurologic signs, including slowly progressive gait ataxia, spasticity, dystonia, proximal muscle atrophy, and dysarthria. Generally, visual acuity and intellectual function are unimpaired. Hexosaminidase A activity alone or hexosaminidases A and B activity is reduced significantly in the serum and leukocytes.

Krabbe Disease (Globoid Cell Leukodystrophy)

Krabbe disease (KD) is a rare autosomal recessive neurodegenerative disorder characterized by severe myelin loss and the presence of globoid bodies in the white matter. The gene for KD *(GALC)* is located on chromosome 14q24.3-q32.1. The disease results from a marked deficiency of the lysosomal enzyme galactocerebroside β-galactosidase. KD is a disorder of myelin destruction rather than abnormal myelin formation. Normally, myelination begins in the 3rd trimester, corresponding with a rapid increase of galactocerebroside β-galactosidase activity in the brain. In patients with KD, galactocerebroside cannot be metabolized during the normal turnover of myelin because of deficiency of galactocerebroside β-galactosidase. When galactocerebroside is injected into the brains of experimental animals, a globoid cell reaction ensues. It is postulated that a similar phenomenon occurs in humans; nonmetabolized galactocerebroside stimulates the formation of globoid cells that reflect the destruction of oligodendroglial cells. Because oligodendroglial cells are responsible for the elaboration of myelin, their loss results in myelin breakdown, thus producing additional galactocerebroside and causing a vicious circle of myelin destruction.

The symptoms of KD become evident in the 1st few mo of life and include excessive irritability and crying, unexplained episodes of hyperpyrexia, vomiting, and difficulty feeding. In the initial stage of KD, children are often treated for colic or milk allergy with frequent formula changes. Generalized seizures may appear early in the course of the disease. Alterations in body tone with rigidity and opisthotonos and visual inattentiveness as a result of optic atrophy become apparent as the disease progresses. In the later stages of the illness, blindness, deafness, absent deep-tendon reflexes, and decerebrate rigidity constitute the major physical findings. Most patients die by 2 yr of age. MRI and magnetic resonance spectroscopy are useful for evaluating the extent of demyelination in KD. Umbilical cord blood (stem cell) transplantation from unrelated donors in asymptomatic babies may favorably alter the natural history but will not help patients who already have neurologic symptoms.

Late-onset KD has been described beginning in childhood or adolescence. Patients present with optic atrophy and cortical blindness, and their condition may be confused with adrenoleukodystrophy. Slowly progressive gait disturbances, including spasticity and ataxia, are prominent. As with classic KD, globoid cells are abundant in the white matter, and leukocytes are deficient in galactocerebroside β-galactosidase. An examination of the cerebrospinal fluid shows an elevated protein content, and the nerve conduction velocities are markedly delayed as a result of segmental demyelination of the peripheral nerves. The VEPs decrease gradually in amplitude with no response in the late stages of the disease, and the auditory brainstem responses are characterized by the presence of only waves I and II. CT scans and MRI studies highlight the marked decrease in white matter, especially of the cerebellum and centrum semiovale, with sparing of the subcortical U fibers. Prenatal diagnosis is possible by the assay of galactocerebroside β-galactosidase activity in chorionic villi or in cultured amniotic fluid cells. Newborn screening may identify patients at risk for late onset disease.

Metachromatic Leukodystrophy

This disorder of myelin metabolism is inherited as an autosomal recessive trait and is characterized by a deficiency of arylsulfatase A activity. The *ARSA* gene is located on chromosome 22q13-13qter. The absence or deficiency of arylsulfatase A leads to accumulation of cerebroside sulfate within the myelin sheath of the central nervous system (CNS) and peripheral nervous system because of the inability to cleave sulfate from galactosyl-3-sulfate ceramide. The excessive cerebroside sulfate is thought to cause myelin breakdown and destruction of oligodendroglia. Prenatal diagnosis of metachromatic leukodystrophy (MLD) is made by assaying of arylsulfatase A activity in chorionic villi or cultured amniotic fluid cells. Cresyl violet applied to tissue specimens produces metachromatic staining of the sulfatide granules, giving the disease its name. Some individuals with low arylsulfatase A enzyme activity are clinically normal and have a pseudodeficiency state that can only be confirmed by additional genetic or biochemical tests. Those affected with MLD are generally classified according to age of onset: late infantile, juvenile, and adult.

Late infantile MLD begins with insidious onset of gait disturbances between 1 and 2 yr of age. The child initially appears awkward and frequently falls, but locomotion is gradually impaired significantly and support is required to walk. The extremities are hypotonic, and the deep-tendon reflexes are absent or diminished. Within the next several months, the child can no longer stand, and deterioration in intellectual function becomes apparent. The speech is slurred and dysarthric, and the child appears dull and apathetic. Visual fixation is diminished, nystagmus is present, and examination of the retina shows optic atrophy. Within 1 yr from the onset of the disease, the child is unable to sit unsupported, and progressive decorticate postures develop. Feeding and swallowing are impaired because of pseudobulbar palsies, and a feeding gastrostomy is required. Patients ultimately become stuporous and die of aspiration or bronchopneumonia by age 5-6 yr. Neurophysiologic evaluation shows slowing of peripheral nerve conduction velocities and progressive changes in the VEPs, auditory brainstem responses, and somatosensory evoked potentials. CT and MRI images of the brain indicate diffuse symmetric attenuation of the cerebellar and cerebral white matter, and examination of the cerebrospinal fluid shows an elevated protein content. Bone marrow transplantation is a promising experimental therapy for the management of late infantile MLD, and early trials of enzyme replacement are being conducted. As with KD, favorable outcomes have been reported only in patients treated with less-severe disease or those identified very early in the course of the disease.

Juvenile MLD has many features in common with late infantile MLD, but the onset of symptoms is delayed to 5-10 yr of age. Deterioration in school performance and alterations in personality may herald the onset of the disease. This is followed by incoordination of gait, urinary incontinence, and dysarthria. Muscle tone becomes increased, and ataxia, dystonia, or tremor may be present. In the terminal stages, generalized tonic–clonic convulsions are prominent and are difficult to control. Patients rarely live beyond mid-adolescence.

Adult MLD occurs from the 2nd to 6th decade. Abnormalities in memory, psychiatric disturbances, and personality changes are prominent features. Slowly progressive neurologic signs, including spasticity, dystonia, optic atrophy, and generalized convulsions, lead eventually to a bedridden state characterized by decorticate postures and unresponsiveness.

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599.2 Neuronal Ceroid Lipofuscinoses

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The neuronal ceroid lipofuscinoses (NCLs) are a group of inherited, neurodegenerative, lysosomal storage disorders characterized by visual loss, progressive dementia, seizures, motor deterioration, and early death. The NCLs are so named because of the intracellular accumulation of fluorescent lipopigments, ceroid and lipofuscin. They comprise a genetically and phenotypically heterogeneous group of disorders (currently there are at least 9 NCL types) that have traditionally been subclassified by age of onset, among other clinical features. They differ from one another in the associated ultrastructural patterns of the inclusions as seen by electron microscopy. Evaluation of neuronal biopsies (either brain, rectal, conjunctival, or skin) was once required for diagnosis. With the advent of enzymatic and molecular testing methods, clinicians can make specific NCL diagnoses using less-invasive methods (Table 599-2).

Infantile-type neuronal ceroid lipofuscinose (INCL, Haltia-Santavuori) begins in the 1st yr of life with myoclonic seizures, intellectual deterioration, and blindness. Optic atrophy and brownish discoloration of the macula are evident on examination of the retina, and cerebellar ataxia is prominent. The electroretinogram typically shows small-amplitude or absent waveforms. Death occurs during childhood. The infantile form is caused by recessive mutations of the gene for the lysosomal enzyme palmitoyl-protein thioesterase-1 (PPT1) on chromosome 1p32. A number of cell types in INCL patients show characteristic intracellular fine granular osmiophilic deposits discernible by electron microscopy.

Table 599-2 Clinical and Genetic Characteristics of the Neuronal Ceroid Lipofuscinoses (NCL)

NCL TYPE	GENE*	PROTEIN	AGE OF ONSET	CLINICAL PRESENTATION
Congenital	*CLN10*	Cathepsin‡	Birth (but can present later)	Severe seizures, blindness, rigidity, early death Can also present similar to late infantile forms
Infantile	*CLN1*	Palmitoyl-protein thioesterase-1 (PPT1)‡	6-24 months	Early onset, often rapid progression of seizures; cognitive and motor decline with visual loss
Variant infantile	*CLN1*		3 yr to adulthood	Chronic course Initial visual loss followed then by slow mental and motor decline and seizures
Late infantile	*CLN2*	Tripeptidyl peptidase-1 (TPP1)‡	2-8 yr	Seizures, often severe and intractable; cognitive and motor decline; and visual loss
	CLN5	Partially soluble protein		
	CLN6	Membrane protein		
	CLN7	Membrane protein		
	CLN8	Membrane protein	5-10 yr	Severe epilepsy, progressive with mental retardation
Juvenile	*CLN3*	Membrane protein	4-10 yr	Visual loss is usually the initial presenting complaint Also have mental, motor disorder and seizures

*Note that all the NCL genes have the prefix CLN. The adult form (also called Kufs disease, with locus CLN4, caused by mutations in DNAJC5) is not well characterized and is not included in the table.

†Direct genetic testing is available for all.

‡Enzyme testing available.

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A subset of children with PPT1 enzyme deficiency has a much less-severe course with clinical features resembling those of the juvenile-onset NCL patients. Clinically, these variant INCL patients have a course that is often quite distinct from the typical, classic rapidly degenerating infantile form. Yet they have PPT1 deficiency and granular osmiophilic deposits on pathology. There is no clear *CLN1* genotype that predicts severity of phenotype.

Late infantile-type neuronal ceroid lipofuscinose (LINCL, Jansky-Bielschowsky) generally presents with myoclonic seizures beginning between 2 and 4 yr of age in a previously normal child. Dementia and ataxia are combined with a progressive loss of visual acuity and microcephaly. Examination of the retina shows marked attenuation of vessels, peripheral black bone spicule pigmentary abnormalities, optic atrophy, and a subtle brown pigment in the macular region. The electroretinogram and VEP are abnormal early in the course of disease. The autofluorescent material is deposited in neurons, fibroblasts, and secretory cells. Electron microscopic examination of the storage material in skin or conjunctival biopsy material typically shows curvilinear profiles. LINCL can be caused by autosomal recessive mutations of several different genes: *CLN2* gene, which codes for a tripeptidyl peptidase-1 (TPP1) that is essential for the degradation of cholecystokinin-8, as well as the *CLN5, CLN6,* and *CLN8* genes that code for membrane proteins that have not been completely characterized. *CLN8* is also known as the locus of Northern epilepsy syndrome, which is often called progressive epilepsy with mental retardation.

Juvenile type neuronal ceroid lipofuscinose (JNCL, Spielmeyer-Vogt or Batten disease) is the most common form of NCL disease and is generally caused by autosomal-recessive mutations in *CLN3*. (Patients who present clinically with JNCL but have PPT1 or TPP1 deficiency are said to have variant INCL or LINCL, respectively.) Children affected with JNCL tend to develop normally for the 1st 5 yr of life. Their initial symptom is usually progressive visual loss and their retinal pigmentary changes often results in an initial diagnosis of retinitis pigmentosa. The funduscopic changes are similar to those for the late infantile type. After disease onset, there may be rapid decline with changes in cognition and personality, motor incoordination, and seizures. Myoclonic seizures are not as prominent as in LINCL, but parkinsonism can develop and impair ambulation. Patients die in their late twenties to early thirties. In JNCL caused by *CLN3*, the electron microscopy of tissues show deposits called fingerprint profiles, and routine light microscopy of a peripheral blood smear may show lymphocyte vacuoles.

Bibliography is available at Expert Consult.

599.3 Adrenoleukodystrophy

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See Chapter 86.2.

599.4 Sialidosis

Jennifer M. Kwon

Sialidosis is the result of lysosomal sialidase deficiency, secondary to autosomal recessive mutations in the sialidase (α-neuraminidase, *NEU1*) gene on chromosome 6p21.3. The accumulation of sialic acid–oligosaccharides with markedly increased urinary excretion of sialic acid–containing oligosaccharides is associated with clinical presentations that range from the milder sialidosis type I to the more severe sialidosis type II associated with both neurologic and somatic features.

Sialidosis type I, the **cherry-red spot myoclonus syndrome**, usually presents in the 2nd decade of life, when a patient complains of visual deterioration. Inspection of the retina shows a cherry-red spot, but, unlike patients with TSD, visual acuity declines slowly in individuals with cherry-red spot myoclonus syndrome. Myoclonus of the extremities is gradually progressive and often debilitating and eventually renders patients nonambulatory. The myoclonus is triggered by voluntary movement, touch, and sound and is not controlled with anticonvulsants. Generalized convulsions responsive to antiepileptic drugs occur in most patients.

Sialidosis type II patients present at a younger age and have cherry-red spots and myoclonus, as well as somatic involvement, including coarse facial features, corneal clouding (rarely), and dysostosis multiplex, producing anterior beaking of the lumbar vertebrae. Type II patients may be further subclassified into congenital and infantile (childhood) forms, depending on the age at presentation. Examination of lymphocytes shows vacuoles in the cytoplasm, biopsy of the liver demonstrates cytoplasmic vacuoles in Kupffer cells, and membrane-bound vacuoles are found in Schwann cell cytoplasm, all attesting to the multiorgan nature of sialidosis type II. No distinctive neuroimaging findings or abnormalities in electrophysiologic studies are noted in this group of disorders. Patients with sialidosis have been reported to live beyond the 5th decade.

Some cases of what appears to be sialidosis type II are the result of combined deficiencies of β-galactosidase and α-neuraminidase resulting from deficiency of protective protein/cathepsin A that prevents premature intracellular degradation of these 2 enzymes. These patients have galactosialidosis and they are clinically indistinguishable from those with sialidosis type II. Consequently, patients who have features of sialidosis type II with marked urinary excretion of oligosaccharides should be tested for protective protein/cathepsin A deficiency as well as sialidase deficiency.

Bibliography is available at Expert Consult.

599.5 Miscellaneous Disorders

Jennifer M. Kwon

PELIZAEUS-MERZBACHER DISEASE

Pelizaeus-Merzbacher disease (PMD) is an X-linked recessive disorder characterized by nystagmus and abnormalities of myelin. PMD is caused by mutations in the proteolipid protein *(PLP1)* gene, on chromosome Xq22, which is essential for CNS myelin formation and oligodendrocyte differentiation. Mutations in the same gene can cause familial spastic paraparesis (progressive spastic paraparesis type 2, SPG2). *PLP1* mutations causing disease include point mutations, deletions, gene duplications, and other gene dosage changes.

Clinically, classic PMD is recognized by nystagmus and roving eye movements with head nodding during infancy. Developmental milestones are delayed; ataxia, choreoathetosis, and spasticity ultimately develop. Optic atrophy and dysarthria are associated findings, and death occurs in the 2nd or 3rd decade. The major pathologic finding is a loss of myelin with intact axons, suggesting a defect in the function of oligodendroglia. An MRI scan shows a symmetric pattern of delayed myelination. Multimodal-evoked potential studies demonstrate early in the course a pattern consisting of loss of waves III-V on the auditory brainstem response. This finding is useful in the investigation of nystagmus in infant boys. VEPs show prolonged latencies, and somatosensory evoked potentials show absent cortical responses or delayed latencies. It is now recognized that a broad spectrum of phenotypes, including SPG2 and peripheral nerve abnormalities, can also result from mutations in the *PLP1* gene.

There is a PMD-like syndrome caused by autosomal recessive mutations in the gap junction protein alpha 12 (*GJA12*, or connexin 47). Individuals with *GJA12* mutations have a clinical and radiologic phenotype like PMD including hypomyelinating leukodystrophy.

ALEXANDER DISEASE

This is a rare disorder that causes progressive macrocephaly and leukodystrophy. Alexander disease is caused by dominant mutations in the glial fibrillary acidic protein *(GFAP)* gene, on chromosome 17q21

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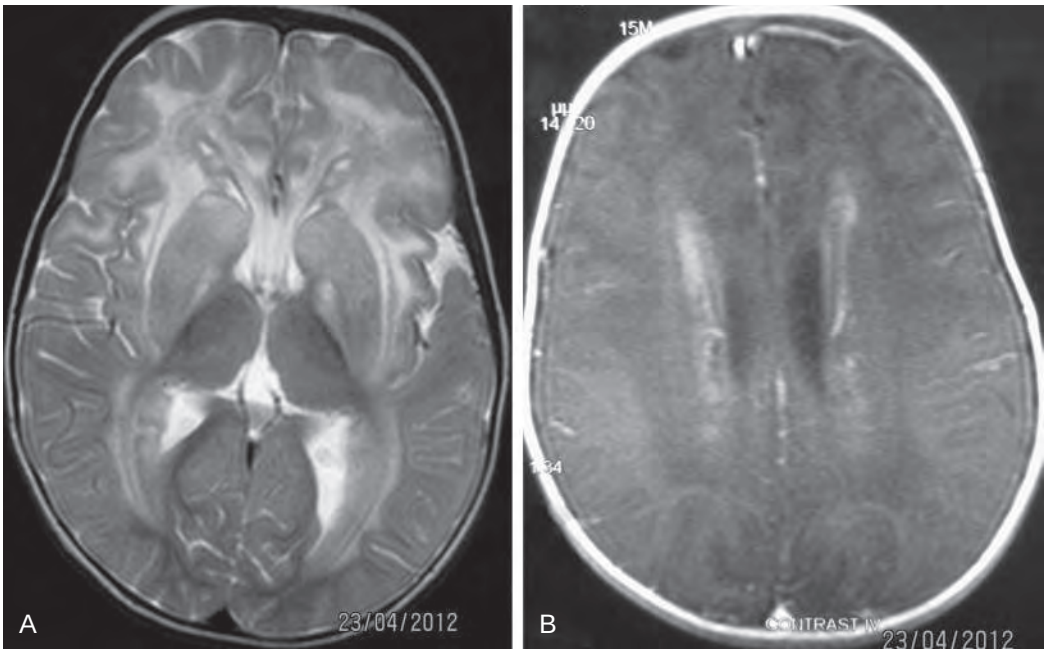


Figure 599-3 Alexander disease. MRI of the index patient at the age of 15 mo. **A,** Axial T2-weighted sequences (TR/TE: 4000/99) at the basal ganglia and thalamus level demonstrating diffuse bilateral, symmetric increased signal predominantly of the frontal periventricular, but also of the subcortical white matter and of the basal ganglia. **B,** Significant periventricular rim after intravenous gadolinium infusion (T1-weighted sequences; TR/TE: 400/88). *(From Zafeiriou DI, Dragoumi P, Vargiami E: Alexander disease.* J Pediatr *162:648, 2013.)*

and cases are usually sporadic in their families. Pathologic examination of the brain discloses deposition of eosinophilic hyaline bodies called Rosenthal fibers in astrocyte processes. These accumulate in a perivascular distribution throughout the brain. In the classic infantile form of Alexander disease, degeneration of white matter is most prominent frontally. Diagnosis may be suggested by MRI (Fig. 599-3) and MR spectroscopy demonstrating abnormal metabolic substrates. Affected children develop progressive loss of intellect, spasticity, and unresponsive seizures causing death by 5 yr of age. However, there are milder forms that present later in life and that may not have the characteristic frontal predominance or megalencephaly.

CANAVAN SPONGY DEGENERATION

See Chapter 85.15.

OTHER LEUKODYSTROPHIES

Metabolic and degenerative disorders can present with significant cerebral white matter changes, such as some mitochondrial disorders (see Chapters 86.1 and 598.2) and glutaric aciduria type 1 (see Chapter 85.14). In addition, the broader use of MRI has brought to light new leukodystrophies. One example is vanishing white matter disease or childhood ataxia with CNS hypomyelination characterized by ataxia and spasticity. Some patients also have optic atrophy, seizures, and cognitive deterioration. The age of presentation and the rapidity of decline can be quite variable. In the early-onset forms, decline is usually rapid and followed quickly by death; in the later-onset forms, mental decline is usually slower and milder. Interestingly, acute demyelination in these disorders can be triggered by fever or fright. The diagnosis of vanishing white matter disease or childhood ataxia with CNS hypomyelination is based on clinical findings, characteristic abnormalities on cranial MRI, and autosomal recessive mutations in 1 of 5 causative genes (*EIF2B1, EIF2B2, EIF2B3, EIF2B4,* and *EIF2B5*) encoding the 5 subunits of the eucaryotic translation initiation factor, eIF2B.

MENKES DISEASE

Menkes disease (kinky hair disease) is a progressive neurodegenerative condition inherited as a X-linked recessive trait. The Menkes gene codes for a copper-transporting, P-type adenosine triphosphatase, and mutations in the protein are associated with low serum copper and ceruloplasmin levels, as well as a defect in intestinal copper absorption and transport. Symptoms begin in the 1st few mo of life and include hypothermia, hypotonia, and generalized myoclonic seizures. The facies are distinctive, with chubby, rosy cheeks and kinky, colorless, friable hair. Microscopic examination of the hair shows several abnormalities, including trichorrhexis nodosa (fractures along the hair shaft) and pili torti (twisted hair). Feeding difficulties are prominent and lead to failure to thrive. Severe mental retardation and optic atrophy are constant features of the disease. Neuropathologic changes include tortuous degeneration of the gray matter and marked changes in the cerebellum with loss of the internal granule cell layer and necrosis of the Purkinje cells. Death occurs by 3 yr of age in untreated patients.

Copper-histidine therapy may be effective in preventing neurologic deterioration in some patients with Menkes disease, particularly when treatment is begun in the neonatal period or, preferably, with the fetus. These presymptomatic children are currently identified because of a family history of an affected brother. Copper is essential in the early stages of CNS development, and its absence probably accounts for the neuropathologic changes. Infants diagnosed presymptomatically in the 1st 10 days of life can be started on an experimental protocol of daily copper-histidine subcutaneous injections (as of 2015, only available at NIH under a program supervised by Dr. Stephen Kaler). Optimal response to copper-histidine injection treatment appears to occur only in patients who are identified in the newborn period and whose mutations permit residual copper-transport activity.

The **occipital horn syndrome,** a skeletal dysplasia caused by different mutations in the same gene as that involved in Menkes disease, is a relatively mild disease. The 2 diseases are often confused, because the biochemical abnormalities are identical. Resolution of the uncertainty about treatment of patients with Menkes disease will require careful genotype-phenotype correlation, along with further clinical trials of copper therapy.

RETT SYNDROME

This syndrome is not strictly speaking a degenerative disease, but a disorder of early brain development marked by a period of developmental regression and deceleration of brain growth after a relatively

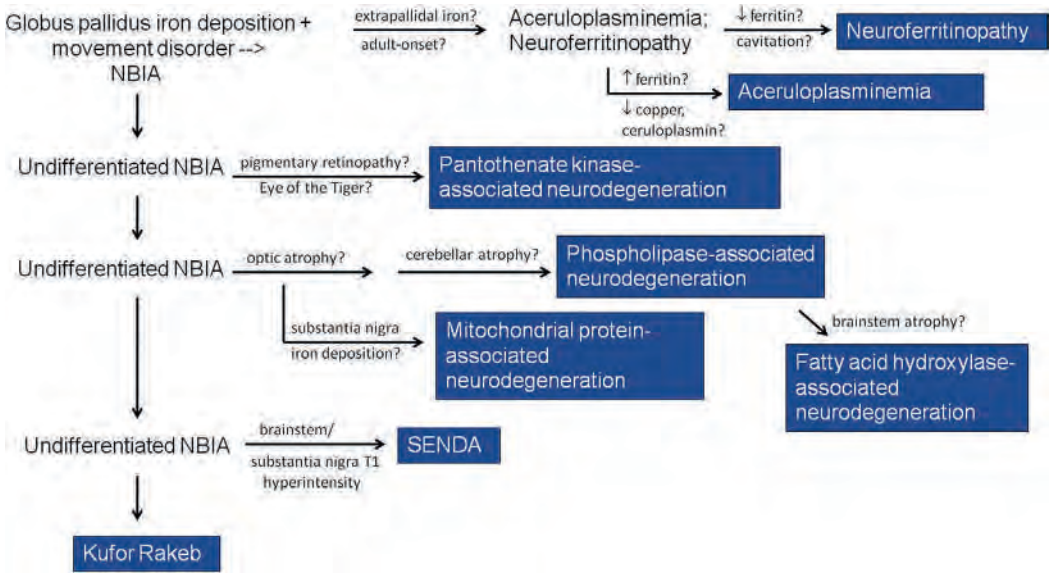


Figure 599-4 Clinical and radiographic approach to neurodegeneration with brain iron accumulation. NBIA, neurodegeneration with brain iron accumulation; SENDA, static encephalopathy of childhood with neurodegeneration in adulthood. *(From Kruer MC, Boddaert N: Neurodegeneration with brain iron accumulation: a diagnostic algorithm.* Semin Pediatr Neurol *19:67–74, 2012, Fig. 1.)*

normal neonatal course. It occurs predominantly in girls. The frequency is approximately 1 in 15,000-22,000 children. Rett syndrome is caused by mutations in *MeCP2,* a transcription factor that binds to methylated CpG islands and silences transcription. Development may proceed normally until 1 yr of age, when regression of language and motor milestones and acquired microcephaly become apparent. An ataxic gait or fine tremor of hand movements is an early neurologic finding. Most children develop peculiar sighing respirations with intermittent periods of apnea that may be associated with cyanosis. The hallmark of Rett syndrome is repetitive hand-wringing movements and a loss of purposeful and spontaneous use of the hands; these features may not appear until 2-3 yr of age. Autistic behavior is a typical finding in all patients. Generalized tonic-clonic convulsions occur in the majority and are usually well controlled by anticonvulsants. Feeding disorders and poor weight gain are common. After the initial period of neurologic regression, the disease process appears to plateau, with persistence of the autistic behavior. Cardiac arrhythmias may result in sudden, unexpected death at a rate that is higher than the general population. Generally girls survive into adulthood.

Postmortem studies show significantly reduced brain weight (60-80% of normal) with a decrease in the number of synapses, associated with a decrease in dendritic length and branching. The phenotype may be related to failure to suppress expression of genes that are normally silent in the early phases of postnatal development. Although very few males survive with the classic Rett syndrome phenotype, genotyping of boys without the classic Rett syndrome phenotype but with intellectual disability and other atypical neurologic features has detected a significant number with mutations in *MeCP2.* Mutations in *MeCP2* have been demonstrated in normal female carriers, females with Angelman syndrome, and in males with fatal encephalopathy, Klinefelter (47 XXY) syndrome, and familial X-linked mental retardation.

Some girls have an atypical Rett phenotype associated with severe myoclonic seizures in infancy, slowing of head growth, and developmental arrest and have mutations in another X-linked gene encoding for cyclin-dependent kinase–like 5 (CDKL5), which may interact with MeCP2 and other proteins regulating gene expression.

SUBACUTE SCLEROSING PANENCEPHALITIS

This is a rare, progressive neurologic disorder caused by persistent measles virus infection of the CNS (see Chapter 246). The number of reported cases has decreased dramatically to 0.06 cases/million population, paralleling the decline in reported measles cases. The initial clinical manifestations include personality changes, aggressive behavior, and impaired cognitive function in individuals who have been exposed to natural measles virus in early childhood. Myoclonic seizures soon dominate the clinical picture. Later, generalized tonic–clonic convulsions, hypertonia, and choreoathetosis become evident, followed by progressive bulbar palsy, hyperthermia, and decerebrate postures. Funduscopic examination early in the course of the disease reveals papilledema in approximately 20% of the cases. Optic atrophy, chorioretinitis, and macular pigmentation are observed in most patients. The diagnosis is established by the typical clinical course and 1 of the following: (1) measles antibody detected in the cerebrospinal fluid, (2) a characteristic electroencephalogram consisting of bursts of high-voltage slow waves interspersed with a normal background that occur with a constant periodicity in the early stages of the disease, and (3) typical histologic findings in the brain biopsy or postmortem specimen. Treatment with a series of antiviral agents has been attempted without success. Death occurs usually within 1-2 yr from the onset of symptoms.

NEURODEGENERATION WITH BRAIN IRON ACCUMULATION

Neurodegeneration with brain iron accumulation represents multiple, age-of-onset-dependent disorders characterized by extrapyramidal symptoms, intellectual deterioration and regression, with iron deposition in the basal ganglia. There is significant phenotype variability of these disorders; however, a characteristic finding on MRI demonstrates symmetric T2 signal homogeneous *hypointensity*. Common neurodegeneration with brain iron accumulation disorders are distinguished in Table 599-3 and an approach to their diagnosis is noted in Figure 599-4. Clinical features, which are highly variable, may include dystonia, parkinsonism, ataxia, spasticity, psychiatric symptoms, and intellectual impairment. Treatment should focus on the specific disorder and is usually symptomatic relief rather than curative. Iron chelation has been attempted without major long-term benefit.

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Table 599-3 Overview of Neurodegeneration with Brain Iron Accumulation Conditions and Genes (if Known)

					CHILDHOOD-ONSET VARIANT		LATE-ONSET VARIANT	
CONDITION (ACRONYM)	**SYNONYM**	**GENE**	**CHROMOSOMAL POSITION**	**LB PATHOLOGY**	**AGE OF ONSET**	**CLINICAL PRESENTATION**	**AGE OF ONSET**	**CLINICAL PRESENTATION**
PKAN	NBIA1	PANK2	20p13	No	Early childhood, around age 3	Typical PKAN	Teens or early adulthood	Atypical PKAN
PLAN	NBIA2, PARK14	PLA2G6	22q12	√	Infancy	Infantile neuroaxonal dystrophy	Teens or early adulthood	Dystonia parkinsonism
FAHN	SPG35	FA2H	16q23	Not known	Childhood	Leukodystrophy, hereditary spastic paraplegia	Adulthood (age range up to 30 yr)	May resemble idiopathic PD
MPAN	—	C19orf12	19q12	√	—	Pyramidal extrapyramidal syndrome		
Kufor-Rakeb disease	PARK9	ATP13A2	1p36	√	Childhood-teens	Parkinsonism, pyramidal tract signs, eye movement disorder		
BPAN	SENDA syndrome	WDR45	Xp11.23	Not known	Childhood	Encephalopathy with psychomotor regression, then static	Then: 20s to 30s	Sudden onset progressive dystonia parkinsonism
Aceruloplasminemia	—	CP	3q23	No	—	—	50s (range: 16-70)	Extrapyramidal, diabetes, dementia
Neuroferritinopathy	—	FTL	19q13	No	—	—	40s	Chorea, dystonia, dementia
Idiopathic late-onset cases	—	Probably heterogeneous	Probably heterogeneous	Heterogeneous	—	—	Heterogeneous	Parkinsonism, in may resemble idiopathic PD

√, Present; BPAN, beta-propeller associated neurodegeneration; CP, ceruloplasmin; FA2H, fatty acid 2-hydroxylase; FAHN, fatty acid 2-hydroxylase-associated neurodegeneration; FTL, ferritin light chain; MPAN, mitochondrial membrane-associated neurodegeneration; NBIA, neurodegeneration with brain iron accumulation; PANK2, pantothenate kinase 2; PD, Parkinson disease; PKAN, pantothenate kinase-associated neurodegeneration; PLA2G6, phospholipase A2; PLAN, PLA2G6-associated neurodegeneration; SENDA, static encephalopathy of childhood with neurodegeneration in adulthood; SPG, spastic paraplegia.

From Schneider SA, Zorzi G, Nardocci N: Pathophysiology and treatment of neurodegeneration with brain iron accumulation in the pediatric population, Curr Treat Option Neurol *15:652-667, 2013, Table 1.*

Chapter 600

Demyelinating Disorders of the Central Nervous System

Jayne M. Ness

Acquired demyelinating disorders of the central nervous system (CNS) result in neurologic dysfunction caused by immune-mediated attacks on white matter insulating the brain, optic nerves and spinal cord. The white matter insulation is formed by myelin contained within oligodendrocytes wrapping around nerve axons. In contrast to genetically determined leukodystrophies (sometimes called dysmyelinating disorders) that produce disrupted white matter, acquired demyelinating disorders generally target normally formed white matter. Pediatric demyelinating syndromes are characterized clinically by (1) localization of neurologic deficits (i.e., single site, such as spinal cord [transverse myelitis], optic nerves [optic neuritis] or brainstem, vs polyregional demyelination); (2) the presence vs absence of encephalopathy; and (3) disease course (i.e., monophasic vs repeated attacks involving either the same or new CNS regions). Major demyelinating disorders in childhood include acute disseminated encephalomyelitis (ADEM), typically a self-limited disorder, and relapsing–remitting multiple sclerosis (MS). MRI of brain and spine is useful to initially characterize symptomatic and clinically silent demyelinating lesions, but serial MRI is often required to distinguish self-limited vs chronic demyelinating syndromes, especially in the younger child. Additional studies, such as cerebrospinal fluid (CSF) analysis, autoimmune and genetic testing, and sometimes even brain biopsy, may be required to evaluate for mimickers of demyelination, such as neoplasm, infection, systemic rheumatologic disorders, isolated CNS angiitis, mitochondrial disease, and leukodystrophies (Tables 600-1 and 600-2).

Table 600-1 Differential Diagnosis of Demyelinating Disorders

Acute disseminated encephalomyelitis (ADEM)
Multiple sclerosis (including tumefactive MS)
Acute hemorrhagic leukoencephalopathy
Clinically isolated syndrome (CIS)
Neuromyelitis optica spectrum disorder
N-methyl-D-aspartate receptor (NMDAR) antibody and other autoimmune encephalitis
Vasculitis/angiopathies
Hashimoto encephalitis (anti–thyroid peroxidase [TPO] antibody)
Familial hemophagocytic lymphohistiocytosis
Langerhans cell histiocytosis
Lymphoma
Gliomatosis cerebri
Glioma
Sarcoidosis
Mitochondrial disorders (Leigh syndrome)
Vitamin E deficiency
Vitamin B_{12} deficiency
Celiac disease
Herpes simplex virus (HSV), enterovirus, arbovirus, Powassan and other viral encephalitides
Rabies
Subacute sclerosing pan-encephalitis (SSPE) (chronic measles)
Charcot-Marie-Tooth syndrome
Leukoencephalopathies (Aicardi-Goutières syndrome)
Vanishing white matter disease
Schilder disease (possibly an adrenoleukodystrophy)
X-linked adrenoleukodystrophy
Griscelli syndrome type 2

600.1 Multiple Sclerosis

Jayne M. Ness

Pediatric MS is a chronic demyelinating disorder of the brain, spinal cord, and optic nerves characterized by a relapsing–remitting course of neurologic events without encephalopathy separated in time and space.

EPIDEMIOLOGY

Pediatric MS is rare, with an estimated 2-5% of MS patients experiencing their first symptoms before age 18 yr. Pediatric MS has a slight male predominance when disease onset is before age 6 yr, but by age 12 yr, females outnumber males 2:1.

PATHOGENESIS

A complex interplay of environmental, infectious, and genetic factors influence MS susceptibility. Immune system dysregulation involving T and B lymphocytes triggers inflammation, axonal demyelination, axonal loss, and regeneration within both white and gray matter. Inflammatory infiltrates within actively demyelinating lesions of relapsing-remitting MS are targets for disease modifying agents (DMAs). Neurodegenerative changes predominate in progressive forms of MS.

CLINICAL MANIFESTATIONS

Presenting symptoms in pediatric MS include hemiparesis or paraparesis; unilateral or, less often, bilateral optic neuritis; focal sensory loss; ataxia; diplopia; dysarthria; or bowel/bladder dysfunction (Table 600-3). Polyregional symptoms are reported in 30% of patients. Encephalopathy is less common and suggests consideration of ADEM or possibly neuromyelitis optica (NMO).

LABORATORY FINDINGS

Cranial MRI exhibits discrete T2 lesions in cerebral white matter, particularly periventricular regions as well as brainstem, cerebellum, and juxtacortical and deep gray matter. Alternatively, large tumefactive T2 lesions may be seen. Spine MRI typically shows partial-width cord lesions restricted to 1-2 spine segments. CSF may be normal or exhibit mild pleocytosis, particularly in younger children. Abnormal MS profiles (increased immunoglobulin [Ig] G index, and/or CSF oligoclonal bands) increase likelihood of MS but may be negative in 10-60% of pediatric MS patients, particularly prepubertal children; they also may be occasionally positive in ADEM or autoimmune encephalitis (Fig. 600-1). Abnormal evoked potential studies can localize disruptions in visual, auditory, or somatosensory pathways.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

Pediatric MS can usually be diagnosed following 2 demyelinating episodes without encephalopathy localizing to distinct CNS regions, lasting longer than 24 hr and separated by more than 30 days, provided no other plausible explanation exists. Current MS diagnostic criteria use MRI to serve as a surrogate for recurrent demyelination, enabling MS diagnosis after the first event. For adults and children >12 yr, the initial MRI may be sufficient to diagnose MS if it demonstrates dissemination in space (≥2 T2 lesions involving juxtacortical, periventricular, infratentorial, or spine regions) and time (presence of asymptomatic gadolinium-enhancing lesion and nonenhancing T2 lesion in same scan). Alternatively, MS can be diagnosed with a follow-up MRI at any time interval exhibiting accumulation of T2 or gadolinium-enhancing lesions in the brain or spine. Challenges arise in distinguishing pediatric MS from other acquired demyelinating

Table 600-2 IPMSSG 2012 Definitions for Pediatric Acute Demyelinating Disorders of the Central Nervous System

DISORDER	IPMSSG 2012
CIS	• A first monofocal or multifocal CNS demyelinating event; encephalopathy is absent, **unless caused by fever**
Monophasic ADEM	• A first polyfocal clinical CNS event with presumed inflammatory cause • Encephalopathy that **cannot be explained by fever** is present MRI typically shows **diffuse, poorly demarcated, large, >1-2 cm lesions** involving predominantly the cerebral white matter; **T1 hypointense white matter lesions are rare**; deep gray-matter lesions (e.g., thalamus or basal ganglia) can be present • No new symptoms, signs or MRI findings after 3 mo of the incident ADEM
Recurrent ADEM	• **See multiphasic ADEM**
Multiphasic ADEM	• New event of ADEM 3 mo or more after the initial event that can be associated with **new or reemergence of prior clinical and MRI findings. Timing in relation to steroids is no longer pertinent**
MS	Any of the following: • Two or more nonencephalopathic CNS clinical events separated by more than 30 days, involving more than 1 area of the CNS • Single clinical event and MRI features rely on 2010 Revised McDonald criteria for DIS and DIT (but criteria relative for DIT for a single attack and single MRI only apply to children ages 2-12 yr and only apply to cases without an ADEM onset)
NMO	All are required: • Optic neuritis • Acute myelitis At least 2 of 3 supportive criteria • Contiguous spinal cord MRI lesion S3 vertebral segments • **Brain MRI not meeting diagnostic criteria for MS** • Anti–aquaporin-4 immunoglobulin G–seropositive status • ADEM followed 3 mo later by a nonencephalopathic clinical event with new lesions on brain MRI consistent with MS

The 2001 McDonald MRI criteria for DIS require 3 of the following 4 MRI features: 29 T2 lesions or 1 gadolinium-enhancing lesion; 23 periventricular lesions; 21 infratentorial lesion(s); 21 juxtacortical lesion(s). The DIT criteria require subsequent white-matter lesions whose timing depends on the temporal relation of the initial MRI with the onset of the clinical symptoms.

The 2010 Revised McDonald MRI criteria for DIS require the presence of at least 2 of the following 4 criteria: 21 lesions in each of the 4 locations; periventricular, juxtacortical, infratentorial, and spinal cord. The 2010 Revised McDonald MRI criteria for DIT can be satisfied either by the emergence of newT2 lesions (with or without enhancement) on serial scan(s) or can be met on a single baseline scan if there exists simultaneous presence of a clinically silent gadolinium-enhancing lesion and a nonenhancing lesion.

ADEM, acute disseminated encephalomyelitis; CIS, clinically isolated syndrome; CNS, central nervous system; DIS, dissemination in space; DIT, dissemination in time; IPMSSG, International Pediatric Multiple Sclerosis Study Group; MS, multiple sclerosis; NMO, neuromyelitis optica.

Modified from Krupp LB, Tardieu M, Amato MP, et al: International Pediatric Multiple Sclerosis Study Group criteria for pediatric multiple sclerosis and immune-mediated central nervous system demyelinating disorders: revision to the 2007 definitions. Mult Scler 19(10):1261–1267, 2013, Appendix 1, p. 1266.

Table 600-3 Symptoms and Signs of Multiple Sclerosis by Site

	SYMPTOMS	SIGNS
Cerebrum	Cognitive impairment	Deficits in attention, reasoning, and executive function (early); dementia (late)
	Hemisensory and motor	Upper motor neuron signs
	Affective (mainly depression)	
	Epilepsy (rare)	
	Focal cortical deficits (rare)	
Optic nerve	Unilateral painful loss of vision	Scotoma, reduced visual acuity, color vision, and relative afferent papillary defect
Cerebellum and cerebellar pathways	Tremor	Postural and action tremor, dysarthria
	Clumsiness and poor balance	Limb incoordination and gait ataxia
Brainstem	Diplopia, oscillopsia	Nystagmus, internuclear and other complex ophthalmoplegias
	Vertigo	
	Impaired swallowing	Dysarthria
	Impaired speech and emotional lability	Pseudobulbar palsy
	Paroxysmal symptoms	
Spinal cord	Weakness	Upper motor neuron signs
	Stiffness and painful spasms	Spasticity
	Bladder dysfunction	
	Erectile impotence	
	Constipation	
Other	Pain	
	Fatigue	
	Temperature sensitivity and exercise intolerance	

Modified from Compston A, Coles A: Multiple sclerosis, Lancet *372:1502–1517, 2008, p. 1503.*

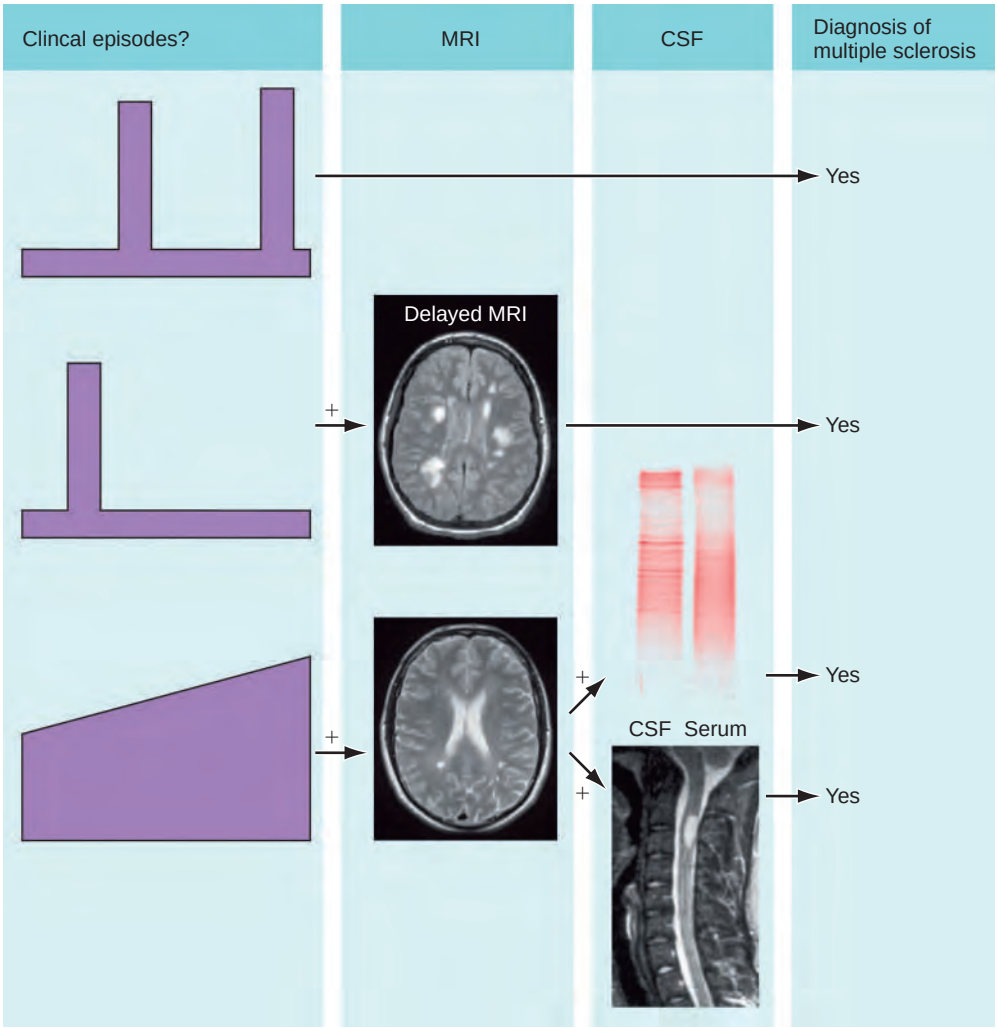


Figure 600-1 Criteria for the diagnosis of multiple sclerosis. The principle is to establish dissemination in time and place of lesions, meaning that episodes affecting separate sites within the central nervous system have occurred at least 30 days apart. MRI can substitute for 1 of these clinical episodes. Dissemination in time of magnetic resonance lesions requires simultaneous presence of asymptomatic gadolinium-enhancing and asymptomatic lesions or followup MRI showing accumulation of a new gadolinium-enhancing lesion or T2 lesion. Criteria for MRI definition of dissemination in space require 2 or more lesions in periventricular, juxtacortical, or infratentorial regions or spine. Primary progressive MS is very rare in childhood but can be diagnosed after 1 yr of a progressive deficit and 2 of the following: (1) a positive brain MRI; (2) a positive spinal cord MRI; and (3) positive oligoclonal bands. Patients having an appropriate clinical presentation but who do not meet all of the diagnostic criteria can be classified as having possible MS. CSF, cerebrospinal fluid. *(From Compston A, Coles A: Multiple sclerosis,* Lancet *372:1502–1517, 2008, Fig. 1.)*

syndromes such as ADEM or NMO, especially in the prepubertal child. ADEM is a self-limited syndrome characterized by encephalopathy, polyregional neurologic deficits, and diffuse multifocal MRI T2 abnormalities followed by subsequent clinical improvement and resolution of MRI T2 lesions (see Tables 600-1, 600-2, 600-4, and 600-5). However, a subset of pediatric MS patients (10-25%) presents with an ADEM phenotype and then experiences multiple relapses with accumulation of MRI T2 lesions. NMO, traditionally thought of as a combined myelitis and optic neuritis with normal brain MRI, now has a broader phenotype with the identification of the NMO antibody against the CNS water channel aquaporin-4 and MRI lesions in the brain. The NMO spectrum includes isolated bilateral optic neuritis or longitudinally extensive transverse myelitis even in the presence of brain MRI abnormalities or encephalopathy.

COMPLICATIONS

Similar to adults with MS, pediatric MS patients can acquire fixed neurologic deficits affecting vision and other cranial nerves, motor and sensory function, balance, and bowel/bladder function. Cognitive impairment can impede academic achievement.

TREATMENT

Relapses causing functional disability may be treated with methylprednisolone, 20-30 mg/kg/day (max: 1,000 mg/day) for 3-5 days, with or without prednisone taper. DMAs reduce relapse frequency and T2 lesion load, mainly by targeting the inflammatory response that predominates during the relapsing-remitting phase of MS (Table 600-6). There are 4 injectable DMAs, 3 oral DMAs, and 2 infused DMAs approved by the FDA for adult MS, but to date, none of these agents has a pediatric MS indication. Injectable agents, first approved in the mid-1990s (interferon-beta1α SC or IM or interferon-beta1β SC; glatiramer acetate SC) have some side effects such as flu-like side effects and risk of transaminase elevation with interferon-beta or requirement for daily injections with glatiramer acetate but otherwise have an excellent safety record so are still recommended as first-line therapy in pediatric MS. Three oral DMAs (fingolimod, teriflunomide, dimethyl fumarate) have been FDA-approved since 2010, but despite ease of oral administration, enthusiasm is tempered by reports of severe side effects or even death from reactivation of latent viruses (fingolimod, dimethyl fumarate) and potential of severe birth defects (teriflunomide). Intravenous DMAs (natalizumab, mitoxantrone) are second-line agents

used only after failure of first-line injectable or oral agents. Natalizumab therapy is associated with the risk of developing progressive multifocal encephalopathy (CNS infection with human polyomavirus JC). Mitoxantrone has a lifetime dose limit because of cardiotoxicity and is associated with subsequent development of acute myelogenous lymphoma in 2 of 802 MS patients (0.25%).

PROGNOSIS

Retrospective studies of patients diagnosed with MS prior to widespread dimethyltryptamine use suggest slower disease progression in pediatric MS patients compared to adults. Despite a longer time to irreversible disability (20-30 yr), pediatric MS patients acquire irreversible disability at a younger age than adults.

Bibliography is available at Expert Consult.

Table 600-4 Clinical Features That May Distinguish ADEM from First Attack of MS

	ADEM	MS
Age	<10 yr	>10 yr
Stupor/coma	+	–
Encephalopathy	+	–
Fever/vomiting	+	–
Family history	No	20%
Sensory complaints	+	+
Optic neuritis	Bilateral	Unilateral
Manifestations	Polysymptomatic	Monosymptomatic
CSF	Pleocytosis (lymphocytosis)	Oligoclonal bands
Response to steroids	+	+
Follow-up	No new lesions	New lesions

Some features that may help distinguish an initial acute episode of demyelination from a first attack of MS in children. Final diagnosis of MS is based on follow-up evaluation and possibly MRI.
+, More likely to be present; –, less likely to be present; ADEM, acute disseminated encephalomyelitis; CSF, cerebrospinal fluid; MS, multiple sclerosis.

600.2 Neuromyelitis Optica

Jayne M. Ness

NMO (Devic disease) is a demyelinating disorder characterized by monophasic or polyphasic episodes of optic neuritis and/or transverse myelitis. It was once thought that NMO was a variant of MS; but identification of the NMO antibody against the aquaporin-4 water channel has broadened the spectrum of NMO to include brainstem syndromes and recurrent forms of optic neuritis and transverse myelitis (see Table 600-2). **NMO spectrum disorder** frequently involves symptomatic or silent MRI lesions demonstrating demyelination of the cerebral cortex and other regions of the brain.

EPIDEMIOLOGY

NMO has an age of onset of 31.2 ± 11 yr. In 1 study, in monophasic patients, the range of age of onset was 1-54 yr; in polyphasic patients, the range was 6-72 yr. NMO is more common in females than in males; 65% of monophasic and 80-85% of polyphasic NMO patients are female. It is also more common in Asians than in blacks or whites and appears to have a higher mortality rate in individuals of African descent than in others.

PATHOGENESIS

NMO is associated with IgG antibodies against the aquaporin-4 water channel, which is most abundant on astrocyte foot processes within periventricular regions, brainstem, optic nerves, and spinal cord. Antibody binding to aquaporin-4 activates the classical complement pathway with C5b-C9 components leading to leukocytes attraction and degranulation, causing astrocyte death. Chemokines from dying astrocytes and activated leukocytes attract macrophages, leading to death of oligodendrocytes and neurons with subsequent necrosis or even cavitation in affected tissues. Although most cases of NMO are idiopathic and only occasional familial cases have been reported, there have been reports of postinfectious NMO. HIV, syphilis, chlamydia, varicella, cytomegalovirus, and Epstein-Barr virus are associated with subsequent development of NMO. Aquaporin-4 antibody–positive NMO may follow or occur simultaneously with *N*-methyl-D-aspartate receptor antibody autoimmune encephalitis.

CLINICAL MANIFESTATIONS

NMO presents with optic neuritis or transverse myelitis or brainstem symptoms such as intractable vomiting or hiccups, diplopia, facial

Table 600-5 MRI Characteristics for Dissemination in Space That Increase the Likelihood of a Pediatric Multiple Sclerosis Diagnosis

BARKHOF*	MIKAELOFF (KIDMUS)†	CALLEN (MS VS ADEM)‡	CALLEN (DIAGNOSTIC MS)§	VERHEY (DIFFERENTIAL)‖	POLMAN (2010 REVISED MCDONALD CRITERIA)¶
3 of 4: ≥9 T2 lesions or 1 gadolinium enhancing ≥3 Periventricular ≥1 Infratentorial ≥1 Juxtacortical	1 of 2: Lesions perpendicular to long axis of the corpus callosum Sole presence of well-defined lesions	2 of 3: Absence of a diffuse bilateral lesion pattern Presence of black holes ≥2 Periventricular lesions	2 of 3: ≥5 Lesions on T2-weighted images 2 Periventricular lesions ≥1 Brainstem lesions	2 of 2: ≥1 Periventricular lesions ≥1 Hypointense lesions on T1 images	2 of 4: ≥1 Periventricular ≥1 Juxtacortical ≥1 Infratentorial ≥1 Spinal cord

*Barkhof F, Filippi M, Miller DH, et al: Comparison of MRI criteria at first presentation to predict conversion to clinically definite multiple sclerosis. *Brain* 120:2059–2069, 1997.
†Mikaeloff Y, Adamsbaum C, Husson HM, et al: MRI prognostic factors for relapse after acute CNS inflammatory demyelination in childhood. Brain 127:1942–1947, 2004.
‡Callen DJ, Shroff MM, Branson HM, et al: Role of MRI in the differentiation of ADEM from MS in children. *Neurology* 72:968–973, 2009.
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‖Verhay LH, Branson HM, Shroff MM, et al: MRI parameters for prediction of multiple sclerosis diagnosis in children with acute CNS demyelination: a prospective national cohort study. *Lancet Neurol* 10:1065–1073, 2011.
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ADEM, acute disseminated encephalomyelitis; MS, multiple sclerosis.
From Krupp LB, Tardieu M, Amato MP, et al: International Pediatric Multiple Sclerosis Study Group criteria for pediatric multiple sclerosis and immune-mediated central nervous system demyelinating disorders: revision to the 2007 definitions. Mult Scler *19(10):1261–1267, 2013, Appendix 3, p. 1267.*

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Table 600-6 Overview of Available and Emerging Therapies in Pediatric Multiple Sclerosis

MEDICATION	MEDICATION CLASS	MECHANISM IN MS	SIDE EFFECTS	STUDIES DESCRIBING DRUG EFFICACY IN PEDIATRIC MS
FIRST-LINE THERAPIES				
Interferon-α or β	Immunomodulator	Modulates T cells and cytokine production	Flu-like symptoms; transaminitis; leukopenia; tissue necrosis at injection site (rare)	Retrospective Prospective multicenter
Glatiramer acetate*	Immunomodulator	Modulates T cells and reduces antigen presentation	Flushing, lipodystrophy at injection sites	Prospective single center Prospective multicenter
SECOND-LINE THERAPIES				
Natalizumab*	Monoclonal antibody	Targets α_4-integrin; prevents T-cell migration into CNS and other tissues	Overall PML rate ~1 in 500 patients, but lower in subgroups; immune reconstitution syndrome after discontinuation; melanoma; infusion reaction; transaminitis (rare)	Retrospective Prospective multicenter
Cyclophosphamide	Chemotherapeutic	DNA alkylation; effects include cytotoxic immune cell depletion	Hemorrhagic cystitis; bladder cancer; late-onset malignancy; infection; infertility	Retrospective multicenter
Mitoxantrone*	Chemotherapeutic	Disrupts DNA synthesis; effects include cytotoxic immune cell depletion	Significant long-term safety risks, including cardiotoxicity (1 in 200 patients) and secondary leukemia (1 in 125 patients); opportunistic infections	Retrospective single center
Daclizumab	Monoclonal antibody	Targets/inactivates interleukin-2 receptor; inhibits activated T cells	Glucose intolerance; pulmonary edema; infusion reaction; gastrointestinal upset; skin reactions	Retrospective multicenter
Rituximab	Monoclonal antibody	Targets CD20, a marker of immature B cells; depletes B-cell populations	PML (rate undefined); infusion-related side effects	No efficacy assessments available in pediatric MS
Azathioprine	Chemotherapeutic	Disrupts purine metabolism; effects include cytotoxic immune cell depletion	Transaminitis; leukopenia; lymphoma	No efficacy assessments available in pediatric MS
Fingolimod*†	Immunomodulator	Sphingosine-1-phosphate agonist; causes T-cell sequestration in lymphoid compartments	Systemic viral infection; cardiac arrhythmia; macular edema; transaminitis	FDA approved for adult MS in September 2010; no reports of use in pediatric MS to date
Teriflunomide*†	Immunomodulator	Impairs immune cell proliferation via pyrimidine synthesis inhibition	Infections; headaches; diarrhea; transaminitis; alopecia; teratogenicity	FDA approved for adult MS in September 2012; no reports of use in pediatric MS to date
EMERGING THERAPIES				
Vitamin D†	Vitamin/hormone	Modulates immune cell expression	Hypercalcemia and kidney stones at a serum 25(OH) vitamin D level >100 ng/mL	Prospective trials in pediatric and adult MS are currently underway
Ocrelizumab	Monoclonal antibody	Targets CD20, a marker of immature B cells; depletes B-cell populations	Headache; infusion-related side effects; theoretical risk of PML (undefined)	Recently completed phase III trial in adult MS; no use in pediatric MS to date
Dimethyl fumarate†	Immunomodulator	Neuroprotectant; antioxidant	Flushing reaction; gastrointestinal upset; headache	FDA approved for adult MS in March 2013; no use in pediatric MS to date
Alemtuzumab	Monoclonal antibody	Anti-CD52 antibody target; depletes mature T cells	Opportunistic infection, autoimmune thyroiditis (20-30% risk), immune thrombocytopenia (1%)	Recently completed phase III trial in adult MS; no use in pediatric MS to date
Laquinimod†	Immunomodulator	Modulates T cell and cytokine production	Transaminitis	Recently completed phase III trial in adult MS; no use in pediatric MS to date

*FDA approved for the treatment of adult MS.
†Orally administered therapy.
CNS, central nervous system; MS, multiple sclerosis; PML, progressive multifocal leukoencephalopathy.

weakness or numbness or dysphagia. Optic neuritis or transverse myelitis may occur simultaneously or may be separated in time by weeks or even years. Some present with an encephalopathy mimicking ADEM. Others exhibit endocrinopathies such as the syndrome of inappropriate antidiuretic hormone secretion, diabetes insipidus, or disrupted puberty. The symptoms and signs of transverse myelitis depend on the spinal level and completeness of the inflammatory changes. NMO differs from MS in that recovery of visual and spinal cord function is generally not as complete after each episode; optic neuritis is more frequently bilateral in NMO than in MS.

LABORATORY FINDINGS

CSF in patients with NMO often has 50 or more white blood cells per microliter. Unlike MS, it is devoid of oligoclonal bands. Serum positivity for anti–aquaporin-4 antibodies (so-called NMO antibodies) has a sensitivity of 73% and a specificity of 91% for NMO. Neuroimaging studies should include the entire spine, optic nerves as well as the cortex that may reveal lesions in the brainstem or thalami or hazy ill-defined lesions in the hemispheres in contrast to the discrete, well-defined oval lesions in the periventricular white matter seen in MS.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

Clinical diagnosis of NMO currently requires optic neuritis and transverse myelitis plus at least 2 of 3 supporting criteria: (1) brain MRI not diagnostic of MS, (2) seropositivity for anti–aquaporin-4 antibody, or (3) spine MRI with longitudinally extensive transverse myelitis involving at least 3 spinal segments (see Table 600-2). NMO spectrum disorder may be diagnosed in relapsing forms of transverse myelitis or optic neuritis with aquaporin-4 seropositivity. The differential diagnosis includes MS; ADEM (see Chapter 600.3); rheumatologic etiologies producing transverse myelitis, and/or optic neuritis, including systemic lupus erythematosus, Behçet disease, and neurosarcoidosis (usually accompanied by other nonneurologic manifestations); idiopathic transverse myelitis, tropical spastic paraparesis, and viral encephalomyelitis (none of which have NMO antibodies in the serum or CSF); and metabolic and idiopathic causes of isolated optic neuritis or other acute monocular or binocular visual loss (see Chapter 631). Additional considerations depending on the location of the lesions include lymphoma, Langerhans cell histiocytosis, tuberculosis, and vitamin B_{12} or E deficiencies.

COMPLICATIONS

Similar to adults with NMO, pediatric NMO patients often are left with fixed neurologic deficits affecting visual acuity, visual fields, color vision, motor and sensory function, balance, and bowel/bladder function.

TREATMENT

Initial episodes and relapses may be treated acutely with methylprednisolone, 20-30 mg/kg/day (max: 1,000 mg/day) for 3-5 days, followed by a slow prednisone taper. Rituximab is effective in preventing relapses of NMO and NMO spectrum disorder. Preliminary evidence suggests that eculizumab also reduced recurrences and may improve disability in patients with severe NMO spectrum disorder.

PROGNOSIS

The prognosis is generally poor for patients with NMO. In 1 study, approximately 20% remained functionally blind (i.e., 20/200 vision or worse) in at least 1 eye and 31% had permanent monoplegia or paraplegia. Five-year survival of the patients with paraplegia is approximately 90%.

Bibliography is available at Expert Consult.

600.3 Acute Disseminated Encephalomyelitis

Jayne M. Ness

ADEM is an initial inflammatory, demyelinating event with multifocal neurologic deficits, typically accompanied by encephalopathy (see Table 600-2).

EPIDEMIOLOGY

ADEM can occur at any age but most series report a mean age between 5 and 8 yr with a slight male predominance. Reported incidence ranges from 0.07-0.4 per 100,000 per year in the pediatric population.

PATHOGENESIS

Molecular mimicry induced by infectious exposure or vaccine may trigger production of CNS autoantigens. Many patients experience a transient febrile illness in the month prior to ADEM onset. Preceding infections associated with ADEM include influenza, Epstein-Barr virus, cytomegalovirus, varicella, enterovirus, measles, mumps, rubella, herpes simplex, and *Mycoplasma pneumoniae*. Postvaccination ADEM has been reported following immunizations for rabies, smallpox, measles, mumps, rubella, Japanese encephalitis B, pertussis, diphtheria-polio-tetanus, and influenza.

CLINICAL MANIFESTATIONS

Initial symptoms of ADEM may include lethargy, fever, headache, vomiting, meningeal signs, and seizures, including status epilepticus. **Encephalopathy** is a hallmark of ADEM, ranging from ongoing confusion to persistent irritability to coma. Focal neurologic deficits can be difficult to ascertain in the obtunded or very young child but common neurologic signs in ADEM include visual loss, cranial neuropathies, ataxia, motor and sensory deficits, plus bladder/bowel dysfunction with concurrent spinal cord demyelination.

NEUROIMAGING

Head CT may be normal or show hypodense regions. Cranial MRI, the imaging study of choice, typically exhibits large, multifocal and sometimes confluent or large edematous mass-like tumefactive T2 lesions with variable enhancement within white and often gray matter of the cerebral hemispheres, cerebellum, and brainstem (Fig. 600-2). Deep gray-matter structures (thalami, basal ganglia) are often involved, although this may not be specific to ADEM. Spinal cord may have abnormal T2 signal or enhancement, with or without clinical signs of myelitis. MRI lesions of ADEM typically appear to be of similar age but their evolution may lag behind the clinical presentation. Serial MRI imaging 3-12 mo following ADEM shows improvement and often complete resolution of T2 abnormalities, although residual gliosis may remain.



Figure 600-2 Axial T2-weighted fluid-attenuated inversion recovery MRI of the brain in a child with acute disseminated encephalomyelitis. High signal (white) lesions in the T2-weighted image reflect areas of demyelination and edema in deep subcortical and periventricular white matter as well as the basal ganglia and thalamus on the left side.

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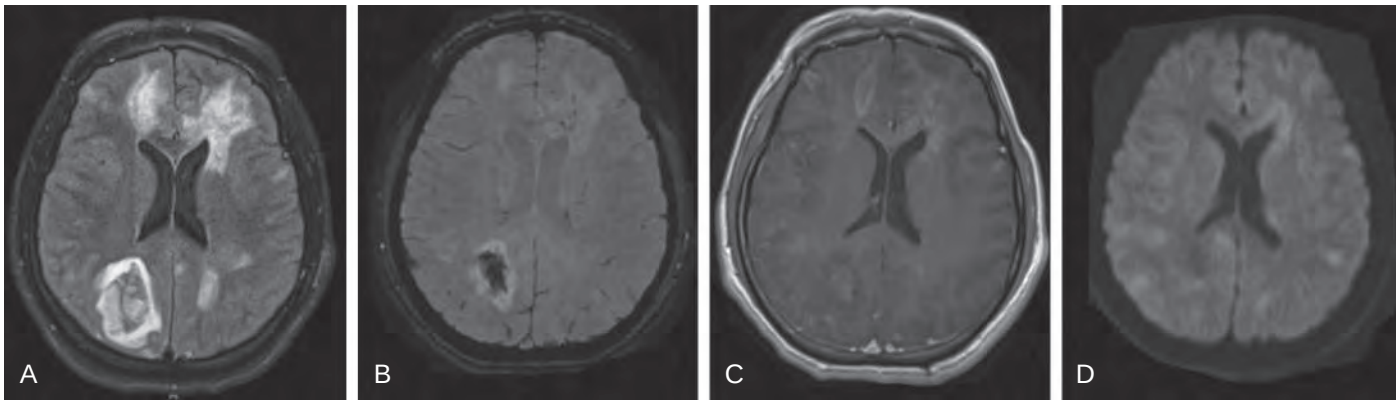


Figure 600-3 MRI findings in acute disseminated encephalomyelitis. Multiple scattered T2 hyperintensities are appreciated on fluid-attenuated inversion recovery images **(A)** with evidence of hemorrhage on susceptibility-weighted images **(B),** contrast enhancement on T1 postgadolinium images **(C),** and without diffusion restriction on diffusion-weighted imaging **(D).** *(From Virmani T, Agarwal A, Klawiter EC: Clinical reasoning: a young adult presents with focal weakness and hemorrhagic brain lesions.* Neurology *76:e105–e109, 2011, Fig. 2.)*

Severe involvement may progress to an **acute hemorrhagic leukoencephalopathy (Hurst disease)** with large lesions, edema, mass affect, and a polymorphonucleated cell pleocytosis (in contrast to lymphocytic pleocytosis in the CSF noted in typical ADEM) (Fig. 600-3).

LABORATORY FINDINGS

There is no biologic marker for ADEM and laboratory findings can vary widely. CSF studies often exhibit pleocytosis with lymphocytic or monocytic predominance. CSF protein can be elevated, especially on repeat studies. Up to 10% of patients with ADEM have oligoclonal bands in the CSF and/or elevated CSF immune globulin production. Patients with ADEM may occasionally demonstrate antibodies against myelin oligodendrocyte glycoprotein, or anti–*N*-methyl-D-aspartate receptor antibodies. Electroencephalograms often show generalized slowing, consistent with encephalopathy, although polyregional demyelination of ADEM can also cause focal slowing or epileptiform discharges.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis for ADEM is broad but can be narrowed by careful history, appropriate laboratory evaluations, and MRI (see Table 600-1). Empirical antibiotic and antiviral treatment should be considered while infectious evaluations are pending. Follow-up MRI examinations 3-12 mo after ADEM should show improvement; new or enlarging T2 lesions should prompt reevaluation for other etiologies such as MS, leukodystrophies, tumor, vasculitis, or mitochondrial, metabolic, or rheumatologic disorders (see Table 600-1 and Table 600-5).

TREATMENT

Although there are no randomized controlled trials to compare acute treatments for ADEM or other demyelinating disorders of childhood, high-dose intravenous steroids are commonly employed (typically methylprednisolone 20-30 mg/kg per day for 5 days with a maximum dose of 1,000 mg per day). An oral prednisone taper over 1 mo may prevent relapse. Other treatment options include intravenous immune globulin (usually 2 g/kg administered over 2-5 days) or plasmapheresis (typically 5-7 exchanges administered every other day). In severe cases of suspected ADEM, rituximab or cyclophosphamide have been used. There is no consensus about timing of these treatments for ADEM.

PROGNOSIS

Many children experience full recovery after ADEM but some are left with residual motor and/or cognitive deficits. ADEM is usually a monophasic illness but demyelinating symptoms can fluctuate for several months. Repeated bouts of demyelination more than 3 mo after ADEM later raise the question of MS vs repeated ADEM.

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Chapter 601

Pediatric Stroke

Adam Kirton and Gabrielle A. deVeber

Stroke is an important cause of acquired brain injury in newborns and children. The ischemic varieties of arterial ischemic stroke (AIS) and cerebral sinovenous thrombosis (CSVT) are more common than brain malignancy (incidence approximately 5 in 100,000 children per year). Perinatal stroke is even more common and is the leading cause of hemiparetic cerebral palsy. A similar number of children suffer from hemorrhagic stroke (HS) and other forms of cerebrovascular disease. Acute stroke is a neurologic emergency; however, delays in recognition are common and delayed treatment worsens outcomes. In contrast to stroke in adults, there are a diverse group of disorders producing stroke in neonates and children.

601.1 Arterial Ischemic Stroke

Adam Kirton and Gabrielle A. deVeber

Arterial blood reaches the brain via the anterior (internal carotid) and posterior (vertebrobasilar) circulations, converging at the circle of Willis. Strokes most often involve the middle cerebral artery territory but can occur in any cerebral artery of any size. AIS is the focal brain infarction that results from occlusion of these arteries and is a leading cause of acquired brain injury in children with the perinatal period carrying the highest risk.

The diagnosis of stroke in children is frequently delayed. This is a consequence of subtle and nonspecific clinical presentations, poor awareness by primary care pediatric physicians, a complicated differential diagnosis (see Chapter 601.4), and a high frequency (>50%) of negative initial CT scan. **The acute onset of a focal neurologic deficit in a child is stroke until proven otherwise.** The most common focal presentation is hemiparesis, but acute visual, speech, sensory, or balance deficits also occur. Children with these presentations require urgent neuroimaging and consultation with a child neurologist, as emergency interventions may be indicated. AIS is a clinical and radiographic diagnosis. Although CT imaging can demonstrate mature AIS and exclude hemorrhage, MRI is required to identify early and small infarcts. **Diffusion-weighted MRI** demonstrates AIS within minutes of onset and up to 7 days postonset; MR angiography can confirm vascular occlusion and suggest possible arteriopathy (Fig. 601-1). Diffusion-weighted MRI can also demonstrate wallerian degeneration

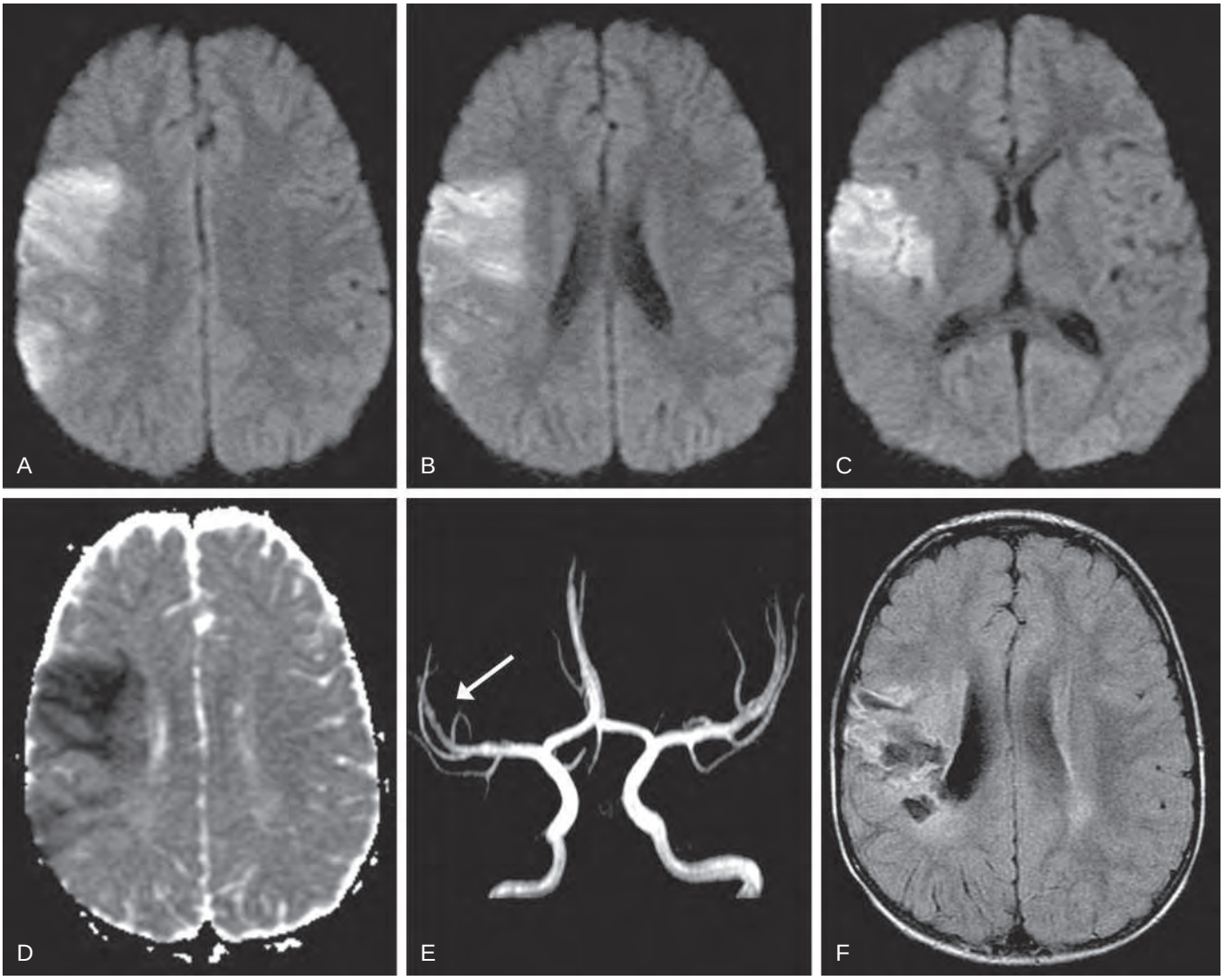


Figure 601-1 Arterial ischemic stroke. A healthy 3 yr old boy had sudden onset of left-sided weakness. Examination also demonstrated left-sided hemisensory loss and neglect. **A** to **C,** Diffusion-weighted MRI shows focal increased signal in the right temporal–parietal region in the territory of the middle cerebral artery (MCA). **D,** Apparent diffusion coefficient map confirms restricted diffusion consistent with infarction (ischemic stroke). **E,** MR angiogram shows decreased flow in the corresponding branch of the MCA. **F,** Follow-up MRI at 3 mo shows atrophy and gliosis in the same region.

in the descending corticospinal tract, which correlates with chronic hemiparesis.

Many possible risk factors for AIS are recognized (Table 601-1), although the specific pathophysiologic mechanisms are often poorly understood. Three main categories of etiology should be considered: **arteriopathy, cardiac,** and **hematologic;** full investigation, however, often reveals multiple risk factors per individual.

Arteriopathy refers to disorders of the cerebral arteries and is a leading cause of childhood AIS, present in more than 50% of children. A common syndrome affecting healthy school-age children features unilateral irregular stenosis of the proximal middle cerebral artery and neighboring arteries presenting with basal ganglia infarction. The description of this entity has been published under multiple names—**transient cerebral arteriopathy**, postvaricella angiopathy, nonprogressive childhood primary angiitis of the central nervous system, and focal cerebral arteriopathy—reflecting uncertainty regarding the pathogenesis.

This entity may represent focal inflammation or intracranial dissection or early moyamoya disease, although it is nearly always self-limited. Diffuse, bilateral, progressive **vasculitis** is rare and can represent progressive childhood primary angiitis of the central nervous system or be associated with systemic vasculitides (Table 601-2). Cranial infections (e.g., bacterial meningitis) also produce arteritis and thrombophlebitis of surface vessels. A**rterial dissection** can be spontaneous or posttraumatic and can affect extra- or intracranial arteries. **Moyamoya syndrome** may be idiopathic or associated with other conditions (neurofibromatosis type 1, trisomy 21, Alagille syndrome, sickle cell anemia, chromosomal microdeletions/microduplications, postirradiation) and demonstrates progressive occlusion of the distal internal carotid arteries. Congenital malformations of the craniocervical arteries, including PHACES (posterior fossa abnormalities, hemangioma, and arterial, cardiac, eye, and sternal abnormalities) syndrome, or fibromuscular dysplasia may predispose to AIS. Vasospasm as occurs in migraine, subarachnoid hemorrhage or reversible cerebral vasoconstriction syndrome (sometimes called Call-Fleming syndrome) can cause AIS.

Cardioembolic stroke makes up approximately 25% of childhood AIS with maximal embolic risk concurrent with catheterization, surgical repair, or ventricular assistive device use. AIS complicates approximately 0.5% of pediatric cardiac surgeries and reoperation increases the risk. Although **complex congenital heart diseases** are most frequently associated with AIS, acquired conditions, including arrhythmia, cardiomyopathy, and infective endocarditis, also should be considered. A patent foramen ovale provides the possibility of paradoxical venous thromboembolism but is not likely an independent risk factor. All children with suspected AIS require thorough cardiovascular examination, electrocardiogram, and echocardiogram.

Table 601-1 Risk Factors for Arterial Ischemic Stroke in Children

MAJOR CATEGORY	EXAMPLES
Arteriopathy	Transient cerebral arteriopathy (TCA) (synonyms: childhood primary angiitis of the central nervous system [cPACNS]; focal cerebral arteriopathy [FCA]) Postvaricella and other viruses angiopathy (PVA) Systemic/secondary vasculitis (e.g., Takayasu arteritis) Moyamoya disease/syndrome Arterial infection (e.g., bacterial meningitis, tuberculosis) Fibromuscular dysplasia Traumatic or spontaneous carotid or vertebral artery dissection Vasospasm (e.g., Call-Fleming syndrome) Migraine (migrainous infarction?) Congenital arterial hypoplasia (e.g., PHACES syndrome)
Cardiac	Complex congenital heart diseases (cyanotic ≫ acyanotic) Cardiac catheterization/procedure (e.g., balloon atrial septostomy) Ventricular assistive device use Cardiac surgery Arrhythmia Valvular heart disease Endocarditis Cardiomyopathy, severe ventricular dysfunction Intracardiac lesions (e.g., atrial myxoma) Septal defects (atrial septal defect, ventricular septal defect, patent foramen ovale [possible paradoxical emboli])
Hematologic	Sickle cell anemia Iron-deficiency anemia Inherited prothrombotic (e.g., factor V Leiden, prothrombin gene mutation 20210A) Acquired prothrombotic (e.g., protein C/S deficiency, antithrombin III deficiency, lipoprotein a, antiphospholipid antibodies, oral contraceptives, pregnancy)
Other including metabolic/genetic etiologies	Acute systemic illness (e.g., dehydration, sepsis, diabetic ketoacidosis) Chronic systemic illness (e.g., systemic lupus erythematosus, leukemia) Illicit drugs and toxins (e.g., cocaine) Extracorporeal membrane oxygenation (ECMO) Hereditary dyslipoproteinemia Familial hypoalphalipoproteinemia Familial hypercholesterolemia Type IV, type III hyperlipoproteinemia Tangier disease Progeria Fabry disease (α-galactosidase A deficiency) Subacute necrotizing encephalomyelopathy (Leigh disease) Sulfite oxidase deficiency 11β-Ketoreductase deficiency 17α-Hydroxylase deficiency Purine nucleoside phosphorylase deficiency Ornithine transcarbamylase deficiency Neurofibromatosis type 1 HERNS Heritable disorders of connective tissue Ehlers-Danlos syndrome (type IV) Marfan syndrome Pseudoxanthoma elasticum Homocystinuria (cystathionine β-synthase deficiency, or 5,20-methylenetetrahydrofolate reductase) Menkes syndrome Organic acidemias Methylmalonic academia Propionic academia Isovaleric academia Glutaric aciduria type II Mitochondrial encephalomyopathies MELAS MERRF MERRF/MELAS overlap syndrome Kearns-Sayre syndrome See also: stroke mimics (see Chapter 601.4)

HERNS, hereditary endotheliopathy with retinopathy, nephropathy, and stroke; MELAS, mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes; MERRF, myoclonic epilepsy with ragged red fibers; PHACES, posterior fossa abnormalities, hemangioma, and arterial, cardiac, eye, and sternal abnormalities.

Modified from Roach ES, Golomb MR, Adams R, et al: Management of stroke in infants and children. Stroke *39:2644–2691, 2008, Table 2, p. 6.*

Table 601-2 Classification of Cerebral Vasculitis

Infectious vasculitis
Bacterial, fungal, parasitic
Spirochetal (syphilis, Lyme disease, leptospirosis)
Viral, rickettsial, mycobacterial, free-living amebae, cysticercosis, other helminths
Necrotizing vasculitides
Classic polyarteritis nodosa
Wegener granulomatosis
Allergic angiitis and granulomatosis (Churg-Strauss syndrome)
Necrotizing systemic vasculitis overlap syndrome
Lymphomatoid granulomatosis
Vasculitis associated with collagen vascular disease
Systemic lupus erythematosus
Rheumatoid arthritis
Scleroderma
Sjögren syndrome
Vasculitis associated with other systemic diseases
Behçet disease
Ulcerative colitis
Sarcoidosis
Relapsing polychondritis
Kohlmeier-Degos disease
Takayasu arteritis
Hypersensitivity vasculitides
Henoch-Schönlein purpura
Drug-induced vasculitides
Chemical vasculitides
Essential mixed cryoglobulinemia
Miscellaneous
Vasculitis associated with neoplasia
Vasculitis associated with radiation
Cogan syndrome
Dermatomyositis-polymyositis
X-linked lymphoproliferative syndrome
Kawasaki disease

Primary central nervous system vasculitis

From Roach ES, Golomb MR, Adams R, et al: Management of stroke in infants and children, Stroke *39:2644–2691, 2008, Table 5, p. 8.*

Prothrombotic coagulation disorders and infection at index stroke increase stroke recurrence risk.

Hematologic disorders associated with AIS include **sickle cell anemia,** in which stroke risk is increased 400-fold, although effective screening (transcranial Doppler) and treatments (transfusions) have reduced the incidence. Iron-deficiency anemia also increases the risk and is easily treatable. Coagulation disorders are associated with childhood AIS. They include hereditary (e.g., factor V Leiden) and acquired (e.g., antiphospholipid antibodies, lipoprotein-a elevation) **prothrombotic states** and **prothrombotic medications,** including oral contraceptives and asparaginase chemotherapy. Additional AIS risk factors include migraine, acute childhood illnesses, chronic systemic illnesses, illicit drugs and toxins, and rare inborn errors of metabolism.

Treatment of childhood AIS is multifaceted and multiple consensus-based guidelines are available. Given the inadequate safety data, emergency thrombolysis is not recommended for children, but safety studies are underway. Early initiation of **antithrombotic strategies** is paramount to prevent early reinfarction. Depending on the suspected cause, this includes anticoagulation with heparins or antiplatelet strategies, usually aspirin. Hyperacute **neuroprotective strategies** are essential to initiate with suspected stroke as they prevent progressive ischemic brain injury. These include control of blood glucose, temperature and seizures and maintenance of cerebral perfusion pressure. Early malignant cerebral edema is life-threatening, more common in children and predictable, and emergency surgical decompression can be life-saving. Disease-specific treatments include transfusion therapy in sickle cell disease, immunosuppression in vasculitis, and revascularization surgery in moyamoya. Long-term treatment goals include **secondary stroke prevention**, including antiplatelet therapy in arteriopathy and anticoagulation in cardiogenic causes. Multimodal, family-centered **rehabilitation** programs are required for most survivors, targeting motor deficits, language and intellectual impairments, behavioral and social disabilities, and epilepsy. Long-term attention to arterial health lifestyle factors may also be important. Outcomes after childhood stroke include recurrent stroke ranging from 10-50% depending on cause and preventative treatment, death in 6-10%, neurologic deficits in 60-70%, and seizure disorders in up to 30%.

PERINATAL ARTERIAL ISCHEMIC STROKE

Perinatal stroke is very common, differs from childhood stroke, and has 2 distinct clinical presentations. Acute symptomatic neonatal AIS presents with focal seizures at 24-28 hr of life (Fig. 601-2). MRI diffusion

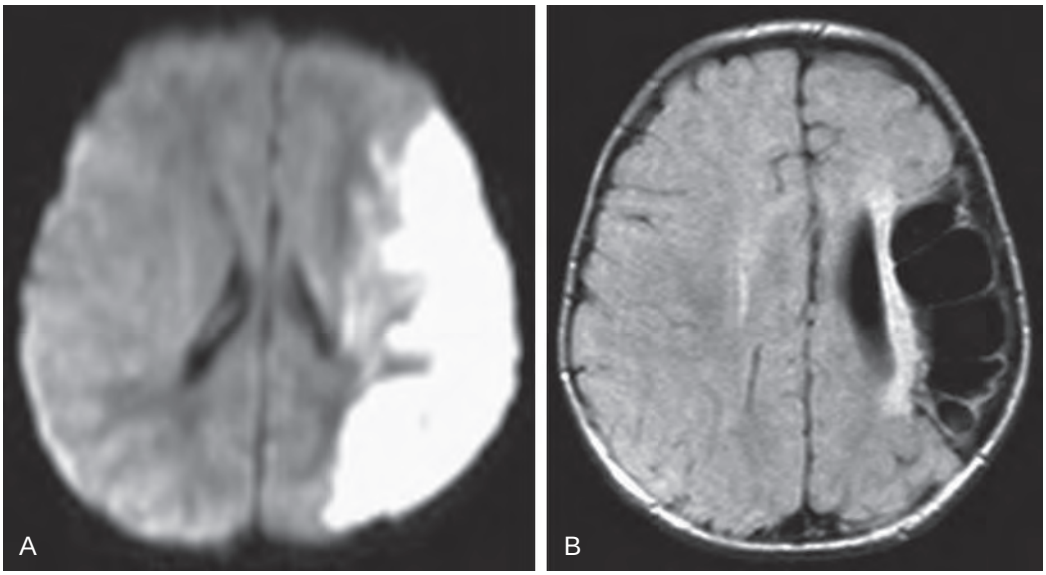


Figure 601-2 Perinatal arterial ischemic stroke. A term newborn developed focal right-sided seizures at 16 hr of life. **A,** Diffusion-weighted MRI on day 2 diagnoses neonatal arterial ischemic stroke by demonstrating restricted diffusion in the left middle cerebral artery territory. **B,** Repeat MRI at 12 mo shows cystic encephalomalacia and scarring in the same territory, a similar appearance to children diagnosed with presumed perinatal arterial ischemic stroke later in infancy.

abnormalities in an arterial territory confirm recent infarction. Alternatively, infants are asymptomatic at birth and present in later infancy with signs of early hand preference and congenital hemiparesis. Hand dominance within the 1st yr of life is abnormal and may be the result of perinatal stroke. Imaging reveals focal encephalomalacia in an arterial territory, typically large middle cerebral artery lesions.

In acute neonatal AIS, seizure control is important, but antithrombotic agents are rarely required (exception: cardiac embolism). Pathophysiology is complex and poorly understood. Most are idiopathic, although established causes include congenital heart disease, thrombotic placentopathy, and other prothrombotic disorders and meningitis. Many other maternal, prenatal, perinatal, obstetrical, and neonatal factors have been investigated with several strong associations found (e.g., infertility, primiparity, multiple gestation). Outcomes are poor, with most children having lifelong disability. Perinatal stroke accounts for most cases of hemiparetic cerebral palsy (congenital hemiplegia, see Chapter 598.1). Additional morbidity, seen in approximately 25%, includes disorders of language, learning, cognition, and behavior and longer-term epilepsy. Stroke recurrence rates for both the child and subsequent pregnancies are extremely low.

Bibliography is available at Expert Consult.

601.2 Cerebral Sinovenous Thrombosis

Adam Kirton and Gabrielle A. deVeber

Cerebral venous drainage occurs via the cerebral sinovenous system. This includes superficial (cortical veins, superior sagittal sinus) and deep (internal cerebral veins, straight sinus) systems that converge at the torcula to exit via the paired transverse and sigmoid sinuses and jugular veins. In CSVT, thrombotic occlusion of these venous structures can create increased intracranial pressure, cerebral edema, and, in 50% of cases, venous infarction or hemorrhage (stroke). CSVT may be more common in children than in adults, and risk is greatest risk in the neonatal period.

Clinical presentations are typically gradual, variable, and nonspecific compared to AIS. Neonates often present with encephalopathy and seizures. Children may present with symptoms mimicking idiopathic intracranial hypertension, including progressive headache, papilledema, diplopia secondary to 6th nerve palsy, or with acute focal deficits. Seizures, lethargy, and confusion are common. Diagnosis requires a high clinical suspicion and purposeful imaging of the cerebral venous system. Nonenhanced CT is very insensitive for CSVT, and contrast **CT venography** or MR venography is necessary to demonstrate filling defects in the cerebral venous system (Fig. 601-3). MRI offers superior parenchymal imaging compared to CT.

Table 601-3 lists the risk factors for CSVT. **Prothrombotic states** associated with childhood CSVT include inherited (e.g., prothrombin gene 20210A mutation) and acquired (e.g., antiphospholipid antibodies) conditions, prothrombotic medications (asparaginase, oral contraceptives) and common childhood illnesses including otitis media, iron-deficiency anemia, and **dehydration. Systemic diseases** associated with increased CSVT risk include leukemia, inflammatory bowel disease, and nephrotic syndrome.

Head and neck disorders can directly involve cerebral veins and sinuses causing CSVT. Common **infections,** including meningitis, otitis media, and mastoiditis, can cause **septic thrombophlebitis** of venous channels. CSVT can complicate head **trauma** especially adjacent to skull fractures. Neurosurgical procedures in proximity to cerebral venous structures may lead to injury and CSVT. Finally, obstruction of the jugular veins and proximal stasis may result in CSVT. In neonates, the unfused status of cranial sutures enables mechanical distortion of underlying venous sinuses during delivery, or postnatally occipital bone compression of the posterior sagittal sinus during supine lying predisposing to CSVT.

Anticoagulation therapy plays an important role in childhood CSVT treatment. Substantial indirect evidence has led to consensus to recommend anticoagulation with unfractionated or low-molecular-weight heparins in most children. Hemorrhagic transformation of venous infarcts is not an absolute contraindication. Treatment is usually planned for 6 mo, although if reimaging at 3 mo confirms recanalization, treatment is usually discontinued. However anticoagulation of neonates is more controversial and guidelines differ. Evidence suggests that 30% of untreated neonates and children will extend their thrombosis in the 1st wk postdiagnosis and additional venous infarction can result. Therefore, if anticoagulation is withheld, early (e.g., 5-7

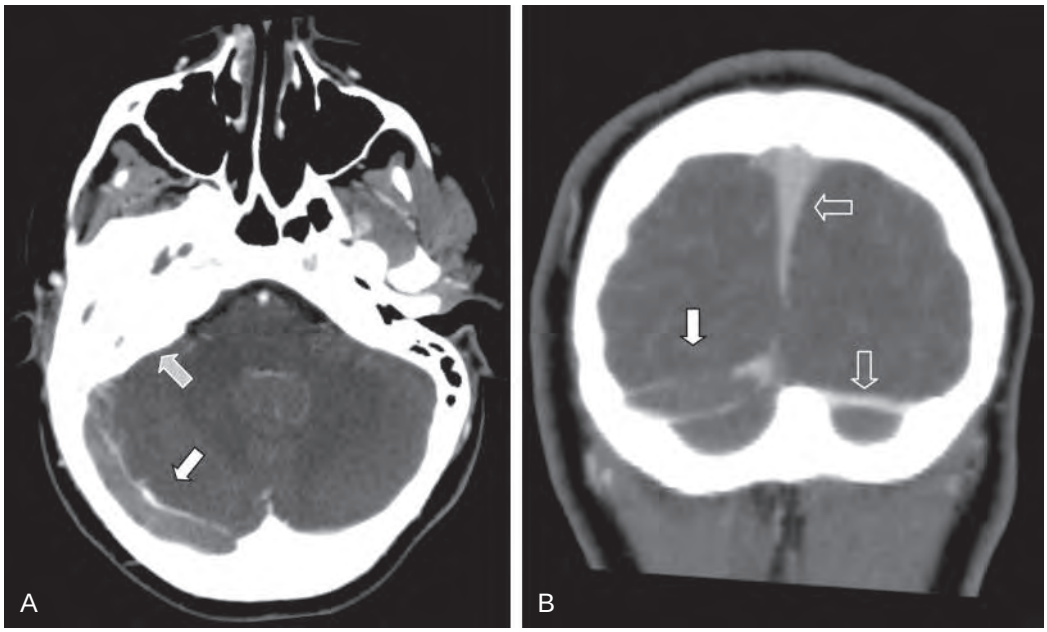


Figure 601-3 Cerebral sinovenous thrombosis. A 9 yr old girl presented with fever and progressive right-sided headache. She complained of double vision and had papilledema on examination. Axial **(A)** and coronal **(B)** CT venography demonstrates a large thrombus in the right transverse sinus that fails to opacify with contrast *(full arrows).* Note normal filling in superior sagittal and in smaller left transverse sinuses *(empty arrows, right)* and opacification of the mastoid air cells *(hatched arrow, left).* Cause was otitis media/mastoiditis with septic thrombophlebitis of transverse sinus.

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Table 601-3 Common Risk Factors for Cerebral Sinovenous Thrombosis in Children

MAJOR CATEGORIES	EXAMPLES
Blood coagulation	Prothrombotic conditions Factor V Leiden, prothrombin gene mutation 20210A, protein C deficiency, protein S deficiency, antithrombin III deficiency, lipoprotein a, antiphospholipid antibodies (lupus anticoagulant, anticardiolipin antibodies), pregnancy/puerperium Dehydration (e.g., gastroenteritis, neonatal failure to thrive) Iron-deficiency anemia Drugs and toxins (e.g., L-asparaginase, oral contraceptives) Acute systemic illness (e.g., sepsis, disseminated intravascular coagulation) Chronic systemic illness (e.g., inflammatory bowel disease, systemic lupus erythematosus, leukemia) Nephrotic syndrome Inborn errors of metabolism (e.g., homocystinuria)
Blood vessel	Infection/thrombophlebitis Otitis media, mastoiditis, bacterial meningitis, sinusitis, dental abscess, pharyngitis Lemierre syndrome Sepsis Trauma: skull fractures, closed hear trauma Compression: birth, occipital bone compression in neonates in supine lying Iatrogenic: neurosurgery, jugular lines, extracorporeal membrane oxygenation Venous malformations (e.g., dural arteriovenous fistulas)

days) repeat venous imaging is paramount. Protocols supporting initial anticoagulation recommend shorter treatment durations (i.e., 6 wk to 3 mo) in neonates. Children with persistent risk factors may require prophylactic long-term anticoagulation. At initial diagnosis, supportive interventions include management of infection, detection and treatment of seizures, and neuroprotective measures (normothermia, normotension, normovolemia, normoglycemia). **Optic neuropathy** secondary to increased intracranial pressure is an important and easily missed complication of CSVT. Regular funduscopic examination by an ophthalmologist and measures to reduce intracranial pressure (e.g., acetazolamide, serial lumbar puncture) may be required to avoid visual loss. Most neurologic morbidity is suffered by those incurring venous infarction and children with bilateral venous infarction can be devastated. Consistent with other forms of childhood stroke, a comprehensive neurorehabilitation program is required.

Bibliography is available at Expert Consult.

601.3 Hemorrhagic Stroke

Adam Kirton and Gabrielle A. deVeber

HS includes nontraumatic intracranial hemorrhage and is classified by the intracranial compartment containing the hemorrhage. Intraparenchymal bleeds may occur in any location, whereas intraventricular hemorrhage may be isolated or an extension of intraparenchymal hemorrhage. Bleeding outside the brain may occur in the subarachnoid, subdural, or epidural spaces.

Clinical presentations vary according to location, cause, and rate of bleeding. Acute hemorrhages may feature instantaneous or **thunderclap headache,** loss of consciousness, and nuchal rigidity in addition to focal neurologic deficits and seizures. HS can be rapidly fatal. In bleeds associated with vascular malformations, pulsatile tinnitus, cranial bruit, macrocephaly, and high-output heart failure may be present. Diagnosis relies on imaging and CT is highly sensitive to acute HS. However, lumbar puncture may be required to exclude subarachnoid hemorrhage. MRI is highly sensitive to even small amounts of both acute and chronic hemorrhage and offers improved diagnostic accuracy (Fig. 601-4). Angiography by CT, MR, or conventional catheter means is often required to exclude underlying vascular abnormalities (e.g., vascular malformations, aneurysms).

Abusive head trauma with intracranial bleeding in children may present as primary subdural or parenchymal hemorrhage with no apparent history of trauma. Subtle scalp, suborbital, or ear bruising; retinal hemorrhages in multiple layers; and chronic failure to thrive should always be sought, and in infants with subdural bleeds, x-rays performed to rule out fractures. Epidural hematoma is nearly always caused by trauma, including middle meningeal artery injury typically associated with skull fracture. Subdural hematoma can occur spontaneously in children with brain atrophy because of stretching of bridging veins.

Causes of and risk factors for HS (Table 601-4) include vascular malformations and systemic disorders. **Arteriovenous malformations**

Table 601-4 Potential Risk Factors for Hemorrhagic Stroke in Children

MAJOR CATEGORIES	EXAMPLES
Vascular disorder	Arteriovenous malformations Cavernous malformations ("cavernomas") Venous angiomas and other venous anomalies Hereditary hemorrhagic telangiectasia Intracranial aneurysm Choroid plexus angiomas (pure intraventricular hemorrhage) Moyamoya disease/syndrome Inflammatory vasculitis (see Chapter 601.1) Neoplastic lesions with unstable vasculature Drugs/toxins (cocaine, amphetamine) Cerebral sinovenous thrombosis
Blood disorder	Idiopathic thrombocytopenic purpura Hemolytic uremic syndrome Hepatic disease/failure coagulopathy Vitamin K deficiency (hemorrhagic disease of the newborn) Disseminated intravascular coagulopathy
Trauma	Middle meningeal artery injury (epidural hematoma) Bridging vein injury (subdural hematoma) Subarachnoid hemorrhage Hemorrhagic contusions (coup and contrecoup) Nonaccidental trauma (subdural hematomas of different ages) Iatrogenic (neurosurgical procedures, angiography) Rupture of arachnoid cyst

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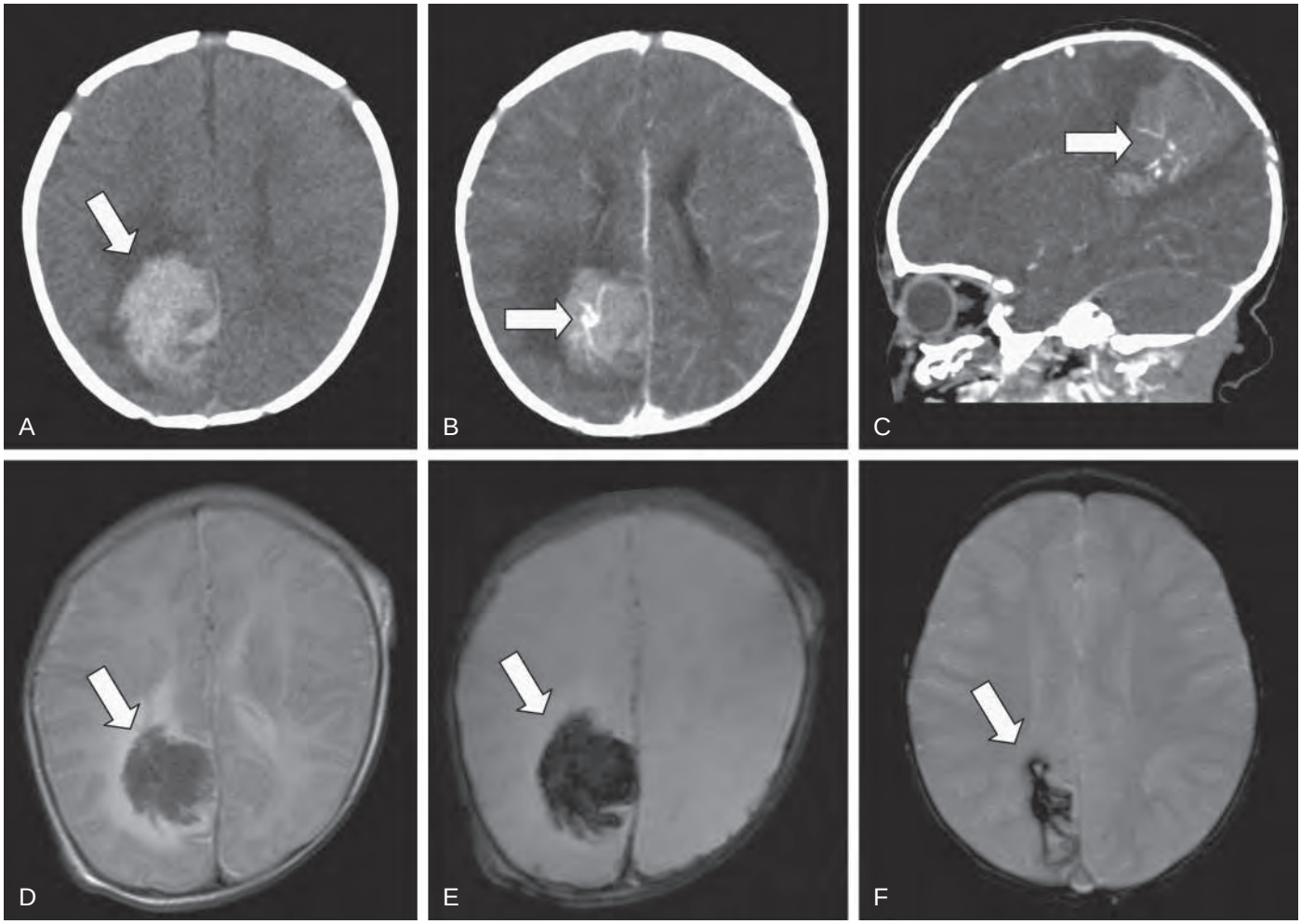


Figure 601-4 Hemorrhagic stroke. A healthy 1 mo old presented with sudden-onset irritability followed by focal left body seizures. Plain CT head demonstrates a large hyperdense lesion in the right parietal region with surrounding edema consistent with acute hemorrhage **(A).** Axial **(B)** and sagittal **(C)** contrast CT scans suggest an abnormal cluster of vessels in the center of the hemorrhage consistent with an AVM. T2-weighted MRI differentiates the acute hemorrhage from surrounding edema **(D).** Gradient echo MRI, both acutely **(E)** and at 3 mo **(F),** demonstrates the presence of blood product.

are the most common cause of childhood subarachnoid and intraparenchymal HS and may occur anywhere. Neonates with vein of Galen malformations may present with heart failure, progressive macrocephaly, or, rarely, hemorrhage. In older children with arteriovenous malformations, the risk of bleeding is approximately 2-4% per year throughout life. Other vascular malformations leading to HS include cavernous angiomas **("cavernomas"),** dural arteriovenous fistulas, and vein of Galen malformations. Cerebral aneurysms are an uncommon cause of subarachnoid hemorrhage in children and may suggest an underlying disorder (e.g., polycystic kidney disease, infective endocarditis). A common cause for HS is bleeding from a preexisting brain tumor. Arterial diseases that usually cause ischemic stroke, including fibromuscular dysplasia, vasculitis, and moyamoya, can also predispose to HS. Additional causes of parenchymal HS include hypertensive hemorrhage and hematologic disorders such as thrombocytopenic purpura, hemophilia, acquired coagulopathies (e.g., disseminated intravascular coagulopathy, liver failure), anticoagulant therapy (e.g., warfarin), or illicit drug use. Ischemic infarcts may undergo hemorrhagic transformation, particularly in CSVT, and may be difficult to differentiate from primary HS.

Management of acute childhood HS may require emergent neurosurgical intervention for large or rapidly expanding hemorrhage. The same principles of neuroprotection for vulnerable brain suggested in the ischemic stroke sections also apply to HS. Reversal of anticoagulant therapy (with, for example, vitamin K, fresh-frozen plasma) may be required, but the role of other medical interventions, such as factor VII, are unstudied in children. Recurrence risk for those with structural lesions is significant and serial imaging may be required. Definitive repair or removal of the vascular malformation may require a combined approach with interventional endovascular methods or neurosurgery. Outcomes from childhood HS are not well studied but likely depend on lesion size, location, and etiology. Compared with ischemic stroke, HS mortality is higher while long-term deficits are less common.

Neonatal HSs have unique features. Cranial ultrasound can detect many neonatal parenchymal bleeds, especially In the preterm infant where bleeds are located centrally within the cranium and include germinal matrix bleeding and intraventricular hemorrhage (see Chapter 99.3). Germinal matrix injury or bleeding may also occur in utero, resulting in periventricular venous infarction that becomes symptomatic in later infancy as congenital hemiparesis. Subarachnoid and subdural blood may be imaged in up to 25% of normal term newborns. Term HS is poorly studied and includes the etiologies listed above, although HS may be idiopathic in more than 50% of cases. Term intraventricular bleeding is often secondary to deep CSVT with specific management implications.

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601.4 Differential Diagnosis of Stroke-Like Events

Adam Kirton and Gabrielle A. deVeber

The diagnosis of stroke in childhood requires a high index of suspicion balanced with awareness of the differential diagnosis for stroke-like events (Table 601-5). Acute onset of a focal neurologic deficit should be considered stroke until proven otherwise and assessed with neuroimaging. However, pediatric stroke must be differentiated from other stroke-like disorders that may require their own urgent specific treatment.

MIGRAINE

Careful history and examination can often suggest migraine as the cause of acute focal deficits. Migraine auras should last between 5 and 60 min and resolve completely. Neurologic deficits associated with migraine typically evolve slowly compared with stroke, with sensory disturbance or weakness "marching" across body areas over minutes. Although evolution into a migrainous headache is expected, headache may also accompany acute infarction. Furthermore, a group of uncommon migraine subtypes can occur without headache and can more closely mimic stroke in children. These include familial hemiplegic migraine, basilar migraine, and migraine aura without headache. Migraine can also (rarely) cause a stroke, referred to as migrainous infarction.

SEIZURE

Prolonged focal seizure activity is frequently followed by a period of focal neurologic deficit ("Todd's paresis") which typically resolves within an hour. Very rarely, focal seizures can manifest with only "negative" symptoms producing acute onset, focal neurologic deficits. A history of clonic jerks or tonic posturing at onset, a known past history of seizures, and electroencephalogram findings may be helpful. Imaging is required in all new cases of seizure with persisting Todd's paresis because stroke in children is often associated with seizures at onset.

INFECTION

Life-threatening and treatable brain infections, including bacterial meningitis and herpes encephalitis, can be mistaken for stroke. However, symptom onset in primary central nervous system infection is typically more gradual and less focal with fever as a consistent feature. Children with bacterial meningitis are at risk for both venous and arterial stroke.

DEMYELINATION

Acute disseminated encephalomyelitis, clinically isolated syndrome, multiple sclerosis, and other demyelinating conditions can present

Table 601-5 Differential Diagnosis of Stroke-Like Episodes in Children

DISORDER	CLINICAL DISTINCTION FROM STROKE	IMAGING DISTINCTION FROM STROKE
Migraine	Evolving or "marching" symptoms, short duration, complete resolution, headache, personal or family history of migraine	Typically normal Migrainous infarction is rare
Seizure	Positive symptoms, Todd paralysis is postseizure and limited	Normal or may identify source of seizures (e.g., malformation, old injury, etc.)
Infection	Fever, encephalopathy, gradual onset, meningismus	Normal or signs of encephalitis/cerebritis, which are typically diffuse and bilateral. Arterial ischemic stroke and cerebral sinovenous thrombosis can occur in bacterial meningitis
Demyelination	Gradual onset, multifocal symptoms, encephalopathy Accompanying optic neuritis or transverse myelitis	Multifocal lesions, characteristic appearance (e.g., patchy in acute disseminated encephalomyelitis, ovoid in multiple sclerosis), typical locations (e.g., pericallosal in multiple sclerosis), less likely to show restricted diffusion
Hypoglycemia	Risk factor (e.g., insulin therapy), related to meals, additional systemic symptoms	Bilateral, symmetrical May see restricted diffusion Posterior dominant pattern
Watershed infarction caused by global hypoxic–ischemic encephalopathy	Risk factor (e.g., hypotension, sepsis, heart disease), bilateral deficits	Bilateral, symmetric restricted diffusion in border zones between major arteries (watershed zones)
Hypertensive encephalopathy (posterior reversible leukoencephalopathy)	Documented hypertension, bilateral visual symptoms, encephalopathy	Posterior dominant, bilateral, patchy lesions involving gray and white matter, usually no restricted diffusion
Inborn errors of metabolism	Preexisting delays/regression, multisystem disease, abnormal biochemical profiles	May have restricted diffusion lesions but bilateral, symmetrical, not within vascular territories. MR spectroscopy changes (e.g., high lactate in mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes)
Vestibulopathy	Symptoms limited to vertigo, imbalance (i.e., no weakness). Gradual onset	Normal
Acute cerebellar ataxia	Sudden-onset bilaterally symmetric ataxia; postviral	Normal
Channelopathy	Syndromic cluster of symptoms not localizing to single lesion. Gradual onset, progressive evolution	Normal
Alternating hemiplegia	History contralateral events Choreoathetosis/dystonia	Normal

with acute focal neurologic deficits. Symptom onset and initial progression is more gradual (typically hours or days) compared with stroke onset (minutes). Multifocal deficits, or concurrent encephalopathy in the case of acute disseminated encephalomyelitis, would decrease the probability of stroke.

HYPOGLYCEMIA

Acute lowering of blood glucose levels can produce focal deficits mimicking stroke. New-onset hypoglycemia in otherwise healthy children is rare, but predisposing conditions include insulin-dependent diabetes, adrenal insufficiency, steroid withdrawal, and ketogenic diet.

GLOBAL HYPOXIC–ISCHEMIC ENCEPHALOPATHY

Generalized decreases in cerebral perfusion can produce focal areas of watershed brain infarction which can be asymmetric and mimic stroke. Watershed ischemic injury should be accompanied by recognized hypotension or conditions predisposing to low cerebral perfusion such as sepsis, dehydration, or cardiac dysfunction. Clinical presentations would involve more generalized and bilateral cerebral dysfunction compared to stroke and the anatomic location of the infarct is in typical bilateral watershed zones rather than a single arterial territory.

HYPERTENSIVE ENCEPHALOPATHY

The posterior reversible leukoencephalopathy syndrome is seen in children with hypertension, often in the context of an acute rise in blood pressure. Posterior regions are selectively involved, possibly resulting in symptoms of bilateral cortical visual dysfunction in addition to encephalopathy and seizures.

INBORN ERRORS OF METABOLISM

Mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes (MELAS; see Chapter 598.2) are the classic examples, though other mitochondrial disease can mimic stroke. Features favoring MELAS would include a history of developmental regression, posterior (and often bilateral) lesions not respecting vascular territories on MRI, and elevated serum or cerebrospinal fluid lactate (MR spectroscopy). In contrast to these types of "metabolic infarction," children with Fabry disease (see Chapter 613.6) and homocystinuria (see Chapter 85.4) are at risk of true ischemic stroke.

VESTIBULOPATHY/ATAXIA

Acute onset vertigo and/or ataxia can be confused with brainstem or cerebellar stroke. Simple bedside tests of vestibular function with otherwise intact brainstem functions are reassuring. This differential diagnosis includes acute vestibular neuronopathy, viral labyrinthitis, and the benign paroxysmal vertigos as well as acute cerebellar ataxia and episodic ataxias.

CHANNELOPATHIES

An increasing number of nervous system ion channel mutations are described that feature sudden focal neurological deficits thereby mimicking stroke. These include the migraine syndromes mentioned above as well as a growing list of episodic ataxias. A strong family history raises suspicion but most require additional investigation.

ALTERNATING HEMIPLEGIA OF CHILDHOOD

Alternating hemiplegia of childhood typically presents in infancy with acute intermittent episodes of hemiplegia that alternate from 1 side of the body to the other. The hemiplegia persists for minutes to weeks and then resolves spontaneously. Choreoathetosis and dystonic movements are commonly observed in the hemiparetic extremity. Signs spontaneously regress with sleep but recur with awakening. Neuroimaging including MRA should be completed to exclude moyamoya disease. Alternating hemiplegia of childhood is linked to mutations in the *ATP1A3* gene.

Chapter 602

Central Nervous System Vasculitis

Heather A. Van Mater, William B. Gallentine, and Susanne M. Benseler

Autoimmune-mediated inflammatory brain diseases are recognized as an etiology for neurologic and neuropsychiatric symptoms in children and adults and include primary central nervous system (CNS) vasculitis, secondary CNS vasculitis, and autoimmune encephalitis (Fig. 602-1; see Chapter 598.4).

Primary angiitis of the CNS (PACNS) is recognized as the underlying etiology of a broad spectrum of neurologic and psychiatric symptoms in children. Criteria characteristic of childhood CNS vasculitis (cPACNS) include (1) newly acquired focal and/or diffuse neurologic deficits and/or psychiatric symptoms in a child 18 yr of age or younger, **plus** (2) angiographic and/or histologic evidence of vasculitis **in the absence of** (3) a systemic underlying condition known to cause or mimic the findings. Two broad categories of cPACNS are recognized based on the predominant vessel size affected: large/medium-vessel cPACNS and small-vessel cPACNS. Large/medium-vessel cPACNS is diagnosed on angiography demonstrating features of vessel wall inflammation, wall swelling and edema, and resulting luminal stenosis. Based on the clinical course and the corresponding distribution of vessel stenosis within the vascular tree of the CNS, children with large/medium-vessel cPACNS are classified as a monophasic, nonprogressive (NPcPACNS) or a progressive subtype (PcPACNS). The latter is characterized by chronic, progressive vessel wall inflammation affecting both proximal and distal vessel segments in 1 or both hemispheres. In contrast, NPcPACNS is a monophasic illness; vessel inflammation occurs in a characteristic distribution and is limited to the proximal vessel segments of the anterior and/or middle cerebral artery and/or distal internal carotid artery of 1 hemisphere. Small vessel cPACNS (SVcPACNS) is considered a progressive illness; the diagnosis is confirmed on brain biopsies because angiography is normal.

Secondary childhood CNS vasculitis can affect all cerebral vessel segments and can occur in the context of infections, rheumatic or other inflammatory conditions or as a result of systemic or local vascular irritation (Table 602-1). The neuropsychiatric manifestations of secondary CNS vasculitis are the same as those of primary CNS vasculitis. Secondary CNS vasculitis is distinguished from primary CNS vasculitis largely by the non-CNS manifestations of the underlying systemic vasculitic disease.

EPIDEMIOLOGY

The incidence and prevalence of primary CNS vasculitis is undetermined. In the past, the majority of children have been diagnosed at autopsy. Increased physician awareness, improved diagnostic markers, sensitive neuroimaging techniques, and brain biopsies have led to dramatically increased recognition and decreased mortality. Exploring the epidemiology of primary CNS vasculitis remains a challenge: the disease has many names including isolated angiitis of the CNS, transient cerebral angiitis, postvaricella angiopathy, and focal cerebral arteriopathy. Furthermore, children are frequently diagnosed with their presenting clinical phenotype, such as stroke, movement disorder, hallucination, or cognitive decline. Within clinical phenotypes, such as arterial ischemic stroke or status epilepticus in children without preexisting epilepsy, cPACNS should be considered an important etiology.

CLINICAL MANIFESTATIONS

Recognition of childhood CNS vasculitis requires a very high level of suspicion; any neurologic or psychiatric presentation can be the result

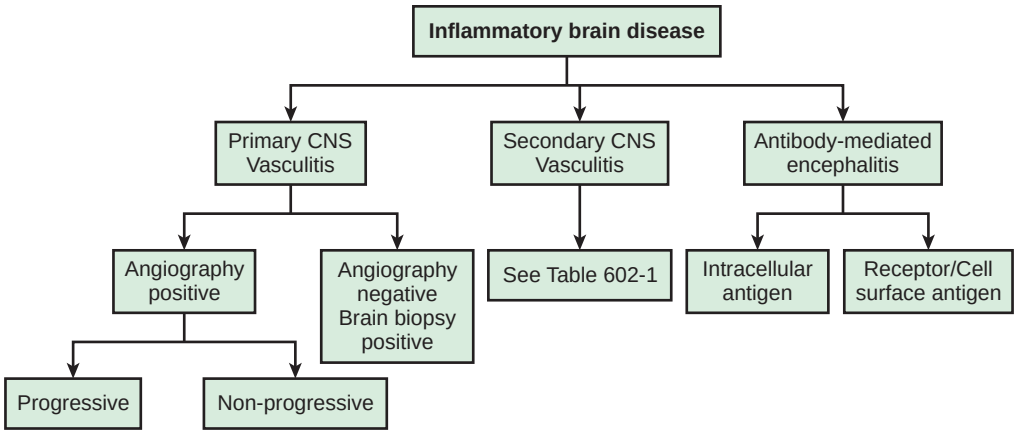


Figure 602-1 CNS vasculitis within the spectrum of immune-mediated inflammatory brain diseases.

Table 602-1 Causes of Secondary CNS Vasculitis

VIRAL INFECTIONS Varicella zoster virus, HIV, hepatitis C virus, cytomegalovirus, parvovirus B19
BACTERIAL INFECTIONS *Treponema pallidum, Borrelia burgdorferi, Mycobacterium tuberculosis, Mycoplasma pneumoniae, Bartonella henselae, Rickettsia* spp.
FUNGAL INFECTIONS Aspergillosis, mucormycosis, coccidioidomycosis, candidosis
PARASITIC INFECTIONS Cysticercosis
SYSTEMIC VASCULITIDES Wegener granulomatosis, Churg-Strauss syndrome, Behçet disease, polyarteritis nodosa, Henoch-Schönlein purpura, Kawasaki disease, giant-cell arteritis, Takayasu arteritis
CONNECTIVE TISSUE DISEASES Systemic lupus erythematosus, rheumatoid arthritis, Sjögren syndrome, dermatomyositis, mixed connective tissue disease
MISCELLANEOUS Antiphospholipid antibodies syndrome, Hodgkin and non-Hodgkin lymphomas, neurosarcoidosis, inflammatory bowel disease, graft-versus-host disease, bacterial endocarditis, acute bacterial meningitis, drug-induced CNS vasculitis (cocaine, amphetamine, ephedrine, phenylpropanolamine)

From Salvarani C, Brown Jr. RD, Hunder GG: Adult primary central nervous system vasculitis. Lancet *380:767–776, 2012, Panel, p. 768.*

of an underlying CNS vasculitis. The clinical phenotype may provide clues to the size of the primarily affected vessel segments and resulting cPACNS subtype: the majority of children with large/medium cPACNS present with arterial ischemic stroke features. Focal neurologic deficits, such as hemiparesis, facial droop, aphasia or any other distinct gross or fine motor deficits, may be the result of large vessel inflammation causing stenosis and decreased blood supply to the specific functional areas of the brain. Initially, these focal deficits wax and wane; they may even briefly resolve without therapeutic intervention and can therefore be easily overlooked. Headaches are a symptom of vascular disease in general and are commonly reported in cPACNS. New onset of vascular-type (e.g., migraine) headaches in children without any family history of migraine can serve as a diagnostic clue. Cognitive dysfunction in cPACNS often includes loss of higher executive function, concentration difficulties, learning and memory problems, atypical behavior or personality changes, and loss of social and emotional control. Seizures are a hallmark of SVcPACNS, as more than 80% of children with SVcPACNS present with seizures; all seizure types are seen. Often there is a disconnection between the clinical presentation and the child's electroencephalogram findings. In many centers, refractory status epilepticus is increasingly recognized as the presenting phenotype of SVcPACNS. Optic neuritis and spinal cord disease are also recognized in SVcPACNS.

Constitutional features of fever or fatigue may point toward an underlying systemic illness causing a secondary CNS vasculitis. All children with suspected or confirmed CNS vasculitis require a careful assessment for a systemic illness.

DIAGNOSIS

The first step is considering vasculitis as a possible underlying etiology of newly acquired neurologic deficits and/or psychiatric symptoms (Table 602-2). The likelihood of CNS vasculitis in general and a specific subtype of CNS vasculitis in particular depends on the demographic characteristics of the patient, the CNS and non-CNS features of the clinical presentation, the preceding symptoms, and the mode of onset of the disease. SVcPACNS is more commonly seen in girls of all ages, whereas large/medium cPACNS has a clear male preponderance. Seizures are a hallmark of SVcPACNS, whereas strokes often reflect large/medium-vessel inflammation. Laboratory markers of vasculitis typically include C-reactive protein, erythrocyte sedimentation rate, and complete blood counts. But inflammatory markers lack sensitivity and specificity in cPACNS, particularly when the CNS is involved in isolation. More than 50% of children with large/medium-vessel cPACNS have normal inflammatory markers at diagnosis. In contrast, the majority of children with SVcPACNS present with mild-moderately raised markers. Von Willebrand factor antigen, an endothelial cell–derived protein, is a proposed biomarker of vasculitis correlating closely with disease activity in cPACNS. It may be of particular importance for distinguishing SVcPACNS from demyelinating diseases. Cerebrospinal fluid (CSF) analysis is abnormal in up to 90% of SVcPACNS patients and less than half of large/medium-vessel cPACNS. Within the latter group, children with the progressive subtype have a higher likelihood of presenting with abnormal CSF findings, including high opening pressure, raised CSF cell count, typically with lymphocyte predominance, and raised CSF protein. Oligoclonal bands are seen in 20% of children with SVcPACNS. They are rarely seen in other subtypes. Autoimmune encephalitis (see Chapter 598.4) is one of the key differential diagnoses of SVcPACNS.

Neuroimaging is a valuable diagnostic modality for cPACNS. Parenchymal lesions may be inflammatory or ischemic in nature and are best viewed on MRI including T2/fluid attenuated inversion recovery (FLAIR) sequences and diffusion-weighted images (DWI) (Fig. 602-2). CNS lesions in children with large/medium-vessel cPACNS are predominantly ischemic in nature and restricted to large vascular territories. In contrast, MRI lesions in children with SVcPACNS are not restricted to major vascular territories; lesions are primarily inflammatory and may enhance with contrast. In this subtype, focal or

Table 602-2 Proposed Diagnostic Evaluation of Suspected Childhood Primary CNS Vasculitis

1. Clinical evaluation: Newly acquired symptom or deficit in a previously healthy child
   - Focal neurologic deficit: hemiparesis, hemisensory loss, aphasia, ataxia, movement abnormality, paresthesia, facial droop, ataxia, vision loss, spinal cord symptoms, others
   - Seizures or (refractory) seizure status
   - Diffuse neurologic deficit including cognitive decline with loss of higher executive function, concentration difficulties, learning or memory problems, behavior or personality changes, loss of social skills or emotional/impulse control, others
   - Headaches
   - Meningitis symptoms, abnormal level of consciousness
   - Psychiatric symptoms including hallucinations, pseudoseizures

   Differential diagnosis approach:
   - Underlying illness known to cause, be associated or mimic CNS vasculitis: check all potential clinical features
2. Laboratory tests
   - Blood inflammatory markers: C-reactive protein, erythrocyte sedimentation rate and complete blood counts
   - Endothelial markers: von Willebrand factor (vWF) antigen
   - Cerebrospinal fluid (CSF) inflammatory markers: opening pressure, cell count, protein, oligoclonal bands

   Differential diagnosis approach:
   - Infections/postinfectious inflammation: cultures, serologies, Gram stains
   - Autoimmune encephalitis: check neuronal antibodies in CSF and blood
   - Systemic inflammation/rheumatic disease: characteristic laboratory markers such as complement, autoantibodies
   - Thromboembolic conditions: procoagulatory profile
3. Neuroimaging
   - Parenchymal imaging on MRI:
     - Inflammatory lesions: T2/fluid attenuated inversion recovery sequences plus gadolinium contrast (lesion enhancement)
     - Ischemic lesions: diffusion-weighted images/apparent diffusion coefficient mapping
   - Vessel imaging
4. Brain biopsy

generalized meningeal enhancement is commonly seen if children are imaged prior to immunosuppressive therapy. Spinal cord parenchymal imaging is challenging; defining the nature of lesions is often difficult.

Evidence of vessel stenosis confirms the diagnosis in large/medium-vessel cPACNS subtypes; brain biopsies are not required. Important information about the disease activity can be obtained from post–gadolinium contrast studies of the vascular wall. The vessel wall of an inflamed cerebral vessel in active large/medium-vessel cPACNS subtypes is thickened and enhances contrast. Conventional angiography when compared to MR angiography has a higher sensitivity in detecting vessel stenosis in the distal vessel segments, the posterior circulation, and in very young children. Vessel wall imaging is often normal in children with SVcPACNS, sometimes mandating an elective brain biopsy to definitively make the diagnosis. Studies of regional blood flow or therapeutic trials of antiinflammatory or immunosuppressive agents are nonsurgical alternatives that do not afford specific diagnostic information. Biopsies should target low-risk, nonfunctional areas identified on MRI. In the appropriate clinical context, nonlesional biopsies have a high yield for confirming the diagnosis of SVcPACNS. Characteristic findings in SVcPACNS include an intramural and/or perivascular mononuclear infiltrate, evidence of endothelial activation, and reactive astrocyte activation. Gliosis and perivascular demyelination are hallmarks of long-standing disease. Findings typically seen in adult PACNS, including granulomas or vessel wall necrosis, are rarely seen in children with SVcPACNS. In children, the diagnostic yield of brain biopsies is 70%. Biopsy-related complications are rarely seen.

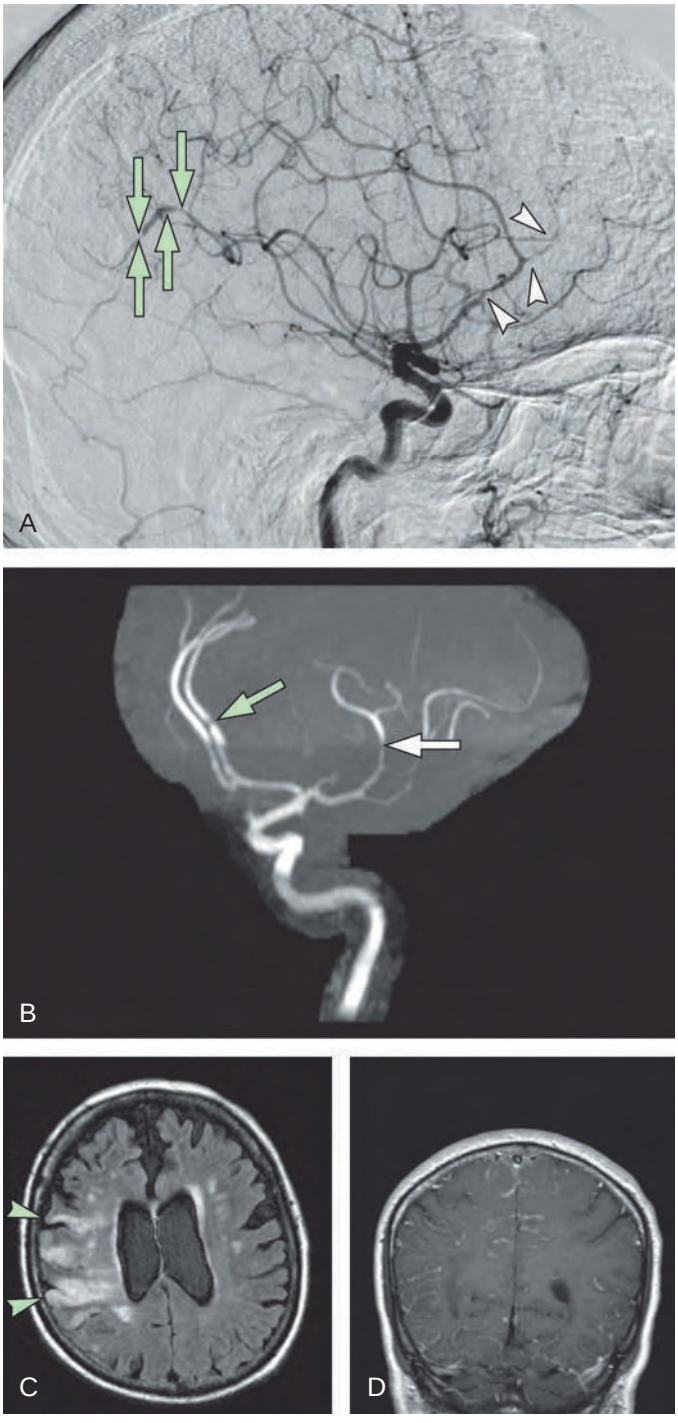


Figure 602-2 Imaging of patients with primary CNS vasculitis. **A,** Cerebral angiogram shows alternating stenosis and dilation of the distal middle cerebral artery *(arrows)* and the anterior cerebral artery *(arrowheads).* **B,** Magnetic resonance angiography of the brain shows a short-segment stenosis of the anterior cerebral artery *(green arrow)* and stenosis of the distal middle cerebral artery *(white arrow).* **C,** Fluid attenuation inversion recovery–weighted MRI shows a large abnormality within the right cerebral hemisphere consistent with ischemia *(arrowheads).* **D,** MRI shows diffuse, asymmetric, nodular, and linear leptomeningeal enhancement, with dura only slightly affected. *(From Salvarani C, Brown Jr. RD, Hunder GG: Adult primary central nervous system vasculitis.* Lancet *380:767–776, 2012, Fig. 2.)*

Table 602-3 Characteristics of Primary CNS Vasculitis and Reversible Cerebral Vasoconstriction Syndrome

	PCNSV	RCVS
Precipitating factor	None	Postpartum onset or onset after exposure to vasoactive substances
Onset	More insidious, progressive course	Acute onset followed by a monophasic course
Headaches	Chronic and progressive	Acute, thunderclap type
CSF findings	Abnormal (leucocytosis and high total protein concentration)	Normal to near normal
MRI	Abnormal in almost all patients	Normal in 70% of patients
Angiography	Possibly normal; otherwise, diffuse abnormalities are often indistinguishable from RCVS; irregular and asymmetrical arterial stenoses or multiple occlusions are more suggestive of PCNSV; abnormalities might be irreversible	Always abnormal, strings of beads appearance of cerebral arteries; abnormalities reversible within 6-12 wk
Cerebral biopsy	Vasculitis	No vasculitic changes
Drug treatment	Prednisone with or without cytotoxic agents	Nimodipine

CSF, cerebrospinal fluid; PCNSV, primary CNS vasculitis; RCVS, reversible cerebral vasoconstriction syndrome.
From Salvarani C, Brown Jr. RD, Hunder GG: Adult primary central nervous system vasculitis. Lancet *380:767–776, 2012, Table 2.*

Disorders that may be seen in adolescents and young adults that produce the reversible vasoconstriction syndrome must also be considered. These include migraine, drug-induced vasospasm, and postpartum angiopathy. Differentiating vasculitis is important for therapy and prognosis (Table 602-3).

TREATMENT

Corticosteroids are the mainstay of acute immunosuppressive management of cPACNS. Usually IV pulse therapy is initially given. Antithrombotic therapy is equally important, particularly in large/medium-vessel cPACNS subtypes, because children are at high risk for recurrent ischemic events. For the distinct cPACNS subtypes, different treatment regimens should be considered. Nonprogressive cPACNS is a monophasic inflammatory attack with the highest risk of poor neurologic outcome. Vessel wall inflammation causes severe proximal stenosis and a high restroke risk. High-dose corticosteroid pulses are commonly given followed by a 6-12 wk course of oral steroids at tapering doses. Second-line immunosuppressive agents are uncommonly used. All children require antithrombotic therapy. No unifying regimen exists. Many centers initially use low-molecular-weight heparin followed by long-term antiplatelet therapy. When reimaged at 3 mo follow-up, children should have stable or improved vessel disease, no newly affected vessel segments, and no evidence of contrast wall enhancement. At this point the immunosuppressive therapy is commonly discontinued and children are only kept on antiplatelet agents.

Progressive cPACNS and SVcPACNS are considered chronic progressive vasculitis subtypes requiring a prolonged course of combination immunosuppression. High-dose corticosteroids are initially used followed by long-term oral corticosteroids with slow taper. Many centers use an induction-maintenance protocol adding IV cyclophosphamide to the corticosteroids as the induction medication, followed by mycophenolate mofetil or other oral second-line agents during maintenance therapy. Symptomatic therapy is essential including anticonvulsants or psychotropic medication if required. Supportive therapy includes bone protection with calcium and vitamin D, prophylaxis against pneumocystis pneumonia, and gastric mucosal protection as required.

PROGNOSIS

The mortality rate of cPACNS has significantly improved. Some treatment protocols for SVcPACNS report a good outcome, defined as no functional neurologic deficits in two-thirds of children. Children presenting with status epilepticus and SVcPACNS have the poorest cognitive outcome.

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Chapter 603

Central Nervous System Infections

Charles G. Prober, Nivedita S. Srinivas, and Roshni Mathew

Infection of the central nervous system (CNS) is the most common cause of fever associated with signs and symptoms of CNS disease in children. Many microorganisms can cause infection. Nonetheless, specific pathogens are identifiable and are influenced by the age and immune status of the host and the epidemiology of the pathogen. In general, viral infections of the CNS are much more common than bacterial infections, which, in turn, are more common than fungal and parasitic infections. Infections caused by rickettsiae (Rocky Mountain spotted fever, *Ehrlichia*) are relatively uncommon but assume important roles under certain epidemiologic circumstances. *Mycoplasma* spp. can also cause infections of the CNS, although their precise contribution is often difficult to determine.

Regardless of etiology, most patients with CNS infection have similar clinical manifestations. **Common symptoms** include headache, nausea, vomiting, anorexia, restlessness, altered state of consciousness, and irritability; most of these symptoms are nonspecific. **Common signs** of CNS infection, in addition to fever, include photophobia, neck pain and rigidity, obtundation, stupor, coma, seizures, and focal neurologic deficits. The severity and constellation of signs are determined by the specific pathogen, the host, and the area of the CNS affected.

Infection of the CNS may be diffuse or focal. Meningitis and encephalitis are examples of diffuse infection. Meningitis implies primary involvement of the meninges, whereas encephalitis indicates brain parenchymal involvement. Because these anatomic boundaries are often not distinct, many patients have evidence of both meningeal and parenchymal involvement and should be considered to have meningoencephalitis. Brain abscess is the best example of a focal infection of the CNS. The neurologic expression of this infection is determined by the site and extent of the abscess(es) (see Chapter 604).

The diagnosis of diffuse CNS infections depends on examination of cerebrospinal fluid (CSF) obtained by lumbar puncture (LP). Table 603-1 provides an overview of the expected CSF abnormalities with various CNS disorders.

Table 603-1 Cerebrospinal Fluid Findings in Central Nervous System Disorders

CONDITION	PRESSURE (mm H_2O)	LEUKOCYTES (mm^3)	PROTEIN (mg/dL)	GLUCOSE (mg/dL)	COMMENTS
Normal	50-80	<5, ≥75% Lymphocytes	20-45	>50 (or 75% serum glucose)	
COMMON FORMS OF MENINGITIS					
Acute bacterial meningitis	Usually elevated (100-300)	100-10,000 or more; usually 300-2,000; PMNs predominate	Usually 100-500	Decreased, usually <40 (or <50% serum glucose)	Organisms usually seen on Gram stain and recovered by culture
Partially treated bacterial meningitis	Normal or elevated	5-10,000; PMNs usual but mononuclear cells may predominate if pretreated for extended period of time	Usually 100-500	Normal or decreased	Organisms may be seen on Gram stain Pretreatment may render CSF sterile. Antigen may be detected by agglutination test
Viral meningitis or meningoencephalitis	Normal or slightly elevated (80-150)	Rarely >1,000 cells. Eastern equine encephalitis and lymphocytic choriomeningitis may have cell counts of several thousand. PMNs early but mononuclear cells predominate through most of the course	Usually 50-200	Generally normal; may be decreased to <40 in some viral diseases, particularly mumps (15-20% of cases)	HSV encephalitis is suggested by focal seizures or by focal findings on CT or MRI scans or EEG. Enteroviruses and HSV infrequently recovered from CSF. HSV and enteroviruses may be detected by PCR of CSF
UNCOMMON FORMS OF MENINGITIS					
Tuberculous meningitis	Usually elevated	10-500; PMNs early, but lymphocytes predominate through most of the course	100-3,000; may be higher in presence of block	<50 in most cases; decreases with time if treatment is not provided	Acid-fast organisms almost never seen on smear. Organisms may be recovered in culture of large volumes of CSF. *Mycobacterium tuberculosis* may be detected by PCR of CSF
Fungal meningitis	Usually elevated	5-500; PMNs early but mononuclear cells predominate through most of the course. Cryptococcal meningitis may have no cellular inflammatory response	25-500	<50; decreases with time if treatment is not provided	Budding yeast may be seen. Organisms may be recovered in culture. Cryptococcal antigen (CSF and serum) may be positive in cryptococcal infection
Syphilis (acute) and leptospirosis	Usually elevated	50-500; lymphocytes predominate	50-200	Usually normal	Positive CSF serology. Spirochetes not demonstrable by usual techniques of smear or culture; dark-field examination may be positive
Amebic (*Naegleria*) meningoencephalitis	Elevated	1,000-10,000 or more; PMNs predominate	50-500	Normal or slightly decreased	Mobile amebas may be seen by hanging-drop examination of CSF at room temperature
BRAIN ABSCESSES AND PARAMENINGEAL FOCUS					
Brain abscess	Usually elevated (100-300)	5-200; CSF rarely acellular; lymphocytes predominate; if abscess ruptures into ventricle, PMNs predominate and cell count may reach >100,000	75-500	Normal unless abscess ruptures into ventricular system	No organisms on smear or culture unless abscess ruptures into ventricular system
Subdural empyema	Usually elevated (100-300)	100-5,000; PMNs predominate	100-500	Normal	No organisms on smear or culture of CSF unless meningitis also present; organisms found on tap of subdural fluid
Cerebral epidural abscess	Normal to slightly elevated	10-500; lymphocytes predominate	50-200	Normal	No organisms on smear or culture of CSF
Spinal epidural abscess	Usually low, with spinal block	10-100; lymphocytes predominate	50-400	Normal	No organisms on smear or culture of CSF
Chemical (drugs, dermoid cysts, myelography dye)	Usually elevated	100-1,000 or more; PMNs predominate	50-100	Normal or slightly decreased	Epithelial cells may be seen within CSF by use of polarized light in some children with dermoids

Continued

Table 603-1 Cerebrospinal Fluid Findings in Central Nervous System Disorders—cont'd

CONDITION	PRESSURE (mm H_2O)	LEUKOCYTES (mm^3)	PROTEIN (mg/dL)	GLUCOSE (mg/dL)	COMMENTS
NONINFECTIOUS CAUSES					
Sarcoidosis	Normal or elevated slightly	0-100; mononuclear	40-100	Normal	No specific findings
Systemic lupus erythematosus with CNS involvement	Slightly elevated	0-500; PMNs usually predominate; lymphocytes may be present	100	Normal or slightly decreased	No organisms on smear or culture. Positive neuronal and ribosomal P protein antibodies in CSF
Tumor, leukemia	Slightly elevated to very high	0-100 or more; mononuclear or blast cells	50-1,000	Normal to decreased (20-40)	Cytology may be positive
Acute disseminated encephalomyelitis	Normal or elevated	~100 lymphocytes	Normal to elevated	Normal	MRI adds to diagnosis
Autoimmune encephalitis	Normal	~100 lymphocytes	Normal to elevated	Normal	Anti-NMDAR antibody–positive

CSF, cerebrospinal fluid; EEG, electroencephalogram; HSV, herpes simplex virus; NMDAR, *N*-methyl-D-aspartate receptor; PCR, polymerase chain reaction; PMN, polymorphonuclear neutrophils.

603.1 Acute Bacterial Meningitis Beyond the Neonatal Period

Charles G. Prober and Roshni Mathew

Bacterial meningitis is one of the most potentially serious infections occurring in infants and older children. This infection is associated with a high rate of acute complications and risk of long-term morbidity. The incidence of bacterial meningitis is sufficiently high in febrile infants that it should be included in the differential diagnosis of those with altered mental status and other evidence of neurologic dysfunction.

ETIOLOGY

The most common causes of bacterial meningitis in children older than 1 mo of age in the United States are *Streptococcus pneumoniae and Neisseria meningitidis.* Bacterial meningitis caused by *S. pneumoniae* and *Haemophilus influenzae* type b has become much less common in developed countries since the introduction of universal immunization against these pathogens beginning at 2 mo of age. Demonstrating the importance of vaccination, invasive *H. influenzae* disease was reported in Minnesota in 2008 in 5 children with no relationship to one another and who were partially or not immunized. It is the largest number of children with invasive *H. influenzae* in Minnesota since 1992. Infection caused by *S. pneumoniae* or *H. influenzae* type b must be considered in incompletely vaccinated individuals or those in developing countries. Those with certain underlying immunologic (HIV infection, immunoglobulin [Ig] G subclass deficiency) or anatomic (splenic dysfunction, cochlear defects or implants) disorders also may be at increased risk of infection caused by these bacteria.

Alterations of host defense resulting from anatomic defects or immune deficits also increase the risk of meningitis from less-common pathogens such as *Pseudomonas aeruginosa, Staphylococcus aureus,* coagulase-negative staphylococci, *Salmonella* spp., anaerobes, and *Listeria monocytogenes.*

EPIDEMIOLOGY

A major risk factor for meningitis is the lack of immunity to specific pathogens associated with young age. Additional risks include recent colonization with pathogenic bacteria, close contact (household, daycare centers, college dormitories, military barracks) with individuals having invasive disease caused by *N. meningitidis* or *H. influenzae* type b, crowding, poverty, black or Native American race, and male gender. The mode of transmission is probably person-to-person contact through respiratory tract secretions or droplets. The risk of meningitis is increased among infants and young children with occult bacteremia; the odds ratio is greater for meningococcus (85 times) and *H. influenzae* type b (12 times) relative to that for pneumococcus.

Specific host defense defects as a result of altered immunoglobulin production in response to encapsulated pathogens may be responsible for the increased risk of bacterial meningitis in Native Americans and Eskimos. Defects of the complement system (C5-C8) are associated with recurrent meningococcal infection, and defects of the properdin system are associated with a significant risk of lethal meningococcal disease. Splenic dysfunction (sickle cell anemia) or asplenia (caused by trauma or congenital defect) is associated with an increased risk of pneumococcal, *H. influenzae* type b (to some extent), and, rarely, meningococcal sepsis and meningitis. T-lymphocyte defects (congenital or acquired by chemotherapy, AIDS, or malignancy) are associated with an increased risk of *L. monocytogenes* infections of the CNS.

A congenital or acquired CSF leak across a mucocutaneous barrier, such as a lumbar dural sinus, cranial or midline facial defects (cribriform plate), and middle ear (stapedial foot plate) or inner ear fistulas (oval window, internal auditory canal, cochlear aqueduct), or CSF leakage through a rupture of the meninges as a result of a basal skull fracture into the cribriform plate or paranasal sinus, is associated with an increased risk of pneumococcal meningitis. The risk of bacterial meningitis, caused by *S. pneumoniae,* in children with cochlear implants, used for the treatment of hearing loss, is more than 30 times the risk in the general U.S. population. Lumbosacral dermal sinus and meningomyelocele are associated with staphylococcal, anaerobic, and Gram-negative enteric bacterial meningitis. CSF shunt infections increase the risk of meningitis caused by staphylococci (especially coagulase-negative species) and other low-virulence bacteria that typically colonize the skin.

Streptococcus pneumoniae

See Chapter 182.

The 7-valent pneumococcal protein polysaccharide conjugate vaccine (PCV7) was introduced into the routine vaccination schedule in 2000 and contained the serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F. These serotypes caused most of the invasive pneumococcal infections in the United States at that time. The vaccine led to a dramatic decrease in rates of invasive pneumococcal disease. However, an increase in invasive disease caused by serotypes not contained in the original vaccine, such as serotype 19A, was observed. As a result, a 13-valent pneumococcal polysaccharide-protein conjugate vaccine (PCV13) was licensed in the United States in February 2010. PCV13 contains the serotypes in PCV7 plus serotypes 1, 3, 5, 6A, 7F, and 19A. This vaccine is recommended for routine administration to all children 2-59 mo of age. The PCV13 vaccine is given as a 4-dose series at 2, 4, 6, and 12-15 mo of age. The incidence of invasive pneumococcal infections

peaks in the 1st 2 yr of life, reaching rates of 228 per 100,000 in children 6-12 mo of age. Children with anatomic or functional asplenia secondary to sickle cell disease and those infected with HIV have infection rates that are 20-100–fold higher than in those of healthy children in the 1st 5 yr of life. Additional risk factors for contracting pneumococcal meningitis include otitis media, sinusitis, pneumonia, CSF otorrhea or rhinorrhea, the presence of a cochlear implant, and chronic graft-versus-host disease following bone marrow transplantation.

Neisseria meningitidis

See Chapter 191.

Five serogroups of meningococcus—A, B, C, Y, and W-135—are responsible for disease. Meningococcal meningitis may be sporadic or may occur in epidemics. In the United States, serogroups B, C, and Y each account for approximately 30% of cases, although serogroup distribution varies by location and time. Epidemic disease, especially in developing countries, is usually caused by serogroup A. Cases occur throughout the year but may be more common in the winter and spring and following influenza virus infections. Nasopharyngeal carriage of *N. meningitidis* occurs in 1-15% of adults. Colonization may last weeks to months; recent colonization places nonimmune younger children at greatest risk for meningitis. The incidence of disease occurring in association with an index case in the family is 1%, a rate that is 1,000-fold the risk in the general population. The risk of secondary cases occurring in contacts at daycare centers is approximately 1 in 1,000. Most infections of children are acquired from a contact in a daycare facility, a colonized adult family member, or an ill patient with meningococcal disease. Children younger than 5 yr have the highest rates of meningococcal infection. A second peak in incidence occurs in persons between 15 and 24 yr of age. College freshmen living in dormitories have an increased incidence of infection compared to non–college-attending, age-matched controls.

The Centers for Disease Control and Prevention (CDC) recommends vaccination against meningococcus (types A, C, W, and Y) with 1 dose of a quadrivalent conjugate meningococcal vaccine between the ages of 11 and 12 yr and for persons 2 mo to 18 yr who are at increased risk for meningococcal disease. The CDC also has specific recommendations for meningococcal vaccination of infants at high risk of meningococcal infection as a consequence of complement pathway deficiencies. College freshmen living in dormitories who have not been previously vaccinated should also be vaccinated.

Haemophilus influenzae Type B

See Chapter 194.

Before universal *H. influenzae* type b vaccination in the United States, approximately 70% of cases of bacterial meningitis occurring in the 1st 5 yr of life were caused by this pathogen. Invasive infections occurred primarily in infants 2 mo to 2 yr of age; peak incidence was at 6-9 mo of age, and 50% of cases occurred in the 1st yr of life. The risk to children was markedly increased among family or daycare center contacts of patients with *H. influenzae* type b disease. Incompletely vaccinated individuals, those in underdeveloped countries who are not vaccinated, and those with blunted immunologic responses to vaccine (such as children with HIV infection) remain at risk for *H. influenzae* type b meningitis.

PATHOLOGY AND PATHOPHYSIOLOGY

A meningeal purulent exudate of varying thickness may be distributed around the cerebral veins, venous sinuses, convexity of the brain, and cerebellum, and in the sulci, sylvian fissures, basal cisterns, and spinal cord. Ventriculitis with bacteria and inflammatory cells in ventricular fluid may be present (more often in neonates), as may subdural effusions and, rarely, empyema. Perivascular inflammatory infiltrates also may be present, and the ependymal membrane may be disrupted. Vascular and parenchymal cerebral changes characterized by polymorphonuclear infiltrates extending to the subintimal region of the small arteries and veins, vasculitis, thrombosis of small cortical veins, occlusion of major venous sinuses, necrotizing arteritis producing subarachnoid hemorrhage, and, rarely, cerebral cortical necrosis in the absence of identifiable thrombosis have been described at autopsy. **Cerebral infarction,** resulting from vascular occlusion because of inflammation, vasospasm, and thrombosis, is a frequent sequela. Infarct size ranges from microscopic to involvement of an entire hemisphere.

Inflammation of spinal nerves and roots produces meningeal signs, and inflammation of the cranial nerves produces cranial neuropathies of optic, oculomotor, facial, and auditory nerves. Increased intracranial pressure (ICP) also produces oculomotor nerve palsy because of the presence of temporal lobe compression of the nerve during tentorial herniation. Abducens nerve palsy may be a nonlocalizing sign of elevated ICP.

Increased ICP is a result of cell death (cytotoxic cerebral edema), cytokine-induced increased capillary vascular permeability (vasogenic cerebral edema), and, possibly, increased hydrostatic pressure (interstitial cerebral edema) after obstructed reabsorption of CSF in the arachnoid villus or obstruction of the flow of fluid from the ventricles. ICP may exceed 300 mm H_2O; cerebral perfusion may be further compromised if the cerebral perfusion pressure (mean arterial pressure minus ICP) is <50 cm H_2O as a result of systemic hypotension with reduced cerebral blood flow. The syndrome of inappropriate antidiuretic hormone secretion (SIADH) may produce excessive water retention and potentially increase the risk of elevated ICP (see Chapter 559). Hypotonicity of brain extracellular spaces may cause cytotoxic edema after cell swelling and lysis. Tentorial, falx, or cerebellar herniation does not usually occur because the increased ICP is transmitted to the entire subarachnoid space and there is little structural displacement. Furthermore, if the fontanels are still patent, increased ICP is not always dissipated.

Hydrocephalus can occur as an acute complication of bacterial meningitis. It most often takes the form of a communicating hydrocephalus caused by adhesive thickening of the arachnoid villi around the cisterns at the base of the brain. Thus, there is interference with the normal resorption of CSF. Less often, obstructive hydrocephalus develops after fibrosis and gliosis of the aqueduct of Sylvius or the foramina of Magendie and Luschka.

Raised CSF protein levels are partly a result of increased vascular permeability of the blood–brain barrier and the loss of albumin-rich fluid from the capillaries and veins traversing the subdural space. Continued transudation may result in subdural effusions, usually found in the later phase of acute bacterial meningitis. **Hypoglycorrhachia** (reduced CSF glucose levels) is attributable to decreased glucose transport by the cerebral tissue.

Damage to the cerebral cortex may be a result of the focal or diffuse effects of vascular occlusion (infarction, necrosis, lactic acidosis), hypoxia, bacterial invasion (cerebritis), toxic encephalopathy (bacterial toxins), elevated ICP, ventriculitis, and transudation (subdural effusions). These pathologic factors result in the clinical manifestations of impaired consciousness, seizures, cranial nerve deficits, motor and sensory deficits, and later psychomotor retardation.

PATHOGENESIS

Bacterial meningitis most commonly results from hematogenous dissemination of microorganisms from a distant site of infection; **bacteremia** usually precedes meningitis or occurs concomitantly. Bacterial colonization of the nasopharynx with a potentially pathogenic microorganism is the usual source of the bacteremia. There may be prolonged carriage of the colonizing organisms without disease or, more likely, rapid invasion after recent colonization. Prior or concurrent viral upper respiratory tract infection may enhance the pathogenicity of bacteria producing meningitis.

N. meningitidis and *H. influenzae* type b attach to mucosal epithelial cell receptors by pili. After attachment to epithelial cells, bacteria breach the mucosa and enter the circulation. *N. meningitidis* may be transported across the mucosal surface within a phagocytic vacuole after ingestion by the epithelial cell. Bacterial survival in the bloodstream is enhanced by large bacterial capsules that interfere with opsonic phagocytosis and are associated with increased virulence. Host-related developmental defects in bacterial opsonic phagocytosis also contribute to the bacteremia. In young, nonimmune hosts, the

defect may be from an absence of preformed IgM or IgG anticapsular antibodies, whereas in immunodeficient patients, various deficiencies of components of the complement or properdin system may interfere with effective opsonic phagocytosis. Splenic dysfunction may also reduce opsonic phagocytosis by the reticuloendothelial system.

Bacteria gain entry to the CSF through the choroid plexus of the lateral ventricles and the meninges and then circulate to the extracerebral CSF and subarachnoid space. Bacteria rapidly multiply because the CSF concentrations of complement and antibody are inadequate to contain bacterial proliferation. Chemotactic factors then incite a local inflammatory response characterized by polymorphonuclear cell infiltration. The presence of bacterial cell wall lipopolysaccharide (endotoxin) of Gram-negative bacteria (*H. influenzae* type b, *N. meningitidis*) and of pneumococcal cell wall components (teichoic acid, peptidoglycan) stimulates a marked inflammatory response, with local production of tumor necrosis factor, interleukin 1, prostaglandin E, and other inflammatory mediators. The subsequent inflammatory response is characterized by neutrophilic infiltration, increased vascular permeability, alterations of the blood–brain barrier, and vascular thrombosis. Meningitis-associated brain injury is not simply caused by viable bacteria but occurs as a consequence of the host reaction to the inflammatory cascade initiated by bacterial components.

Rarely, meningitis may follow bacterial invasion from a contiguous focus of infection such as paranasal sinusitis, otitis media, mastoiditis, orbital cellulitis, or cranial or vertebral osteomyelitis or may occur after introduction of bacteria via penetrating cranial trauma, dermal sinus tracts, or meningomyeloceles.

CLINICAL MANIFESTATIONS

The onset of acute meningitis has 2 predominant patterns. The more dramatic and, fortunately, less common presentation is sudden onset with rapidly progressive manifestations of shock, purpura, disseminated intravascular coagulation, and reduced levels of consciousness often resulting in progression to coma or death within 24 hr. More often, meningitis is preceded by several days of fever accompanied by upper respiratory tract or gastrointestinal symptoms, followed by nonspecific signs of CNS infection, such as increasing lethargy and irritability.

The signs and symptoms of meningitis are related to the nonspecific findings associated with a systemic infection and to manifestations of meningeal irritation. Nonspecific findings include fever, anorexia and poor feeding, headache, symptoms of upper respiratory tract infection, myalgias, arthralgias, tachycardia, hypotension, and various cutaneous signs, such as petechiae, purpura, or an erythematous macular rash. Meningeal irritation is manifested as nuchal rigidity, back pain, **Kernig sign** (flexion of the hip 90 degrees with subsequent pain with extension of the leg), and **Brudzinski sign** (involuntary flexion of the knees and hips after passive flexion of the neck while supine). In children, particularly in those younger than 12-18 mo, Kernig and Brudzinski signs are not consistently present. Indeed fever, headache, and nuchal rigidity are present in only 40% of adults with bacterial meningitis. Increased ICP is suggested by headache, emesis, bulging fontanel or diastasis (widening) of the sutures, oculomotor (anisocoria, ptosis) or abducens nerve paralysis, hypertension with bradycardia, apnea or hyperventilation, decorticate or decerebrate posturing, stupor, coma, or signs of herniation. Papilledema is uncommon in uncomplicated meningitis and should suggest a more chronic process, such as the presence of an intracranial abscess, subdural empyema, or occlusion of a dural venous sinus. Focal neurologic signs usually are a result of vascular occlusion. Cranial neuropathies of the ocular, oculomotor, abducens, facial, and auditory nerves may also be the result of focal inflammation. Overall, approximately 10-20% of children with bacterial meningitis have focal neurologic signs.

Seizures (focal or generalized) caused by cerebritis, infarction, or electrolyte disturbances occur in 20-30% of patients with meningitis. Seizures that occur on presentation or within the 1st 4 days of onset are usually of no prognostic significance. Seizures that persist after the 4th day of illness and those that are difficult to treat may be associated with a poor prognosis.

Alterations of mental status are common among patients with meningitis and may be the consequence of increased ICP, cerebritis, or hypotension; manifestations include irritability, lethargy, stupor, obtundation, and coma. Comatose patients have a poor prognosis. Additional manifestations of meningitis include photophobia and tache cérébrale, which is elicited by stroking the skin with a blunt object and observing a raised red streak within 30-60 sec.

DIAGNOSIS

The diagnosis of acute pyogenic meningitis is confirmed by analysis of the CSF, which typically reveals microorganisms on Gram stain and culture, a neutrophilic pleocytosis, elevated protein, and reduced glucose concentrations (see Table 603-1). LP should be performed when bacterial meningitis is suspected. **Contraindications** for an immediate LP include (1) evidence of increased ICP (other than a bulging fontanel), such as 3rd or 6th cranial nerve palsy with a depressed level of consciousness, or hypertension and bradycardia with respiratory abnormalities (see Chapter 590); (2) severe cardiopulmonary compromise requiring prompt resuscitative measures for shock or in patients in whom positioning for the LP would further compromise cardiopulmonary function; and (3) infection of the skin overlying the site of the LP. Thrombocytopenia is a relative contraindication for LP. If an LP is delayed, empirical antibiotic therapy should be initiated. CT scanning for evidence of a brain abscess or increased ICP should not delay therapy. LP may be performed after increased ICP has been treated or a brain abscess has been excluded.

Blood cultures should be performed in all patients with suspected meningitis. Blood cultures reveal the responsible bacteria in up to 80-90% of cases of meningitis. Elevations of the C-reactive protein, erythrocyte sedimentation rate, and procalcitonin have been used to differentiate bacterial (usually elevated) from viral causes of meningitis.

Lumbar Puncture

See Chapter 590.

The CSF leukocyte count in bacterial meningitis usually is elevated to >1,000/mm^3 and, typically, there is a neutrophilic predominance (75-95%). Turbid CSF is present when the CSF leukocyte count exceeds 200-400/mm^3. Normal healthy neonates may have as many as 30 leukocytes/mm^3 (usually <10), but older children without viral or bacterial meningitis have <5 leukocytes/mm^3 in the CSF; in both age groups there is a predominance of lymphocytes or monocytes.

A CSF leukocyte count <250/mm^3 may be present in as many as 20% of patients with acute bacterial meningitis; pleocytosis may be absent in patients with severe overwhelming sepsis and meningitis and is a poor prognostic sign. Pleocytosis with a lymphocyte predominance may be present during the early stage of acute bacterial meningitis; conversely, neutrophilic pleocytosis may be present in patients in the early stages of acute viral meningitis. The shift to lymphocytic-monocytic predominance in viral meningitis invariably occurs within 8-24 hr of the initial LP. The Gram stain is positive in 70-90% of patients with untreated bacterial meningitis.

A diagnostic conundrum in the evaluation of children with suspected bacterial meningitis is the analysis of CSF obtained from children already receiving antibiotic (usually oral) therapy. This is an important issue, because 25-50% of children being evaluated for bacterial meningitis are receiving oral antibiotics when their CSF is obtained. CSF obtained from children with bacterial meningitis, after the initiation of antibiotics, may be negative on Gram stain and culture. Pleocytosis with a predominance of neutrophils, elevated protein level, and a reduced concentration of CSF glucose usually persist for several days after the administration of appropriate intravenous antibiotics. Therefore, despite negative cultures, the presumptive diagnosis of bacterial meningitis can be made. Some clinicians test CSF for the presence of bacterial antigens if the child has been pretreated with antibiotics and the diagnosis of bacterial meningitis is in doubt. These tests have technical limitations. Polymerase chain reactions using broad-based bacterial 16S ribosomal RNA gene patterns may be useful in diagnosing the

cause of culture-negative meningitis because of prior antibiotic therapy or the presence of a nonculturable fastidious pathogen.

A traumatic LP may complicate the diagnosis of meningitis. Repeat LP at a higher interspace may produce less hemorrhagic fluid, but this fluid usually also contains red blood cells. Interpretation of CSF leukocytes and protein concentration are affected by LPs that are traumatic, although the Gram stain, culture, and glucose level may not be influenced. Although methods for correcting for the presence of red blood cells have been proposed, it is prudent to rely on the bacteriologic results rather than attempt to interpret the CSF leukocyte and protein results of a traumatic LP. Children with seizure, particularly those with fever associated status epilepticus *do not* have a CSF pleocytosis in the absence of CNS infection or inflammatory disease.

Differential Diagnosis

In addition to *S. pneumoniae, N. meningitidis,* and *H. influenzae* type b, many other microorganisms can cause generalized infection of the CNS with similar clinical manifestations. These organisms include less-typical bacteria, such as *Mycobacterium tuberculosis, Nocardia* spp., *Treponema pallidum* (syphilis), and *Borrelia burgdorferi* (Lyme disease); fungi, such as those endemic to specific geographic areas (*Coccidioides, Histoplasma,* and *Blastomyces*) and those responsible for infections in compromised hosts (*Candida, Cryptococcus,* and *Aspergillus*); parasites, such as *Toxoplasma gondii* and those that cause cysticercosis and, most frequently, viruses (see Chapter 603.2; Table 603-2). Focal infections of the CNS including brain abscess and parameningeal abscess (subdural empyema, cranial and spinal epidural abscess) may also be confused with meningitis. In addition, noninfectious illnesses can cause generalized inflammation of the CNS. Relative to infections, these disorders are uncommon and include malignancy, collagen vascular syndromes, and exposure to toxins (Table 603-2).

Determining the specific cause of CNS infection is facilitated by careful examination of the CSF with specific stains (Kinyoun carbol fuchsin for mycobacteria, India ink for fungi), cytology, antigen detection *(Cryptococcus),* serology (syphilis, West Nile virus, arboviruses), viral culture (enterovirus), and polymerase chain reaction (herpes simplex, enterovirus, and others). Other potentially valuable diagnostic tests include blood cultures, CT or MRI of the brain, serologic tests, and, rarely, meningeal or brain biopsy. A unique MRI finding in patients suspected of CNS infection is pachymeningitis (Fig. 603-1). In addition to bacterial, tuberculous, or fungal infection (Fig. 603-1), the differential diagnosis also includes immune or inflammatory diseases such as Sweet syndrome, CNS vasculitis, sarcoidosis, lymphoma, and neonatal-onset multisystem inflammatory disease.

Acute viral meningoencephalitis is the most likely infection to be confused with bacterial meningitis (see Tables 603-2 and 603-3). Although, in general, children with viral meningoencephalitis appear less ill than those with bacterial meningitis, both types of infection have a spectrum of severity. Some children with bacterial meningitis may have relatively mild signs and symptoms, whereas some with viral meningoencephalitis may be critically ill. Although classic CSF profiles associated with bacterial vs viral infection tend to be distinct (see Table 603-1), specific test results may have considerable overlap.

TREATMENT

The therapeutic approach to patients with presumed bacterial meningitis depends on the nature of the initial manifestations of the illness. A child with rapidly progressing disease of less than 24 hr duration, in the absence of increased ICP, should receive antibiotics as soon as possible after an LP is performed. If there are signs of increased ICP or focal neurologic findings, antibiotics should be given without performing an LP and before obtaining a CT scan. Increased ICP should be treated simultaneously (see Chapter 68). Immediate treatment of associated multiple organ system failure, shock (see Chapter 70), and acute respiratory distress syndrome (see Chapter 71) is also indicated.

Patients who have a more protracted subacute course and become ill over a 4-7 day period should also be evaluated for signs of increased ICP and focal neurologic deficits. Unilateral headache, papilledema, and other signs of increased ICP suggest a focal lesion, such as a brain or epidural abscess, or subdural empyema. Under these circumstances, antibiotic therapy should be initiated before LP and CT scanning. If signs of increased ICP and/or focal neurologic signs are present, CT scanning should be performed first to determine the safety of performing an LP.

Initial Antibiotic Therapy

The initial (empirical) choice of therapy for meningitis in immunocompetent infants and children is primarily influenced by the antibiotic susceptibilities (Table 603-4) of *S. pneumoniae.* Selected antibiotics should achieve bactericidal levels in the CSF. Although there are substantial geographic differences in the frequency of resistance of *S. pneumoniae* to antibiotics, rates are increasing throughout the world. In the United States, 25-50% of strains of *S. pneumoniae* are currently resistant to penicillin; relative resistance (minimal inhibitory concentration = 0.1-1.0 μg/mL) is more common than high-level resistance (minimal inhibitory concentration = 2.0 μg/mL). Resistance to cefotaxime and ceftriaxone is also evident in up to 25% of isolates. In contrast, most strains of *N. meningitidis* are sensitive to penicillin and cephalosporins, although rare resistant isolates have been reported. Approximately 30-40% of isolates of *H. influenzae* type b produce β-lactamases and, therefore, are resistant to ampicillin. These β-lactamase–producing strains are sensitive to the extended-spectrum cephalosporins.

Based on the substantial rate of resistance of *S. pneumoniae* to β-lactam drugs, vancomycin (60 mg/kg/24 hr, given every 6 hr) is recommended as part of initial empirical therapy. Because of the efficacy of third-generation cephalosporins in the therapy of meningitis caused by sensitive *S. pneumoniae, N. meningitidis,* and *H. influenzae* type b, cefotaxime (300 mg/kg/24 hr, given every 6 hr) or ceftriaxone (100 mg/kg/24 hr administered once per day or 50 mg/kg/dose, given every 12 hr) should also be used in initial empirical therapy. Patients allergic to β-lactam antibiotics and >1 mo of age can be treated with chloramphenicol, 100 mg/kg/24 hr, given every 6 hr. Another option for patients with allergy to β-lactam antibiotics is a combination of vancomycin and rifampin. Alternatively, patients can be desensitized to the antibiotic (see Chapter 152).

If *L. monocytogenes* infection is suspected, as in young infants or those with a T-lymphocyte deficiency, ampicillin (200 mg/kg/24 hr, given every 6 hr) also should also be given because cephalosporins are inactive against *L. monocytogenes.* Intravenous trimethoprim-sulfamethoxazole is an alternative treatment for *L. monocytogenes.*

If a patient is immunocompromised and Gram-negative bacterial meningitis is suspected, initial therapy might include ceftazidime and an aminoglycoside or meropenem.

DURATION OF ANTIBIOTIC THERAPY

Therapy for uncomplicated penicillin-sensitive *S. pneumoniae* meningitis should be for 10-14 days with a third-generation cephalosporin or intravenous penicillin (400,000 units/kg/24 hr, given every 4-6 hr). If the isolate is resistant to penicillin and the third-generation cephalosporin, therapy should be completed with vancomycin. Intravenous penicillin (300,000 units/kg/24 hr) for 5-7 days is the treatment of choice for uncomplicated *N. meningitidis* meningitis. Uncomplicated *H. influenzae* type b meningitis should be treated for 7-10 days. Patients who receive intravenous or oral antibiotics before LP and who do not have an identifiable pathogen, but do have evidence of an acute bacterial infection on the basis of their CSF profile, should continue to receive therapy with ceftriaxone or cefotaxime for 7-10 days. If focal signs are present or the child does not respond to treatment, a parameningeal focus may be present and a CT or MRI scan should be performed.

A routine repeat LP is not indicated in all patients with uncomplicated meningitis caused by antibiotic-sensitive *S. pneumoniae, N. meningitidis,* or *H. influenzae* type b. Repeat examination of CSF is indicated in some neonates, in all patients with Gram-negative bacillary meningitis, or in infection caused by a β-lactam–resistant *S. pneumoniae.* The CSF should be sterile within 24-48 hr of initiation of appropriate antibiotic therapy.

Table 603-2 Clinical Conditions and Infectious Agents Associated with Aseptic Meningitis

VIRUSES
Enteroviruses (coxsackievirus, echovirus, poliovirus, enterovirus)
Arboviruses: Eastern equine, Western equine, Venezuelan equine, St. Louis encephalitis, Powassan and California encephalitis, West Nile virus, Colorado tick fever
Parechovirus
Herpes simplex (types 1, 2)
Human herpesvirus type 6
Varicella-zoster virus
Epstein-Barr virus
Parvovirus B19
Cytomegalovirus
Adenovirus
Variola (smallpox)
Measles
Mumps
Rubella
Influenza A and B
Parainfluenza
Rhinovirus
Rabies
Lymphocytic choriomeningitis
Rotaviruses
Coronaviruses
Human immunodeficiency virus type 1

BACTERIA
Mycobacterium tuberculosis (early and late)
Leptospira species (leptospirosis)
Treponema pallidum (syphilis)
Borrelia species (relapsing fever)
Borrelia burgdorferi (Lyme disease)
Nocardia species (nocardiosis)
Brucella species
Bartonella species (cat-scratch disease)
Rickettsia rickettsii (Rocky Mountain spotted fever)
Rickettsia prowazekii (typhus)
Ehrlichia canis
Coxiella burnetii
Mycoplasma pneumoniae
Mycoplasma hominis
Chlamydia trachomatis
Chlamydia psittaci
Chlamydia pneumoniae
Partially treated bacterial meningitis

BACTERIAL PARAMENINGEAL FOCUS
Sinusitis
Mastoiditis
Brain abscess
Subdural-epidural empyema
Cranial osteomyelitis

FUNGI
Coccidioides immitis (coccidioidomycosis)
Blastomyces dermatitidis (blastomycosis)
Cryptococcus neoformans (cryptococcosis)
Histoplasma capsulatum (histoplasmosis)
Candida species
Other fungi *(Alternaria, Aspergillus, Cephalosporium, Cladosporium, Drechslera hawaiiensis, Paracoccidioides brasiliensis, Petriellidium boydii, Sporotrichum schenckii, Ustilago* spp., *Zygomycetes)*

PARASITES (EOSINOPHILIC)
Angiostrongylus cantonensis
Gnathostoma spinigerum
Baylisascaris procyonis
Strongyloides stercoralis
Trichinella spiralis
Toxocara canis
Taenia solium (cysticercosis)
Paragonimus westermani
Schistosoma spp.
Fasciola spp.

PARASITES (NONEOSINOPHILIC)
Toxoplasma gondii (toxoplasmosis)
Acanthamoeba spp.
Naegleria fowleri
Malaria

POSTINFECTIOUS
Vaccines: rabies, influenza, measles, poliovirus
Demyelinating or allergic encephalitis

SYSTEMIC OR IMMUNOLOGICALLY MEDIATED
Acute Disseminated Encephalomyelitis (ADEM)
Autoimmune Encephalitis
Bacterial endocarditis
Kawasaki disease
Systemic lupus erythematosus
Vasculitis, including polyarteritis nodosa
Sjögren syndrome
Mixed connective tissue disease
Rheumatoid arthritis
Behçet syndrome
Wegener granulomatosis
Lymphomatoid granulomatosis
Granulomatous arteritis
Sarcoidosis
Familial Mediterranean fever
Vogt-Koyanagi-Harada syndrome

MALIGNANCY
Leukemia
Lymphoma
Metastatic carcinoma
Central nervous system tumor (e.g., craniopharyngioma, glioma, ependymoma, astrocytoma, medulloblastoma, teratoma)

DRUGS
Intrathecal infections (contrast media, serum, antibiotics, antineoplastic agents)
Nonsteroidal antiinflammatory agents
OKT3 monoclonal antibodies
Carbamazepine
Azathioprine
Intravenous immune globulins
Antibiotics (trimethoprim-sulfamethoxazole, sulfasalazine, ciprofloxacin, isoniazid)

MISCELLANEOUS
Heavy metal poisoning (lead, arsenic)
Foreign bodies (shunt, reservoir)
Subarachnoid hemorrhage
Postictal state
Postmigraine state
Mollaret syndrome (recurrent)
Intraventricular hemorrhage (neonate)
Familial hemophagocytic syndrome
Postneurosurgery
Dermoid–epidermoid cyst
Headache, neurologic deficits
CSF lymphocytosis (syndrome of transient headache and neurologic deficits with cerebrospinal fluid lymphocytosis [HaNDL])

Compiled from Cherry JD: Aseptic meningitis and viral meningitis. In Feigin RD, Cherry JD, editors: *Textbook of pediatric infectious diseases*, ed 4, Philadelphia, 1998, WB Saunders, p. 450; Davis LE: Aseptic and viral meningitis. In Long SS, Pickering LK, Prober CG, editors: *Principles and practice of pediatric infectious disease*, New York, 1997, Churchill Livingstone, p. 329; and Kliegman RM, Greenbaum LA, Lye PS: *Practical strategies in pediatric diagnosis therapy*, ed 2, Philadelphia, 2004, Elsevier, p. 961.

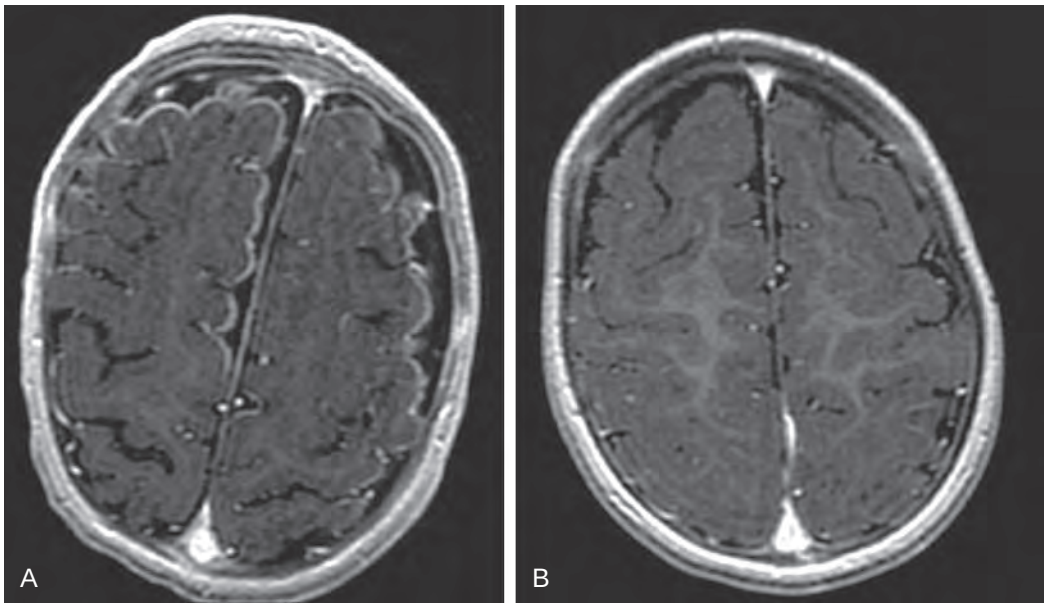


Figure 603-1 Cerebral MRI. Three-dimensional T1 sequence with fast-spoiled gradient-echo gadolinium injection. **A,** Day 11 following meningococcal infection. **B,** Day 9 following meningococcal infection. *(From Toubiana J, Heilbronner C, Gitiaux C, et al: Pachymeningitis after meningococcal infection.* Lancet *381:1596–1597, 2013.)*

Meningitis caused by *Escherichia coli* or *P. aeruginosa* requires therapy with a third-generation cephalosporin active against the isolate in vitro. Most isolates of *E. coli* are sensitive to cefotaxime or ceftriaxone, and most isolates of *P. aeruginosa* are sensitive to ceftazidime. Gram-negative bacillary meningitis should be treated for 3 wk or for at least 2 wk after CSF sterilization, which may occur after 2-10 days of treatment.

Side effects of antibiotic therapy of meningitis include phlebitis, drug fever, rash, emesis, oral candidiasis, and diarrhea. Ceftriaxone may cause reversible gallbladder pseudolithiasis, detectable by abdominal ultrasonography. This is usually asymptomatic but may be associated with emesis and upper right quadrant pain.

Corticosteroids

Rapid killing of bacteria in the CSF effectively sterilizes the meningeal infection but releases toxic cell products after cell lysis (cell wall endotoxin) that precipitate the cytokine-mediated inflammatory cascade. The resultant edema formation and neutrophilic infiltration may produce additional neurologic injury with worsening of CNS signs and symptoms. Therefore, agents that limit production of inflammatory mediators may be of benefit to patients with bacterial meningitis.

Data support the use of intravenous dexamethasone, 0.15 mg/kg/dose given every 6 hr for 2 days, in the treatment of children older than 6 wk with acute bacterial meningitis caused by *H. influenzae* type b. Among children with meningitis caused by *H. influenzae* type b, corticosteroid recipients have a shorter duration of fever, lower CSF protein and lactate levels, and a reduction in sensorineural hearing loss. Data in children regarding benefits, if any, of corticosteroids in the treatment of meningitis caused by other bacteria are inconclusive. Early steroid treatment of adults with bacterial meningitis, especially those with pneumococcal meningitis, results in improved outcome.

Corticosteroids appear to have maximum benefit if given 1-2 hr before antibiotics are initiated. They also may be effective if given concurrently with or soon after the first dose of antibiotics. Complications of corticosteroids include gastrointestinal bleeding, hypertension, hyperglycemia, leukocytosis, and rebound fever after the last dose.

Supportive Care

Repeated medical and neurologic assessments of patients with bacterial meningitis are essential to identify early signs of cardiovascular, CNS, and metabolic complications. Pulse rate, blood pressure, and respiratory rate should be monitored frequently. Neurologic assessment, including pupillary reflexes, level of consciousness, motor strength, cranial nerve signs, and evaluation for seizures, should be made frequently in the 1st 72 hr, when the risk of neurologic complications is greatest. Important laboratory studies include an assessment of blood urea nitrogen; serum sodium, chloride, potassium, and bicarbonate levels; urine output and specific gravity; complete blood and platelet counts; and, in the presence of petechiae, purpura, or abnormal bleeding, measures of coagulation function (fibrinogen, prothrombin, and partial thromboplastin times).

Patients should initially receive nothing by mouth. If a patient is judged to be normovolemic, with normal blood pressure, intravenous fluid administration should be restricted to one-half to two-thirds of maintenance, or 800-1,000 mL/m^2/24 hr, until it can be established that increased ICP or SIADH is not present. Fluid administration may be returned to normal (1,500-1,700 mL/m^2/24 hr) when serum sodium levels are normal. Fluid restriction is not appropriate in the presence of systemic hypotension because reduced blood pressure may result in reduced cerebral perfusion pressure and CNS ischemia. Therefore, shock must be treated aggressively to prevent brain and other organ dysfunction (acute tubular necrosis, acute respiratory distress syndrome). Patients with shock, a markedly elevated ICP, coma, and refractory seizures require intensive monitoring with central arterial and venous access and frequent vital signs, necessitating admission to a pediatric intensive care unit. Patients with septic shock may require fluid resuscitation and therapy with vasoactive agents such as dopamine and epinephrine. The goal of such therapy in patients with meningitis is to avoid excessive increases in ICP without compromising blood flow and oxygen delivery to vital organs.

Neurologic complications include increased ICP with subsequent herniation, seizures, and an enlarging head circumference because of a subdural effusion or hydrocephalus. Signs of increased ICP should be treated emergently with endotracheal intubation and hyperventilation (to maintain the pCO_2 at approximately 25 mm Hg). In addition, intravenous furosemide (Lasix, 1 mg/kg) and mannitol (0.5-1.0 g/kg) osmotherapy may reduce ICP (see Chapter 68). Furosemide reduces brain swelling by venodilation and diuresis without increasing intracranial blood volume, whereas mannitol produces an osmolar gradient between the brain and plasma, thus shifting fluid from the CNS to the plasma, with subsequent excretion during an osmotic diuresis. Another approach to treating reductions of cerebral perfusion pressure caused by elevations of intracranial pressure is to increase systemic blood

Table 603-3 Classification of Encephalitis by Cause and Source

I. INFECTIONS: VIRAL
- A. Spread: person to person only
  1. Mumps: frequent in an unimmunized population; often mild
  2. Measles: may have serious sequelae
  3. Enteroviruses: frequent at all ages; more serious in newborns
  4. Parechovirus
  5. Rubella: uncommon; sequelae rare except in congenital rubella
  6. Herpesvirus group
     - a. Herpes simplex (types 1 and 2, possibly 6): relatively common; sequelae frequent; devastating in newborns
     - b. Varicella-zoster virus: uncommon; serious sequelae not rare
     - c. Cytomegalovirus, congenital or acquired: may have delayed sequelae in congenital type
     - d. Epstein-Barr virus (infectious mononucleosis): not common
  7. Pox group
     - a. Vaccinia and variola: uncommon, but serious CNS damage occurs
  8. Parvovirus (erythema infectiosum): not common
  9. Influenzas A and B
  10. Adenovirus
  11. Other: reoviruses, respiratory syncytial, parainfluenza, hepatitis B
- B. Arthropod-borne agents
- C. Arboviruses: spread to humans by mosquitoes or ticks; seasonal epidemics depend on ecology of the insect vector; the following occur in the United States:

Eastern equine	California
Western equine	Powassan
Venezuelan equine	Dengue
St. Louis	Colorado tick fever
West Nile	

- D. Spread by warm-blooded mammals
  1. Rabies: saliva of many domestic and wild mammalian species
  2. Herpesvirus simiae ("B" virus): monkeys' saliva
  3. Lymphocytic choriomeningitis: rodents' excreta

II. INFECTIONS: NONVIRAL
- A. Rickettsial: in Rocky Mountain spotted fever and typhus; encephalitic component from cerebral vasculitis
- B. *Mycoplasma pneumoniae:* interval of some days between respiratory and CNS symptoms
- C. Bacterial: tuberculous and other bacterial meningitis; often has encephalitic component
- D. Spirochetal: syphilis, congenital or acquired; leptospirosis; Lyme disease
- E. Cat-scratch disease
- F. Fungal: immunologically compromised patients at special risk: cryptococcosis; histoplasmosis; aspergillosis; mucormycosis; candidosis; coccidioidomycosis
- G. Protozoal: *Plasmodium*, *Trypanosoma*, *Naegleria*, and *Acanthamoeba* spp.; Toxoplasma gondii
- H. Metazoal: trichinosis; echinococcosis; cysticercosis; schistosomiasis

III. PARAINFECTIOUS: POSTINFECTIOUS, ALLERGIC, AUTOIMMUNE

Patients in whom an infectious agent or 1 of its components plays a contributory role in etiology, but the intact infectious agent is not isolated in vitro from the nervous system; it is postulated that in this group, the influence of cell-mediated antigen–antibody complexes plus complement is especially important in producing the observed tissue damage
- A. Associated with specific diseases (these agents may also cause direct CNS damage; see I and II)
  - Measles
  - Rickettsial infections
  - Rubella
  - Influenzas A and B
  - Mumps
  - Varicella-zoster
  - M. *pneumoniae*
- B. Associated with vaccines
  - Rabies
  - Measles
  - Vaccinia
  - Yellow fever
- C. Autoimmune encephalitis
- D. Acute disseminated encephalomyelitis (ADEM)
  - Paraneoplastic
  - Idiopathic

IV. HUMAN SLOW-VIRUS DISEASES

Accumulating evidence that viruses frequently acquired earlier in life, not necessarily with detectable acute illness, participate in later chronic neurologic disease (similar events also known to occur in animals)
- A. Subacute sclerosing panencephalitis; measles; rubella?
- B. Creutzfeldt-Jakob disease (spongiform encephalopathy)
- C. Progressive multifocal leukoencephalopathy
- D. Kuru (Fore tribe in New Guinea only)
- E. Human immunodeficiency virus

V. UNKNOWN: COMPLEX GROUP

This group constitutes more than two-thirds of the cases of encephalitis reported to the Centers for Disease Control and Prevention, Atlanta, Georgia; the yearly epidemic curve of these undiagnosed cases suggests that the majority are probably caused by enteroviruses and/or arboviruses.

There is also a miscellaneous group that is based on clinical criteria: Reye syndrome is 1 current example; others include the extinct von Economo encephalitis (epidemic during 1918-1928); myoclonic encephalopathy of infancy; retinomeningoencephalitis with papilledema and retinal hemorrhage; recurrent encephalomyelitis (? allergic or autoimmune); pseudotumor cerebri; and epidemic neuromyasthenia (Iceland disease).

An encephalitic clinical pattern may follow ingestion or absorption of a number of known and unknown toxic substances; these include ingestion of lead and mercury, and percutaneous absorption of hexachlorophene as a skin disinfectant and gamma benzene hexachloride as a scabicide.

CNS, central nervous system.

Modified from Behrman RE, editor: Nelson textbook of pediatrics, ed 14, Philadelphia, 1992, WB Saunders, p. 667. From Kliegman RM, Greenbaum LA, Lye PS: Practical strategies in pediatric diagnosis and therapy, ed 2, Philadelphia, 2004, Elsevier, p. 967.

pressure using fluids (normal saline) and vasopressor agents (dopamine, norepinephrine). This method reduces the risk of systemic hypotension and may improve survival and reduce disability.

Seizures are common during the course of bacterial meningitis. Immediate therapy for seizures includes intravenous diazepam (0.1-0.2 mg/kg/dose) or lorazepam (0.05-0.10 mg/kg/dose), and careful attention paid to the risk of respiratory suppression. Serum glucose, calcium, and sodium levels should be monitored. After immediate management of seizures, patients should receive phenytoin (15-20 mg/kg loading dose, 5 mg/kg/24 hr maintenance) to reduce the likelihood of recurrence. Phenytoin is preferred to phenobarbital because it produces less CNS depression and permits assessment of a patient's level of consciousness. Serum phenytoin levels should be monitored to maintain them in the therapeutic range (10-20 μg/mL).

COMPLICATIONS

During the treatment of meningitis, acute CNS complications can include seizures, increased ICP, cranial nerve palsies, stroke,

Table 603-4 Antibiotics Used for the Treatment of Bacterial Meningitis*

DRUGS	Neonates		INFANTS AND CHILDREN
	0-7 DAYS	8-28 DAYS	
Amikacin†‡	15-20 divided q12h	30 divided q8h	20-30 divided q8h
Ampicillin	150 divided q8h	200 divided q6h or q8h	300 divided q6h
Cefotaxime	100-150 divided q8h or q12h	150-200 divided q6h or q8h	225-300 divided q6h or q8h
Ceftriaxone§	—	—	100 divided q12h or q24h
Ceftazidime	100-150 divided q8h or q12h	150 divided q8h	150 divided q8h
Gentamicin†‡	5 divided q12h	7.5 divided q8h	7.5 divided q8h
Meropenem	—	—	120 divided q8h
Nafcillin	75 divided q8h or q12h	100-150 divided q6h or q8h	200 divided q6h
Penicillin G	150,000 divided q8h or q12h	200,000 divided q6h or q8h	300,000 divided q4h or q6h
Rifampin	—	10-20 divided q12h	10-20 divided q12h or q24h
Tobramycin†‡	5 divided q12h	7.5 divided q8h	7.5 divided q8h
Vancomycin†‡	20-30 divided q8h or q12h	30-45 divided q6h or q8h	60 divided q6h

*Dosages in mg/kg (units/kg for penicillin G) per day.
†Smaller doses and longer dosing intervals, especially for aminoglycosides and vancomycin for very-low-birthweight neonates, may be advisable.
‡Monitoring of serum levels is recommended to ensure safe and therapeutic values.
§Use in neonates is not recommended because of inadequate experience in neonatal meningitis.
Adapted from Tunkel AR, Hartman BJ, Kaplan SL, et al: Practice guidelines for the management of bacterial meningitis. *Clin Infect Dis* 39(9):1267–1284, 2004, Table 6.

cerebral or cerebellar herniation, and thrombosis of the dural venous sinuses.

Collections of fluid in the subdural space develop in 10-30% of patients with meningitis and are asymptomatic in 85-90% of patients. **Subdural effusions** are especially common in infants. Symptomatic subdural effusions may result in a bulging fontanel, diastasis of sutures, enlarging head circumference, emesis, seizures, fever, and abnormal results of cranial transillumination. CT or MRI scanning confirms the presence of a subdural effusion. In the presence of increased ICP or a depressed level of consciousness, symptomatic subdural effusion should be treated by aspiration through the open fontanel (see Chapters 68 and 590). Fever alone is not an indication for aspiration.

SIADH occurs in some patients with meningitis, resulting in hyponatremia and reduced serum osmolality. This may exacerbate cerebral edema or result in hyponatremic seizures (see Chapter 55).

Fever associated with bacterial meningitis usually resolves within 5-7 days of the onset of therapy. **Prolonged fever** (>10 days) is noted in approximately 10% of patients. Prolonged fever is usually caused by intercurrent viral infection, nosocomial or secondary bacterial infection, thrombophlebitis, or drug reaction. Secondary fever refers to the recrudescence of elevated temperature after an afebrile interval. Nosocomial infections are especially important to consider in the evaluation of these patients. Pericarditis or arthritis may occur in patients being treated for meningitis, especially that caused by *N. meningitidis*. Involvement of these sites may result either from bacterial dissemination or from immune complex deposition. In general, infectious pericarditis or arthritis occurs earlier in the course of treatment than does immune-mediated disease.

Thrombocytosis, eosinophilia, and anemia may develop during therapy for meningitis. Anemia may be a result of hemolysis or bone marrow suppression. Disseminated intravascular coagulation is most often associated with the rapidly progressive pattern of presentation and is noted most commonly in patients with shock and purpura. The combination of endotoxemia and severe hypotension initiates the coagulation cascade; the coexistence of ongoing thrombosis may produce symmetric peripheral gangrene.

PROGNOSIS

Appropriate antibiotic therapy and supportive care have reduced the mortality of bacterial meningitis after the neonatal period to <10%. The highest mortality rates are observed with pneumococcal meningitis. Severe neurodevelopmental sequelae may occur in 10-20% of patients recovering from bacterial meningitis, and as many as 50% have some, albeit subtle, neurobehavioral morbidity. The prognosis is poorest among infants younger than 6 mo and in those with high concentrations of bacteria/bacterial products in their CSF. Those with seizures occurring more than 4 days into therapy or with coma or focal neurologic signs on presentation have an increased risk of long-term sequelae. There does not appear to be a correlation between duration of symptoms before diagnosis of meningitis and outcome.

The most common neurologic sequelae include hearing loss, cognitive impairment, recurrent seizures, delay in acquisition of language, visual impairment, and behavioral problems. **Sensorineural hearing** loss is the most common sequela of bacterial meningitis and, usually, is already present at the time of initial presentation. It is a result of cochlear infection and occurs in as many as 30% of patients with pneumococcal meningitis, 10% with meningococcal, and 5-20% of those with *H. influenzae* type b meningitis. Hearing loss may also be caused by direct inflammation of the auditory nerve. All patients with bacterial meningitis should undergo careful audiologic assessment before or soon after discharge from the hospital. Frequent reassessment on an outpatient basis is indicated for patients who have a hearing deficit.

PREVENTION

Vaccination and antibiotic prophylaxis of susceptible at-risk contacts represent the 2 available means of reducing the likelihood of bacterial meningitis. The availability and application of each of these approaches depend on the specific infecting bacteria.

Neisseria meningitidis

Chemoprophylaxis is recommended for all close contacts of patients with meningococcal meningitis regardless of age or immunization status. Close contacts should be treated with rifampin 10 mg/kg/dose every 12 hr (maximum dose of 600 mg) for 2 days as soon as possible after identification of a case of suspected meningococcal meningitis or sepsis. Close contacts include household, daycare center, and nursery school contacts, and healthcare workers who have direct exposure to oral secretions (mouth-to-mouth resuscitation, suctioning, intubation). Exposed contacts should be treated immediately on suspicion of

infection in the index patient; bacteriologic confirmation of infection should not be awaited. In addition, all contacts should be educated about the early signs of meningococcal disease and the need to seek prompt medical attention if these signs develop.

Two quadrivalent (A, C, Y, W-135), conjugated vaccines (MCV-4; Menactra and Menveo) are licensed by the FDA. The Advisory Committee on Immunization Practices (ACIP) to the CDC recommends routine administration of this vaccine to 11-12 yr old adolescents. Menactra is licensed for use in infants older than 9 mo of age, and Menveo for use in children older than 2 yr of age. There is also a bivalent meningococcal polysaccharide protein conjugate vaccine that provides protection against serogroups C and Y along with *H. influenzae* type b. This vaccine is licensed for use in children ages 6 wk through 18 mo. High-risk patients include those with anatomic or functional asplenia or deficiencies of terminal complement proteins. Use of meningococcal vaccine should be considered for college freshmen, especially those who live in dormitories, because of an observed increased risk of invasive meningococcal infections compared to the risk in non–college-attending, age-matched controls.

Haemophilus influenzae Type B

Rifampin prophylaxis should be given to all household contacts of patients with invasive disease caused by *H. influenzae* type b, if any close family member younger than 48 mo has not been fully immunized or if an immunocompromised person, of any age, resides in the household. A household contact is one who lives in the residence of the index case or who has spent a minimum of 4 hr with the index case for at least 5 of the 7 days preceding the patient's hospitalization. Family members should receive rifampin prophylaxis immediately after the diagnosis is suspected in the index case because >50% of secondary family cases occur in the 1st wk after the index patient has been hospitalized.

The dose of rifampin is 20 mg/kg/24 hr (maximum dose of 600 mg) given once each day for 4 days. Rifampin colors the urine and perspiration red-orange, stains contact lenses, and reduces the serum concentrations of some drugs, including oral contraceptives. Rifampin is contraindicated during pregnancy.

The most striking advance in the prevention of childhood bacterial meningitis followed the development and licensure of conjugated vaccines against *H. influenzae* type b. Three conjugate vaccines are licensed in the United States. Although each vaccine elicits different profiles of antibody response in infants immunized at 2-6 mo of age, all result in protective levels of antibody with an efficacy rate against invasive infections after primary series at 93%. Efficacy is not as consistent in Native American populations, a group recognized as having an especially high incidence of disease. All children should be immunized with *H. influenzae* type b conjugate vaccine beginning at 2 mo of age (see Chapter 172).

Streptococcus pneumoniae

Routine administration of conjugate vaccine against *S. pneumoniae* is recommended for children younger than 5 yr of age. The initial dose is given at about 2 mo of age. Children who are at high risk of invasive pneumococcal infections, including those with functional or anatomic asplenia and those with underlying immunodeficiency (such as infection with HIV, primary immunodeficiency, and those receiving immunosuppressive therapy) should also receive the vaccine.

Bibliography is available at Expert Consult.

603.2 Viral Meningoencephalitis

Charles G. Prober and Nivedita S. Srinivas

Viral meningoencephalitis is an acute inflammatory process involving the meninges and, to a variable degree, brain tissue. These infections are relatively common and may be caused by a number of different agents. The CSF is characterized by pleocytosis and the absence of microorganisms on Gram stain and routine bacterial culture. In most instances, the infections are self-limited. In some cases, substantial morbidity and mortality occur.

ETIOLOGY

Enteroviruses are the most common cause of viral meningoencephalitis. As of 2014, more than 70 serotypes of these small RNA viruses have been identified. The severity of infection caused by enteroviruses ranges from mild, self-limited illness with primarily meningeal involvement to severe encephalitis resulting in death or significant sequelae. Human enterovirus 68 has been associated with neurologic symptoms including flaccid paralysis. **Parechoviruses** may be an important cause of aseptic meningitis or encephalitis in infants. The clinical manifestations are similar to that of the enteroviruses with the exception of more severe MRI lesions of the cerebral cortex and at times an absence of a CSF pleocytosis.

Arboviruses are arthropod-borne agents, responsible for some cases of meningoencephalitis during summer months. Mosquitoes and ticks are the most common vectors, spreading disease to humans and other vertebrates, such as horses, after biting infected birds or small animals. Encephalitis in horses ("blind staggers") may be the first indication of an incipient epidemic. Although rural exposure is most common, urban and suburban outbreaks also are frequent. The most common arboviruses responsible for CNS infection in the United States are West Nile virus (WNV), La Crosse, Powassan, and St. Louis encephalitis viruses (see Chapter 267). WNV made its appearance in the Western hemisphere in 1999. It has gradually made its way from the east to the west coast over successive summers. Cumulatively, from 1999 through 2008, a total of 47 states reported roughly 30,000 human infections caused by WNV. WNV may also be transmitted by blood transfusion, organ transplantation, or vertically across the placenta. Most children with WNV are either asymptomatic or have a nonspecific viral-like illness. Approximately 1% develop CNS disease; adults are more severely affected than children.

Several members of the **herpes family** of viruses can cause meningoencephalitis. Herpes simplex virus (HSV) type 1 is an important cause of severe, sporadic encephalitis in children and adults. Brain involvement usually is focal; progression to coma and death occurs in 70% of cases without antiviral therapy. Severe encephalitis with diffuse brain involvement is caused by HSV type 2 in neonates who usually contract the virus from their mothers at delivery. A mild transient form of meningoencephalitis may accompany genital herpes infection in sexually active adolescents; most of these infections are caused by HSV type 2. Varicella-zoster virus may cause CNS infection in close temporal relationship with chickenpox. The most common manifestation of CNS involvement is cerebellar ataxia, and the most severe is acute encephalitis. After primary infection, varicella-zoster virus becomes latent in spinal and cranial nerve roots and ganglia, expressing itself later as herpes zoster, sometimes with accompanying mild meningoencephalitis. Cytomegalovirus infection of the CNS may be part of congenital infection or disseminated disease in immunocompromised hosts, but it does not cause meningoencephalitis in normal infants and children. Epstein-Barr virus is associated with myriad CNS syndromes (see Chapter 254). Human herpes virus 6 can cause encephalitis, especially among immunocompromised hosts.

Mumps is a common pathogen in regions where mumps vaccine is not widely used. Mumps meningoencephalitis is mild, but deafness from damage of the 8th cranial nerve may be a sequela. Meningoencephalitis is caused occasionally by respiratory viruses (adenovirus, influenza virus, parainfluenza virus), rubeola, rubella, or rabies; it may follow live virus vaccinations against polio, measles, mumps, or rubella.

EPIDEMIOLOGY

The epidemiologic pattern of viral meningoencephalitis is primarily determined by the prevalence of enteroviruses, the most common etiology. Infection with enteroviruses is spread directly from person

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to person, with a usual incubation period of 4-6 days. Most cases in temperate climates occur in the summer and fall. Epidemiologic considerations in aseptic meningitis due to agents other than enteroviruses also include season, geography (travel), climatic conditions, animal exposures, mosquito or tick bites, and factors related to the specific pathogen.

PATHOGENESIS AND PATHOLOGY

Neurologic damage is caused by direct invasion and destruction of neural tissues by actively multiplying viruses or by a host reaction to viral antigens. Tissue sections of the brain generally are characterized by meningeal congestion and mononuclear infiltration, perivascular cuffs of lymphocytes and plasma cells, some perivascular tissue necrosis with myelin breakdown, and neuronal disruption in various stages, including, ultimately, neuronophagia and endothelial proliferation or necrosis. A marked degree of demyelination with preservation of neurons and their axons is considered to represent predominantly "postinfectious" or an autoimmune encephalitis.

The cerebral cortex, especially the temporal lobe, is often severely affected by HSV; the arboviruses tend to affect the entire brain; rabies has a predilection for the basal structures. Involvement of the spinal cord, nerve roots, and peripheral nerves is variable.

CLINICAL MANIFESTATIONS

The progression and severity of disease are determined by the relative degree of meningeal and parenchymal involvement, which, in part, is determined by the specific etiology. The clinical course resulting from infection with the same pathogen varies widely. Some children may appear to be mildly affected initially, only to lapse into coma and die suddenly. In others, the illness may be ushered in by high fever, violent convulsions interspersed with bizarre movements, and hallucinations alternating with brief periods of clarity, followed by complete recovery.

The onset of illness is generally acute, although CNS signs and symptoms are often preceded by a nonspecific febrile illness of a few days' duration. The presenting manifestations in older children are headache and hyperesthesia, and in infants, irritability and lethargy. Headache is most often frontal or generalized; adolescents frequently complain of retrobulbar pain. Fever, nausea and vomiting, photophobia, and pain in the neck, back, and legs are common. As body temperature increases, there may be mental dullness, progressing to stupor in combination with bizarre movements and convulsions. Focal neurologic signs may be stationary, progressive, or fluctuating. WNV and nonpolio enteroviruses may cause anterior horn cell injury and a flaccid paralysis. For those reported with WNV, encephalitis is more common than aseptic meningitis; acute flaccid paralysis may be noted in approximately 5% of patients. Nonetheless, many patients have a nonspecific febrile illness "West Nile fever" and may never seek medical attention. Loss of bowel and bladder control and unprovoked emotional outbursts may occur.

Exanthems often precede or accompany the CNS signs, especially with echoviruses, coxsackieviruses, varicella-zoster virus, measles, rubella, and, occasionally, WNV. Examination often reveals nuchal rigidity without significant localizing neurologic changes, at least at the onset.

Specific forms or complicating manifestations of CNS viral infection include Guillain-Barré syndrome, transverse myelitis, hemiplegia, and cerebellar ataxia.

DIAGNOSIS

The diagnosis of viral encephalitis is usually made on the basis of the clinical presentation of nonspecific prodrome followed by progressive CNS symptoms. The diagnosis is supported by examination of the CSF, which usually shows a mild mononuclear predominance (see Table 603-1). Other tests of potential value in the evaluation of patients with suspected viral meningoencephalitis include an electroencephalogram (EEG) and neuroimaging studies. The EEG typically shows diffuse slow-wave activity, usually without focal changes. Neuroimaging studies (CT or MRI) may show swelling of the brain parenchyma. Focal seizures or focal findings on EEG, CT, or MRI, especially involving the temporal lobes, suggest HSV encephalitis.

Differential Diagnosis

A number of clinical conditions that cause CNS inflammation mimic viral meningoencephalitis (see Table 603-2). The most important group of alternative infectious agents to consider is bacteria. Most children with acute bacterial meningitis appear more critically ill than those with CNS viral infection. Parameningeal bacterial infections, such as brain abscess or subdural or epidural empyema, may have features similar to viral CNS infections. Infections caused by *M. tuberculosis, T. pallidum* (syphilis), *B. burgdorferi* (Lyme disease), and *Bartonella henselae,* the bacillus associated with cat scratch disease, tend to result in indolent courses. Analysis of CSF and appropriate serologic tests are necessary to differentiate these various pathogens.

Infections caused by fungi, rickettsiae, mycoplasma, protozoa, and other parasites may also need to be included in the differential diagnosis. Consideration of these agents usually arises as a result of accompanying symptoms, geographic locality of infection, or host immune factors.

Various noninfectious disorders may be associated with CNS inflammation and have manifestations overlapping with those associated with viral meningoencephalitis. Some of these disorders include malignancy, autoimmune diseases, intracranial hemorrhage, and exposure to certain drugs or toxins. Attention to history and other organ involvement usually allow elimination of these diagnostic possibilities. Autoimmune encephalitis owing to anti–*N*-methyl-D-aspartate receptor antibodies is an important cause of noninfectious encephalitis in children. Detection of these antibodies in the serum or CSF confirms this diagnosis. Acute disseminated encephalomyelitis may also initially be confused with encephalitis.

Laboratory Findings

The CSF contains from a few to several thousand cells per cubic millimeter. Early in the disease, the cells are often polymorphonuclear; later, mononuclear cells predominate. This change in cellular type is often demonstrated in CSF samples obtained as little as 8-12 hr apart. The protein concentration in CSF tends to be normal or slightly elevated, but concentrations may be very high if brain destruction is extensive, such as that accompanying HSV encephalitis. The glucose level is usually normal, although with certain viruses, for example, mumps, a substantial depression of CSF glucose concentrations may be observed. The CSF may be normal with parechovirus and in those who have encephalitis in the absence of meningeal involvement.

The success of isolating viruses from the CSF of children with viral meningoencephalitis is determined by the time in the clinical course that the specimen is obtained, the specific etiologic agent, whether the infection is a meningitic as opposed to a localized encephalitic process, and the skill of the diagnostic laboratory staff. Isolating a virus is most likely early in the illness, and the enteroviruses tend to be the easiest to isolate, although recovery of these agents from the CSF rarely exceeds 70%. To increase the likelihood of identifying the putative viral pathogen, specimens for culture should also be obtained from nasopharyngeal swabs, feces, and urine. Although isolating a virus from 1 or more of these sites does not prove causality, it is highly suggestive. *Detection of viral DNA or RNA by polymerase chain reaction is the test of choice in the diagnosis of CNS infection caused by HSV, parechovirus and enteroviruses, respectively.* CSF serology is the diagnostic test of choice for WNV.

A serum specimen should be obtained early in the course of illness and, if viral cultures are not diagnostic, again 2-3 wk later for serologic studies. Serologic methods are not practical for diagnosing CNS infections caused by the enteroviruses because there are too many serotypes. This approach may be useful, however, in confirming that a case is caused by a known circulating serotype. Serologic tests may also be of value in determining the etiology of nonenteroviral CNS infection, such as arboviral infection.

TREATMENT

With the exception of the use of acyclovir for HSV encephalitis (see Chapter 252), treatment of viral meningoencephalitis is supportive. Treatment of mild disease may require only symptomatic relief. Headache and hyperesthesia are treated with rest, non–aspirin-containing analgesics, and a reduction in room light, noise, and visitors. Acetaminophen is recommended for fever. Opioid agents and medications to reduce nausea may be useful, but if possible, their use in children should be minimized because they may induce misleading signs and symptoms. Intravenous fluids are occasionally necessary because of poor oral intake. More-severe disease may require hospitalization and intensive care.

It is important to monitor patients with severe encephalitis closely for convulsions, cerebral edema, inadequate respiratory exchange, disturbed fluid and electrolyte balance, aspiration and asphyxia, and cardiac or respiratory arrest of central origin. In patients with evidence of increased ICP, placement of a pressure transducer in the epidural space may be indicated. The risks of cardiac and respiratory failure or arrest are high with severe disease. All fluids, electrolytes, and medications are initially given parenterally. In prolonged states of coma, parenteral alimentation is indicated. SIADH is common in acute CNS disorders; monitoring of serum sodium concentrations is required for early detection (see Chapter 559). Normal blood levels of glucose, magnesium, and calcium must be maintained to minimize the likelihood of convulsions. If cerebral edema or seizures become evident, vigorous treatment should be instituted.

PROGNOSIS

Supportive and rehabilitative efforts are very important after patients recover from the acute phase of illness. Motor incoordination, convulsive disorders, total or partial deafness, and behavioral disturbances may follow viral CNS infections. Visual disturbances from chorioretinopathy and perceptual amblyopia may also occur. Special facilities and, at times, institutional placement may become necessary. Some sequelae of infection may be very subtle. Therefore, neurodevelopmental and audiologic evaluations should be part of the routine follow-up of children who have recovered from viral meningoencephalitis.

Most children completely recover from viral infections of the CNS, although the prognosis depends on the severity of the clinical illness, the specific causative organism, and the age of the child. If the clinical illness is severe and substantial parenchymal involvement is evident, the prognosis is poor, with potential deficits being intellectual, motor, psychiatric, epileptic, visual, or auditory in nature. Severe sequelae should also be anticipated in those with infection caused by HSV. Although some literature suggests that infants who contract viral meningoencephalitis have a poorer long-term outcome than older children, most other data refute this observation. Approximately 10% of children younger than 2 yr of age with enteroviral CNS infections suffer an acute complication such as seizures, increased ICP, or coma. Almost all have favorable long-term neurologic outcomes.

PREVENTION

Widespread use of effective viral vaccines for polio, measles, mumps, rubella, and varicella has almost eliminated CNS complications from these diseases in the United States. The availability of domestic animal vaccine programs against rabies has reduced the frequency of rabies encephalitis. Control of encephalitis caused by arboviruses has been less successful because specific vaccines for the arboviral diseases that occur in North America are not available. Control of insect vectors by suitable spraying methods and eradication of insect breeding sites, however, reduces the incidence of these infections. Furthermore, minimizing mosquito bites through the application of *N,N*-diethyl-3-methylbenzamide (DEET)-containing insect repellents on exposed skin and wearing long-sleeved shirts, long pants, and socks when outdoors, especially at dawn and dusk, reduces the risk of arboviral infection.

Bibliography is available at Expert Consult.

603.3 Eosinophilic Meningitis

Charles G. Prober and Nivedita S. Srinivas

Eosinophilic meningitis is defined as 10 or more eosinophils/mm^3 of CSF. The most common cause worldwide of eosinophilic pleocytosis is CNS infection with helminthic parasites. In countries such as the United States, where helminthic infestation is uncommon, however, the differential diagnosis of CSF eosinophilic pleocytosis is broad.

ETIOLOGY

Although any tissue-migrating helminth may cause eosinophilic meningitis, the most common cause is human infection with the rat lungworm, *Angiostrongylus cantonensis* (see Chapter 297). Other parasites that can cause eosinophilic meningitis include *Gnathostoma spinigerum* (dog and cat roundworm) (see Chapter 297), *Baylisascaris procyonis* (raccoon roundworm), *Ascaris lumbricoides* (human roundworm), *Trichinella spiralis, Toxocara canis, T. gondii, Paragonimus westermani, Echinococcus granulosus, Schistosoma japonicum, Onchocerca volvulus,* and *Taenia solium.* Eosinophilic meningitis may also occur as an unusual manifestation of more common viral, bacterial, or fungal infections of the CNS. Noninfectious causes of eosinophilic meningitis include multiple sclerosis, malignancy, hypereosinophilic syndrome, or a reaction to medications or a ventriculoperitoneal shunt.

EPIDEMIOLOGY

A. cantonensis is found in Southeast Asia, the South Pacific, Japan, Taiwan, Egypt, Ivory Coast, and Cuba. Infection is acquired by eating raw or undercooked freshwater snails, slugs, prawns, or crabs containing infectious 3rd-stage larvae. *Gnathostoma* infections are found in Japan, China, India, Bangladesh, and Southeast Asia. Gnathostomiasis is acquired by eating undercooked or raw fish, frog, bird, or snake meat.

CLINICAL MANIFESTATIONS

When eosinophilic meningitis results from helminthic infestation, patients become ill 1-3 wk after exposure. This reflects the transit time for parasites to migrate from the gastrointestinal tract to the CNS. Common concomitant findings include fever, peripheral eosinophilia, vomiting, abdominal pain, creeping skin eruptions, or pleurisy. Neurologic symptoms may include headache, meningismus, ataxia, cranial nerve palsies, and paresthesias. Paraparesis or incontinence can result from radiculitis or myelitis.

DIAGNOSIS

The presumptive diagnosis of helminth-induced eosinophilic meningitis is most often based on travel and exposure history in the presence of typical clinical and laboratory findings. Direct visualization of helminths in CSF is affected by the relatively low organism burden, resulting in limited diagnostic sensitivity. Serologic assays for helminthic infections are also of limited utility because they are not readily available commercially and there is substantial cross-reactivity between different helminth species.

TREATMENT

Treatment is supportive, because infection is self-limited and anthelmintic drugs do not appear to influence the outcome of infection. Analgesics should be given for headache and radiculitis, and CSF removal or shunting should be performed to relieve hydrocephalus, if present. Steroids may decrease the duration of headaches in adults with eosinophilic meningitis.

PROGNOSIS

The prognosis is good; 70% of patients improve sufficiently to leave the hospital in 1-2 wk. Mortality associated with eosinophilic meningitis is <1%.

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Chapter 604

Brain Abscess

Charles G. Prober and Roshni Mathew

Brain abscesses can occur in children of any age but are most common in children between 4 and 8 yr old and in neonates. The causes of brain abscess include embolization as a result of congenital heart disease with right-to-left shunts (especially tetralogy of Fallot), endocarditis, meningitis, chronic otitis media and mastoiditis, sinusitis, soft-tissue infection of the face or scalp, orbital cellulitis, dental infections, severe complicated pneumonia, penetrating head injuries, immunodeficiency states, and infection of ventriculoperitoneal shunts.

PATHOLOGY

Cerebral abscesses are evenly distributed between the 2 hemispheres, and 80% of cases are divided equally between the frontal, parietal, and temporal lobes. Brain abscesses in the occipital lobe, cerebellum, and brainstem account for approximately 20% of the cases. Most brain abscesses are single, but 30% are multiple and may involve more than 1 lobe. The pathogenesis is undetermined in 10-15% of cases. An abscess in the frontal lobe is often caused by extension from sinusitis or orbital cellulitis, whereas abscesses located in the temporal lobe or cerebellum are frequently associated with chronic otitis media and mastoiditis. Abscesses resulting from penetrating injuries tend to be singular and caused by *Staphylococcus aureus,* whereas those resulting from septic emboli, congenital heart disease, or meningitis often have several causal organisms.



Figure 604-1 CT with contrast. Note the large, wall-enhancing abscess in the left frontal lobe causing a shift of the brain to the right. The patient had no neurologic signs until just before the CT scan because the abscess is located in the frontal lobe, a "silent" area of the brain.

ETIOLOGY

The predominant organisms causing brain abscesses in children are aerobic and anaerobic streptococci (60-70% of the cases) with *Streptococcus milleri* gp (*Streptococcus anginosus, Streptococcus constellatus,* and *Streptococcus intermedius*) being increasingly isolated from surgically drained brain abscesses. Other important streptococci include group A and *B streptococci*, *Streptococcus pneumoniae,* and *Enterococcus faecalis.* Other bacteria isolated from brain abscesses include anaerobic organisms (Gram-positive cocci, *Bacteroides* spp., *Fusobacterium* spp., *Prevotella* spp., *Actinomyces* spp.) and Gram-negative aerobic bacilli (*Haemophilus aphrophilus, Haemophilus parainfluenzae, Haemophilus influenzae, Enterobacter, Escherichia coli, Proteus* spp.). *Citrobacter* is most common in neonates. One organism is cultured in 70% of abscesses, 2 in 20%, and 3 or more in 10% of cases. Abscesses associated with mucosal infections (sinusitis) frequently have anaerobic bacteria. Fungi *(Aspergillus, Candida)*, *Nocardia, Mycobacterium*, and *Listeria* spp. are more common in children with impaired host defenses.

CLINICAL MANIFESTATIONS

The early stages of cerebritis and abscess formation are associated with nonspecific symptoms, including low-grade fever, headache, and lethargy. The significance of these symptoms is generally not recognized, and an oral antibiotic is often prescribed with resultant transient relief. As the inflammatory process proceeds, vomiting, severe headache, seizures, papilledema, focal neurologic signs (hemiparesis), and coma may develop. A cerebellar abscess is characterized by nystagmus, ipsilateral ataxia and dysmetria, vomiting, and headache. If the abscess ruptures into the ventricular cavity, overwhelming shock and death usually ensue.

DIAGNOSIS

The peripheral white blood cell count can be normal or elevated, and the blood culture is positive in 10% of cases. Examination of the cerebrospinal fluid shows variable results; the white blood cells and protein may be minimally elevated or normal, and the glucose level may be low. Cerebrospinal fluid cultures are rarely positive; culture of pus from the neurosurgical drainage is the key to establishing a bacteriologic diagnosis. However, the culture can be sterile in a substantial number of cases and 16S bacterial ribosomal RNA polymerase chain reaction amplification and sequencing may be used to identify unculturable bacteria in brain abscesses. Because examination of the cerebrospinal fluid is seldom useful and a lumbar puncture may cause herniation of the cerebellar tonsils, the procedure should not be undertaken in a child suspected of having a brain abscess. The electroencephalogram shows corresponding focal slowing, and the radionuclide brain scan indicates an area of enhancement caused by disruption of the blood–brain barrier in more than 80% of cases. CT with contrast and MRI are the most reliable methods of demonstrating cerebritis and abscess formation (Fig. 604-1). MRI is the diagnostic test of choice. The CT findings of cerebritis are characterized by a parenchymal low-density lesion, and MRI T2-weighted images indicate increased signal intensity. An abscess cavity shows a ring-enhancing lesion by contrast CT, and the MRI also demonstrates an abscess capsule with gadolinium administration.

TREATMENT

The initial management of a brain abscess includes prompt diagnosis and institution of an antibiotic regimen that is based on the probable pathogenesis and the most likely organism. When the cause is unknown, the combination of vancomycin, a third-generation cephalosporin, and metronidazole is commonly used. The same regimen is initiated when otitis media, sinusitis, or mastoiditis is the likely cause. If there is a history of penetrating head injury, head trauma, or neurosurgery, vancomycin plus a third-generation cephalosporin is appropriate. When cyanotic congenital heart disease is the predisposing factor, ampicillin-sulbactam alone or a third-generation cephalosporin plus metronidazole may be used. Meropenem has good activity against Gram-negative bacilli, anaerobes, staphylococci, and streptococci,

including most antibiotic-resistant pneumococci, and may be used alone to replace the combination of metronidazole and a β-lactam in the previous regimens. Notably, meropenem does not provide activity against methicillin-resistant *S. aureus* and may have decreased activity against penicillin-resistant strains of *S. pneumoniae,* indicating that vancomycin should remain a part of the initial regimen when these organisms are suspected. Abscesses secondary to an infected ventriculoperitoneal shunt may be initially treated with vancomycin and ceftazidime. When *Citrobacter* meningitis (often in neonates) leads to abscess formation, a third-generation cephalosporin is used, typically in combination with an aminoglycoside. *Listeria monocytogenes* may cause a brain abscess in the neonate and if suspected, ampicillin should be added to the cephalosporin. In immunocompromised patients, broad-spectrum antibiotic coverage is used, and amphotericin B therapy should be considered.

A brain abscess can be treated with antibiotics without surgery if the abscess is <2 cm in diameter, the illness is of short duration (<2 wk), there are no signs of increased intracranial pressure, and the child is neurologically intact. If the decision is made to treat with antibiotics alone, the child should have follow-up neuroimaging studies to ensure the abscess is decreasing in size. An encapsulated abscess, particularly if the lesion is causing a mass effect or increased intracranial pressure, should be treated with a combination of antibiotics and aspiration. Surgical excision of an abscess is rarely required, because the procedure may be associated with greater morbidity compared with aspiration of a cavity. Surgery is indicated when the abscess is >2.5 cm in diameter, gas is present in the abscess, the lesion is multiloculated, the lesion is located in the posterior fossa, or a fungus is identified. Associated infectious processes, such as mastoiditis, sinusitis, or a periorbital abscess, may require surgical drainage. The duration of antibiotic therapy depends on the organism and response to treatment but is usually 4-6 wk.

PROGNOSIS

Mortality rates prior to 1980s ranged from 11-53%. More recent mortality rates accompanying wider use of CT and MRI, improved microbiologic techniques and prompt antibiotic and surgical management, range from 5-10%. Factors associated with high mortality rate at the time of admission include age younger than 1 yr, multiple abscesses and coma. Long-term sequelae occur in about one-third of the survivors and include hemiparesis, seizures, hydrocephalus, cranial nerve abnormalities, and behavior and learning problems.

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Chapter 605

Idiopathic Intracranial Hypertension/ Pseudotumor Cerebri

Misha L. Pless

Idiopathic intracranial hypertension, also known as pseudotumor cerebri, is a clinical syndrome that mimics brain tumors and is characterized by increased intracranial pressure ≥280 mm Hg in sedated or obese children; ≥250 mm Hg in nonobese, nonsedated children with a normal cerebrospinal fluid (CSF) cell count and protein content and normal to slightly decreased ventricular size, and normal ventricular anatomy and position documented by MRI. Papilledema is universally present in children old enough to have a closed fontanel (Fig. 605-1).

ETIOLOGY

Table 605-1 lists the many causes of pseudotumor cerebri. There are many explanations for the development of pseudotumor cerebri, including alterations in CSF absorption and production, subtle cerebral edema, abnormalities in vasomotor control and cerebral blood flow, and venous obstruction. The causes of pseudotumor are numerous and include metabolic disorders (galactosemia, hypoparathyroidism, pseudohypoparathyroidism, hypophosphatasia, prolonged corticosteroid therapy or rapid corticosteroid withdrawal, possibly growth hormone treatment, refeeding of a significantly malnourished child, hypervitaminosis A, severe vitamin A deficiency, Addison disease, obesity, menarche, oral contraceptives, and pregnancy), infections (roseola infantum, sinusitis, chronic otitis media and mastoiditis, Guillain-Barré syndrome), drugs (nalidixic acid, doxycycline, minocycline, tetracycline, nitrofurantoin, isotretinoin used for acne therapy especially when combined with tetracycline), hematologic disorders (polycythemia, hemolytic and iron-deficiency anemias [see Fig. 605-1],

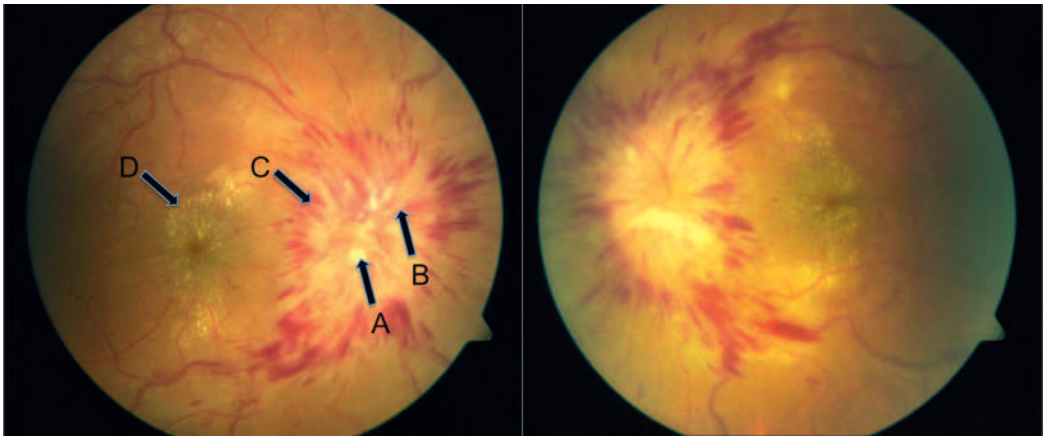


Figure 605-1 Optic nerve photos of the right and left eyes, respectively, demonstrating grade 5 optic nerve head edema with characteristics, including **(A)** total obscuration of the optic cup; **(B)** total obscuration of a segment of a major blood vessel; **(C)** total obscuration of disc margin; and **(D)** macular star. *(From Vickers AL, El-Dairi MA: Subacute vision loss in young, obese female.* J Pediatr *163:1518–1519, 2013, Fig. 1.)*

Table 605-1 Etiology of Childhood Pseudotumor Cerebri

HEMATOLOGIC	**NUTRITIONAL**
Wiskott-Aldrich syndrome	Hypovitaminosis A
Iron-deficiency anemia	Vitamin A intoxication
Aplastic anemia	Hyperalimentation in malnourished patient
Sickle cell disease	Vitamin D–dependent rickets
Polycythemia?	
Bone marrow transplantation and associated treatments?	**CONNECTIVE TISSUE DISORDERS**
Prothrombotic states	Antiphospholipid antibody syndrome
Fanconi anemia	Systemic lupus erythematosus?
	Behçet disease
INFECTIONS	
Acute sinusitis	**ENDOCRINE**
Otitis media (lateral sinus thrombosis)	Menarche
Mastoiditis	Polycystic ovarian syndrome
Tonsillitis	Hypothyroidism
Measles	Hypoparathyroidism/ hyperparathyroidism
Roseola	Congenital adrenal hyperplasia
Varicella, recurrent varicella-zoster virus infection	Addison disease
Lyme disease?	Recombinant growth hormone
HIV or associated treatment complications?	
	OTHER
DRUGS	Dural sinus thrombosis
Tetracyclines	Obesity (in pubertal patients)
Sulfonamides	Bariatric surgery
Nalidixic acid	Head trauma
Fluoroquinolones	Superior vena cava syndrome
Corticosteroid therapy and withdrawal	Arteriovenous malformation
Nitrofurantoin	Sleep apnea
Cytarabine	Guillain-Barré syndrome
Cyclosporine	Crohn disease
Phenytoin	Ulcerative colitis?
Mesalamine	Turner syndrome
Isotretinoin	
Amiodarone?	**POSSIBLE ASSOCIATIONS**
1-Deamino-8-D-arginine vasopressin (DDAVP)?	Cystic fibrosis
Lithium?	Cystinosis
Levonorgestrel implants?	Down syndrome
Oral contraceptive pills	Hypomagnesemia–hypercalciuria
	Galactokinase deficiency
RENAL	Galactosemia
Nephrotic syndrome	Atrial septal defect repair
Chronic renal insufficiency?	Moebius syndrome
Post–renal transplantation?	Sarcoidosis?
Peritoneal dialysis?	

Wiskott-Aldrich syndrome), obstruction of intracranial drainage by venous thrombosis (lateral sinus or posterior sagittal sinus thrombosis), head injury, and obstruction of the superior vena cava. When a cause is not identified, the condition is classified as idiopathic intracranial hypertension.

CLINICAL MANIFESTATIONS

The most frequent symptom is chronic (weeks to months), progressive, frontal headache that may worsen with postural changes or a Valsalva maneuver, and although vomiting also occurs, the vomiting is rarely as persistent and insidious as that associated with a posterior fossa tumor. Transient visual obscuration lasting seconds and diplopia (secondary to dysfunction of the abducens nerve) may also occur as may pulsatile tinnitus. Most patients are alert and lack constitutional symptoms. Examination of the infant with pseudotumor cerebri characteristically reveals a bulging fontanel and a "cracked pot sound" or Macewen sign (percussion of the skull produces a resonant sound) resulting from separation of the cranial sutures. **Papilledema** with an enlarged blind spot is the most consistent sign in a child beyond infancy. Papilledema may be absent or mild in infants with pseudotumor cerebri because high CSF pressure may be transmitted to the soft fontanels earlier than the optic nerves. Early optic nerve edema may be noted with orbit ultrasonography. Inferior nasal or peripheral visual field defects may be detected on formal tangent screen testing. The presence of focal neurologic signs should prompt an investigation to uncover a process other than pseudotumor cerebri. Any patient suspected of pseudotumor cerebri should undergo an MRI. MR angiography/MR venography should be considered in patients suspected of having dural sinus thrombosis.

TREATMENT

The key objective in management is recognition and treatment of the underlying cause. There are no randomized clinical trials to guide the treatment of pseudotumor cerebri. Pseudotumor cerebri can be a self-limited condition, but optic atrophy and blindness are the most significant complications of untreated pseudotumor cerebri (Fig. 605-2). The obese patient should be treated with a weight-loss regimen, and if a drug is thought to be responsible, it should be discontinued. For most patients old enough to participate in such testing, serial monitoring of visual function is required. Serial determination of visual acuity, color vision, and visual fields is critical in this disease. Serial optic nerve examination is essential as well. Optical coherence tomography is useful to serially follow changes in papilledema. Serial visual-evoked potentials are useful if the visual acuity cannot be reliably documented. The initial lumbar tap that follows a CT or MRI scan is diagnostic and may be therapeutic. The spinal needle produces a small rent in the dura that allows CSF to escape the subarachnoid space, thus reducing the intracranial pressure. Several additional lumbar taps and the removal

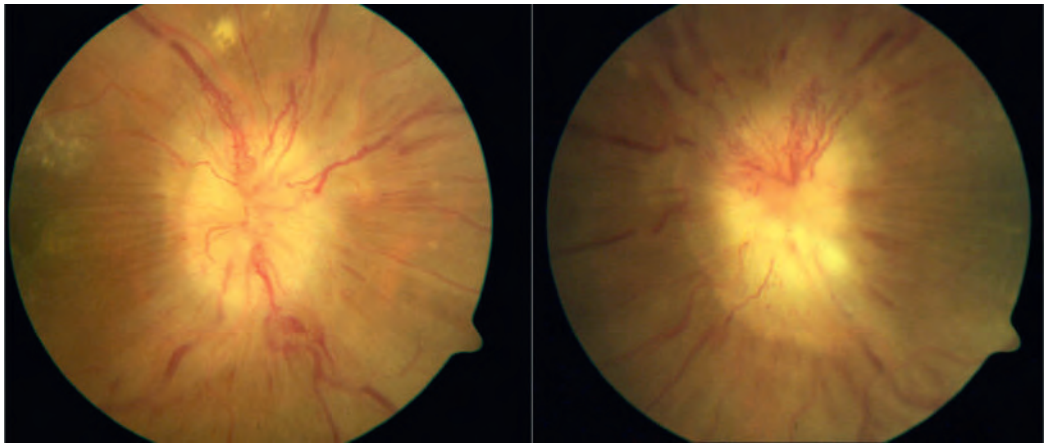


Figure 605-2 Bilateral optic atrophy is evident upon resolution of the papilledema, 1 mo after bilateral optic nerve sheath fenestrations. *(From Vickers AL, El-Dairi MA: Subacute vision loss in young, obese female.* J Pediatr *163:1518–1519, 2013, Fig. 2.)*

of sufficient CSF to reduce the opening pressure by 50% occasionally lead to resolution of the process. Acetazolamide, 10-30 mg/kg/24 hr, is an effective regimen. Corticosteroids are not routinely administered, although they may be used in a patient with severe intracranial pressure elevation who is at risk of losing visual function and is awaiting a surgical decompression. Sinus thrombosis is typically addressed by anticoagulation therapy. Rarely, a ventriculoperitoneal shunt or subtemporal decompression is necessary, if the aforementioned approaches are unsuccessful and optic nerve atrophy supervenes. Some centers perform optic nerve sheath fenestration to prevent visual loss. Any patient whose intracranial pressure proves to be refractory to treatment warrants consideration for repeat neuroradiologic studies. A **slow-growing tumor** or **obstruction of a venous sinus** may become evident by the time of reinvestigation.

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Chapter 606

Spinal Cord Disorders

Harold L. Rekate

606.1 Tethered Cord

Harold L. Rekate

Beyond infancy the spinal cord in humans ends in the conus medullaris at about the level of L1. The position of the conus below L2 is consistent with a congenital tethered spinal cord. For normal humans as the spine flexes and extends, the spinal cord is free to move up and down within the spinal canal. If the spinal cord is fixed at any point, this movement is restricted and the spinal cord and nerve roots become stretched. This fixing of the spinal cord, regardless of the underlying cause of the fixation, is called a tethered cord. When severe pain or neurologic deterioration occurs in response to the fixation, it is called the **tethered cord syndrome.**

In its simplest form the tethered cord syndrome results from a thickened filum terminale, which normally extends as a thin, very mobile structure from the tip of the conus to the sacrococcygeal region where it attaches. When this structure is thickened and shortened, the conus is found to end at levels below L2. This stretching between 2 points is likely to cause symptoms later in life. Fatty infiltration is often seen in the thickened filum (Fig. 606-1).

Any condition that fixes the spinal cord can be the cause of the tethered cord syndrome. Conditions that are well established to cause symptomatic tethering include various forms of occult dysraphism such as lipomyelomeningocele, myelocystocele, and diastematomyelia. These conditions are associated with cutaneous manifestations such as midline lipomas often with asymmetry of the gluteal fold (Fig. 606-2), and hairy patches called hypertrichosis (Fig. 606-3). Probably the most common type of symptomatic tethered cord involves patients who had previously undergone closure of an open myelomeningocele and later become symptomatic with pain or neurologic deterioration. Tethered cord syndrome can also be associated with attachment of the spinal cord in patients who undergo surgical procedures that disrupt the pial surface of the spinal cord.

It is possible that a patient can be suffering from a tethered cord with the conus medullaris in a completely normal position. Although this concept remains controversial, recent reports suggest that half of children with new onset of incontinence found to be neurologic in nature by urodynamic measurements can be successfully treated by sectioning of the filum terminale in the context of normal radiology. This concept will require a randomized controlled trial to evaluate the efficacy of this approach.



Figure 606-1 Sagittal MRI showing thickening of the filum terminale in a patient with a symptomatic tethered spinal cord. *(Used with permission from Barrow Neurological Institute.)*



Figure 606-2 Child with a lipomyelomeningocele demonstrating an extraspinal mass and an asymmetry of the gluteal fold indicative of underlying occult dysraphism. *(Used with permission from Barrow Neurological Institute.)*

CLINICAL MANIFESTATIONS

Patients at risk for the subsequent development of the tethered cord syndrome can often be identified at birth by the presence of an open myelomeningocele or by cutaneous manifestations of dysraphism. It is important to examine the back of the newborn for cutaneous midline lesions (lipoma, dermal sinus, tail, or hairy patch) that may signal an



Figure 606-3 Hairy patch or hypertrichosis usually associated with diastematomyelia. *(Used with permission from Barrow Neurological Institute.)*



Figure 606-4 Example of the neuroorthopedic syndrome involving a larger left foot than right foot, a high arch, and absent ankle jerk frequently associated with tethered cord regardless of the etiology. *(Used with permission from Barrow Neurological Institute.)*

underlying form of occult dysraphism. Dermal sinuses are usually located above the gluteal fold. Cutaneous abnormalities are not found in patients with an isolated thickened filum terminale. Patients who become symptomatic later in life often exhibit an asymmetry of the feet (i.e., 1 is smaller than the other). The smaller foot will show a high arch and clawing of the toes (Fig. 606-4). Characteristically, there is no ankle jerk on the involved side and the calf is atrophied. This condition is termed the **neuroorthopedic syndrome**.

Three clinical syndromes can occur at the time of deterioration. The most likely clinical presentation is increasing urinary urgency and, finally, incontinence. Deterioration of motor and sensory function in the lower extremities is a compelling reason for intervention. Finally, severe generalized back pain, often radiating into the lower extremities, can occur, particularly in older adolescents and adults.

DIAGNOSTIC EVALUATION

When patients present with symptoms related to the tethered cord syndrome, a thorough motor and sensory examination of the patient must be documented. Assessment of bladder function with an ultrasound of the bladder and urodynamic studies is useful in analyzing bladder innervation. MRI is the diagnostic study of choice to reflect the anatomy of the tethering lesion and to provide information about the risks of surgical intervention.

TREATMENT

There are no nonsurgical options for the management of tethered cord syndrome. Because the presence of tethering is most likely to be at least suspected in the newborn, prophylactic surgery to prevent late deterioration has been advocated by some neurosurgeons. This strategy remains controversial and depends to some extent on a careful assessment of the risks compared to the benefits. If surgical intervention is chosen, microsurgical dissection with release of the spinal cord attachment to the overlying dura is the goal of treatment.

OUTCOME

The outcome of releasing a thickened filum terminale or detethering of patients with diastematomyelia is routinely good, and the chance of recurrent symptoms is very low. Patients with symptomatic tethered cord who undergo repair of a myelomeningocele or a lipomyelomeningocele have a significant possibility of recurrent tethering and recurrent symptoms.

Bibliography is available at Expert Consult.

606.2 Diastematomyelia

Harold L. Rekate

DIASTEMATOMYELIA: SPLIT-CORD MALFORMATION

Diastematomyelia is a relatively rare form of occult dysraphism in which the spinal cord is divided into 2 halves. In type 1 split-cord malformation, there are 2 spinal cords, each in its own dural tube and separated by a spicule of bone and cartilage (Fig. 606-5*A*). In a type 2 split-cord malformation, the 2 spinal cords are enclosed in a single dural sac with a fibrous septum between the 2 spinal segments (Fig. 606-5*B*). In both cases the anatomy of the outer half of the spinal cord is essentially normal while the medial half is extremely underdeveloped. Undeveloped nerve roots and dentate ligaments terminate medially into the medial dural tube in type 1 cases and terminate in the membranous septum in type 2 cases. Both types have an associated defect in the bony spinal segment. In the case of type 2 lesions, this defect can be quite subtle.

CLINICAL MANIFESTATIONS

Patients with both type 1 and type 2 split-cord malformations may have subtle signs of neurologic involvement such as unilateral calf atrophy and a high arch to 1 or both feet early in life, but they are more likely to be neurologically normal. These patients are tethered by the adherence of the spinal cord to the median membrane or dural sac. Later they may develop progressive loss of bowel and bladder function and sensory and motor difficulties in the lower extremities. Back pain is a common symptom in adolescents and adults with split-cord malformation but is uncommon in small children.

Cutaneous manifestations of dysraphism are present in 90% of patients with split-cord malformations. Large, hairy, midline patches called hypertrichosis, the most common cutaneous manifestations, are present in approximately 60% of the cases.

DIAGNOSTIC EVALUATION

MRI, the study of choice, shows the 2 spinal cords. The frequent association of bony abnormalities in this condition may require further evaluation with radiography or computed tomography.

TREATMENT

The treatment of split-cord malformations is surgical. This abnormality is a form of tethered cord syndrome, and its treatment is to release the spinal cord to move freely with movement of the spine. In type 1 split-cord malformations, the 2 half cords are in separate dural sacs with medial attachment to the dura and bony septum. In this case the dura needs to be opened, the bony septum removed, the medial attachments to the dura lysed, and a single dural tube created. For type 2 lesions,

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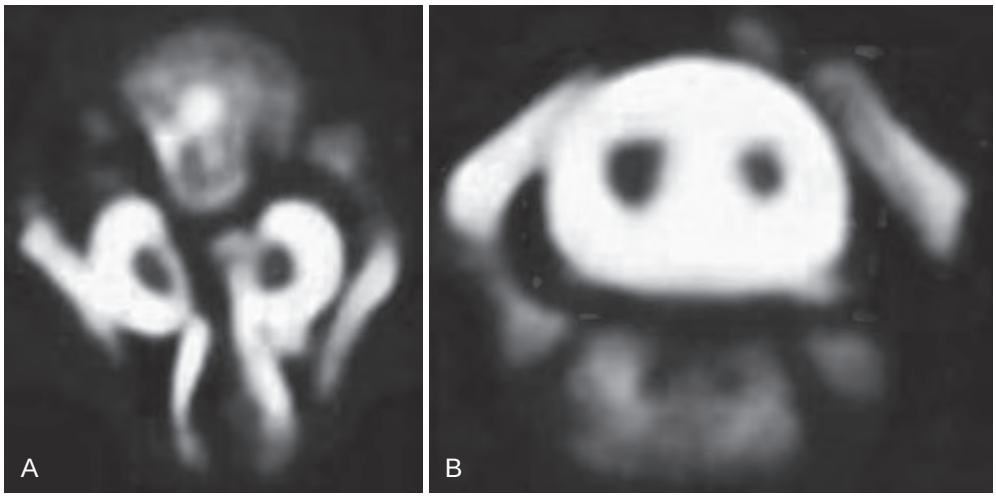


Figure 606-5 **A,** T2-weighted axial MRI of a type 1 split cord malformation showing the 2 spinal cords within 2 separate dural compartments. **B,** Type 2 split cord malformation with 2 spinal cords sharing a single dural compartment. (***A*** *and* ***B*** *used with permission from Barrow Neurological Institute.)*

the membranous septum should be lysed. An attachment of this membrane to the anterior dura should be explored and lysed as well. Retethering of this type is rare as there is no reason to disrupt the pial layer of the spinal cord.

Bibliography is available at Expert Consult.

606.3 Syringomyelia

Harold L. Rekate

Syringomyelia is a cystic distention of the spinal cord caused by obstruction of the flow of spinal fluid from within the spinal cord to its point of absorption. There are 3 recognized forms of syringomyelia depending on the underlying cause. Communicating syringomyelia implies that cerebrospinal fluid (CSF) from within the ventricles communicates with the fluid within the spinal cord and is assumed to be the source of the CSF that distends the spinal cord. Noncommunicating syringomyelia implies that ventricular CSF does not communicate with the fluid within the spinal cord. It primarily occurs in the context of intramedullary tumors and obstructive lesions. In the final form of syringomyelia, that is, posttraumatic syringomyelia, spinal cord injury results in damage and subsequent softening of the spinal cord. This softening, combined with the scarring of the surrounding spinal cord tissue, results in progressive distention of the cyst. Syringomyelia has been associated with Chiari anomalies and in patients with Ehlers-Danlos syndrome; most are isolated findings unassociated with syndromes.

CLINICAL MANIFESTATIONS

Signs and symptoms of syringomyelia develop insidiously over years or decades. The classic presentation is the **central cord syndrome.** In this situation the patient develops numbness beginning in the shoulder in a cape-like distribution followed by the development of atrophy and weakness in the upper extremities. Trophic ulcers of the hands are characteristic of advanced cases. The central cord syndrome results from damage to the central spinal cord and the orientation of spinal tracts from proximal to distal leading to selective involvement of the upper rather than the lower extremities.

Other forms of presentation include scoliosis that may be rapidly progressive and often can be presumed from the absence of superficial abdominal reflexes. Urgency and bladder dysfunction as well as lower extremity spasticity also may be part of the presentation.

In patients with syringomyelia related to spinal cord injury, the presentation is usually severe pain in the area of the spinal cord distention above the level of the initial injury. There is also an ascending level of motor and sensory dysfunction.



Figure 606-6 Sagittal MRI of patient with a Chiari I malformation and a holocord syrinx. *(Used with permission from Barrow Neurological Institute.)*

DIAGNOSTIC EVALUATION

MRI is the radiologic study of choice (Figs. 606-6 and 606-7). The study should include the entire spine and should include gadolinium-enhanced sequences. Specific attention should be paid to the craniovertebral junction because of the frequent association of syringomyelia with Chiari I and II malformations. Obstruction to the flow of CSF from the fourth ventricle can cause syringomyelia; therefore, most patients also should undergo imaging of the brain.

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TREATMENT

The treatment of syringomyelia should be tailored to the underlying cause. If that cause can be removed or ameliorated, the syrinx should improve. Traumatic syrinxes result from hematomyelia in the substance of the spinal cord coupled with severe arachnoidal scarring around the circumference of the spinal cord. When progressive this form of syringomyelia is treated by exploration and lysis of the adhesions that fix the spinal cord to the overlying dura. In cases of complete spinal cord injury, as is usually found in the thoracic spinal cord, the most effective treatment is the transection of the spinal cord, which would both drain the syrinx and detether the spinal cord. Doing so drains the fluid from the spinal cord. In cases of incomplete spinal cord injury, functioning neurologic elements must be protected. Microscopic lysis of the scar surrounding the spinal cord at the point of injury allows the spinal cord to collapse and prevents it from being distorted by a hydrostatic column.

Communicating syringomyelia is most frequently seen in the context of abnormalities at the craniovertebral junction caused by inflammatory conditions such as chronic meningitis as seen in tuberculosis or meningeal carcinomatosis. There is frequently a causative association with hindbrain herniation as in Chiari malformations (see Fig. 606-6). In such cases decompression of the craniovertebral junction is usually effective in the management of the syringomyelia. In the context of the Chiari II malformation associated with spina bifida, syringomyelia usually results from an insidious failure of the shunt used to treat the hydrocephalus. This distention of the spinal cord results in a rapid development of scoliosis and occasionally spasticity in the lower extremities. Repair of the shunt is effective treatment.

Noncommunicating syringomyelia results from blocking the flow of spinal cord extracellular fluid or CSF within the central canal by an intramedullary spinal cord tumor or severe external compression of the spinal cord. In such cases, management should be directed to tumor resection or to decompression of constricting elements.

Drainage procedures can result in symptomatic and radiographic improvement. Syrinx-to-subarachnoid shunting with a small piece of shunt tubing is 1 form of treatment. Syrinx-to-pleural or syrinx-to-peritoneal shunting is more likely to result in improvement in the radiographic appearance of the syrinx. In patients with syringomyelia that extends to the conus medullaris, remnants of the central canal can be found in the filum terminale. Lysis of this structure near the conus can provide effective drainage.

Some children who show no testable neurologic findings are being referred to pediatric neurosurgeons with the diagnosis of syringomyelia. Many of these children were scanned because of back pain or as part of a screening for scoliosis. They are found on MRI to have a **persistent central canal** and the diagnosis of syringomyelia is made. Some have been scanned sequentially for follow up and banned from athletic activities. These syrinxes are 1-3 mm in diameter and extend over 2 segments (see Fig. 606-7). There is no distortion of the spinal cord in the region and no change in signal of the surrounding spinal cord. These syrinxes have been called "idiopathic" syrinxes. Follow-up of significant numbers of such children has shown them to be benign in nature and probably represent a normal variant. There does not seem to be a need for routine follow-up imaging without new symptoms. They need no treatment and do not require limitations of activity.

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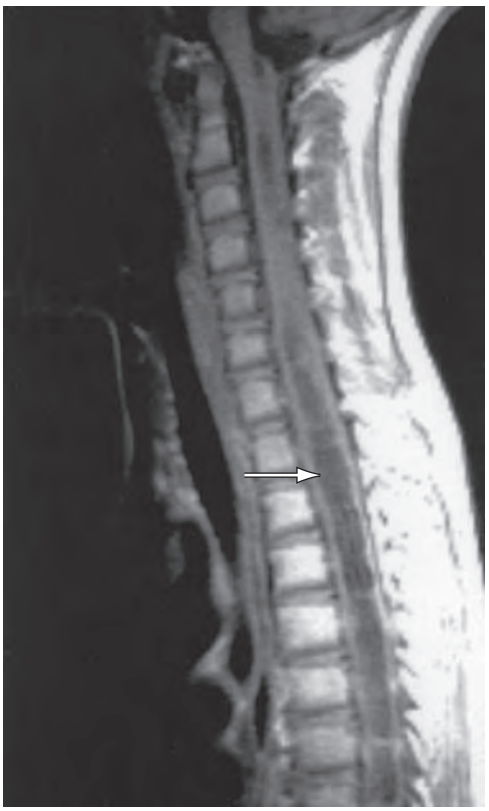


Figure 606-7 T1-weighted MRI scan of upper spinal cord showing an extensive syringomyelia *(arrow)*.

606.4 Spinal Cord Tumors

Harold L. Rekate

Tumors of the spine and spinal cord are rare in children. Different types of tumors have different relationships with the spinal cord, meninges, and bony elements of the spine (Fig. 606-8). Intramedullary spinal cord tumors arise within the substance of the spinal cord itself (Fig. 606-9). They represent between 5% and 15% of primary central nervous system tumors. This percentage may well reflect the total volume of spinal cord as opposed to brain. Approximately 10% of intramedullary spinal cord tumors are malignant astrocytic tumors, but most are World Health Organization grade I or II tumors of glial or ependymal origin. In children, low-grade astrocytomas and gangliogliomas represent the most common tumor types with ependymomas being less common than in adults. Ependymomas in children are frequently associated with neurofibromatosis (NF-2).

Except in the context of NF-1 and NF-2, intradural extramedullary tumors are extremely rare in children. Most are nerve sheath tumors,

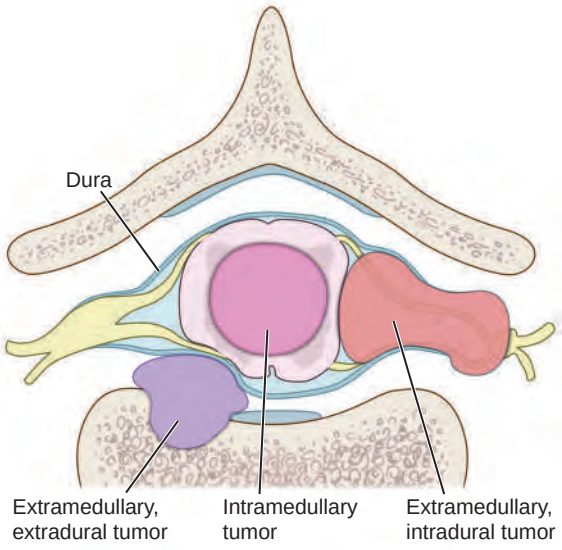


Figure 606-8 Diagram of the relationship of various tumors to the spine, nerve roots, and spinal cord. *(Used with permission from Barrow Neurological Institute.)*

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Figure 606-9 T1-weighted MRI scan of a spinal cord tumor *(arrow)*. The fusiform expansion of the cervical cord enhances after intravenous gadolinium injection.

either schwannomas or, in the case of NF-2, neurofibromas. Intraspinal meningiomas in children are essentially found only in patients with NF-2. The intradural extramedullary compartment is also a site for metastatic tumors from primary cancers such as leukemia or primitive neuroectodermal tumors.

Extradural spinal tumors characteristically begin in the bones of the spine. Primary tumors in this location include aneurysmal bone cysts, Langerhans cell histiocytosis (formerly called eosinophilic granuloma), and giant cell tumors. In infants, the extradural space is often the site of neuroblastomas or ganglioneuroblastomas, which tend to be present in the epidural space and in the paraspinous tissue through the intervertebral foramen. In older patients, the bones of the spine may be the site of multiple myeloma and metastases from common malignant tumors.

CLINICAL MANIFESTATIONS

With the exception of the uncommon malignant glial tumors of the spinal cord, which tend to present precipitously, intramedullary spinal cord tumors present in a very insidious manner. Back pain related to the level of the tumor is a common presenting complaint. It is likely that this pain will awaken the child from sleep and improve as the day progresses. Before the use of MRI became routine, the time from the first onset of symptoms to diagnosis of the tumor could be as long as 9 yr. Weakness, gait disturbance, and sensory deficits are usually minor and are often found when formal neurologic examinations are performed. Scoliosis, urinary urgency, and incontinence may be the presenting complaints associated with intramedullary spinal cord tumors.

Extramedullary extradural tumors have a propensity to cause an acute block of the CSF pathways owing to rapid growth within a confined space. Such children present with a flaccid paraplegia, urinary retention, and a patulous anus. Some extramedullary tumors produce the *Brown-Séquard syndrome,* which consists of ipsilateral weakness, spasticity, and ataxia, with contralateral loss of pain and temperature sensation. Papilledema is observed in a few patients, usually in association with markedly elevated CSF protein levels that presumably interfere with normal CSF flow dynamics.

Nerve sheath tumors primarily arise from the sensory rootlet of the exiting spinal nerve. They are very slow-growing tumors and present with symptoms and signs relative to the nerve root involved. Pain in a band-like distribution around the chest or into an extremity is the most common presenting complaint. Tumor growth eventually leads to spinal cord compression and involvement of adjacent nerve roots.

Tumors rarely arise in the fat of the epidural space; most epidural tumors arise in the bony compartment of the spine. They can present abruptly with severe pain and neurologic deficit at the time of pathologic fracture of the vertebral body. Benign tumors such as giant cell tumors and aneurysmal bone cysts present more insidiously as the tumor slowly grows and begins to compress neural structures.

DIAGNOSTIC EVALUATION

MRI with and without gadolinium enhancement of the spinal cord is the diagnostic study of choice and is essential in the diagnosis of spinal cord tumors, especially intramedullary spinal cord tumors. Most astrocytic tumors of the spinal cord and most ependymomas show diffuse enhancement and will distend the spinal cord focally. These tumors may involve the entire length of the spinal cord (holocord astrocytomas). MRI also shows the relationship between the normal spinal cord and tumor embedded within spinal cord tissue. These tumors are frequently associated with a syrinx, which is usually distal to the tumor. Nerve sheath tumors characteristically enhance and are focal. They may exit through the neural foramen and distend the canal as can be seen on MRI. They also may be visualized on plain radiographs of the affected area of the spine.

Plain radiographs of the spine are helpful in defining the relationship of extradural tumors to the bony spine and in documenting evidence of instability in the case of pathologic compression fractures. When a pathologic fracture occurs, CT is essential to determine the effect of the tumor on the bone. Because many of these tumors occur as metastatic lesions, a general staging of the extent of disease is essential. In the case of Langerhans cell histiocytosis, a thorough bone survey should be conducted to look for other lesions. Radionucleotide bone scanning is also useful in determining the extent of the disease.

TREATMENT

The primary treatment of both intramedullary and extramedullary intradural tumors is surgical removal. For both low-grade astrocytomas and ependymomas, microsurgical removal with the intent of total removal is the treatment of choice. This goal should be attainable in all patients with ependymomas and in most patients with low-grade astrocytomas and gangliogliomas. Adjunctive treatment of these tumors is unwarranted in patients treated with adequate surgical resection. Likewise, schwannomas should be resectable. Occasionally, however, the nerve root must be resected. Doing so may be of no consequence in the thoracic spinal cord, but an attempt to remove the tumor while salvaging the motor root in the cervical and lumbosacral region is critical to preserve movement. Malignant astrocytic tumors cannot be resected without major morbidity and, in any case, carry an extremely poor prognosis. In the case of grades III and IV astrocytomas of the spinal cord, decompression and biopsy followed by radiation therapy and possibly chemotherapy are utilized.

The diagnosis and treatment of extramedullary spinal cord tumors must be individualized. Patients with distention of the vertebral body or with unstable pathologic fractures benefit from extensive resection of the involved vertebral bodies and will likely need fusion. For extramedullary tumors with soft-tissue components such as neuroblastomas, treatment is determined by the nature of the tumor and degree of spinal cord compression, and directed following needle biopsy of the lesion. In the absence of significant neurologic compression, surgical intervention is rarely indicated.

OUTCOME

The prognosis for patients with benign intramedullary spinal cord tumors depends, to some extent, on the patient's condition at the time of surgical intervention. It is very unlikely that nonambulatory patients will improve after surgery. If, however, patients are ambulatory at the time of surgery, they may experience increased weakness after surgery.

They are likely to recover at least their preoperative level of function. Malignant spinal cord tumors are usually lethal with death resulting from diffuse metastases via the CSF pathways. Successful resection of nerve sheath tumors should be curative. In the context of neurofibromatosis, however, many more tumors can be found at other levels or can be expected to develop later in life. Surgical intervention in the context of neurofibromatoses should be performed only on clearly symptomatic lesions.

The outcome of treatment of extramedullary tumors depends on the cell type and, in most cases, on the efficacy of nonsurgical, adjunctive therapies. For aneurysmal bone cysts and giant cell tumors, resection of the tumor and fusion of the spine are the treatments of choice.

The significant majority of spinal cord tumors in children are benign (World Health Organization grades 2 and 3). The intramedullary low-grade glial tumors for the most part act the same as the same histology in the brain. The evidence would point to the fact that intramedullary ependymomas act in a more benign fashion than they do in the fourth ventricle. Gross total removal without adjuvant treatment is the preferred method of treatment and carries not only much longer progression free survival but improved quality of life as well.

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606.5 Spinal Cord Injuries in Children

Harold L. Rekate

Spine and spinal cord injuries are very rare in children, particularly in young children. The spine of a small child is very mobile, and fractures of the spine are exceedingly rare. This increased mobility is not always a positive feature. Transfer of energy leading to spinal distortion can maintain the structural integrity of the spine but lead to significant injuries of the spinal cord. Spinal cord injury without radiographic bone (vertebral) abnormalities, called **SCIWORA,** is more common in children than adults. There seem to be 2 distinct forms. The infantile form involves severe injury of the cervical or thoracic spine. These patients have a poor likelihood of complete recovery. In older children and adolescents, SCIWORA is more likely to cause a less-severe injury and the likelihood of complete recovery over time is high. The adolescent form is assumed to be a spinal cord concussion or mild contusion as opposed to the severe spinal cord injury related to the mobility of the spine in small children.

Although the mechanisms of spinal cord injury in children include birth trauma, falls, and child abuse, the major cause of morbidity and mortality remains motor vehicle injuries. Although the mechanisms of injury and diagnosis are distinct in very small children, adolescents incur spinal cord injuries with epidemiology similar to that of adults, including significant male predominance and a high likelihood of fracture dislocations of the lower cervical spine or thoracolumbar region. In infants and children younger than age 5 yr, fractures and mechanical disruption of spinal elements are limited to the upper cervical spine between the occiput and C3.

CLINICAL MANIFESTATIONS

One in 3 patients with significant trauma to the spine and spinal cord will have a concomitant severe head injury, which makes early diagnosis challenging. For these patients clinical evaluation may be difficult. They need to be maintained in a protective environment such as a collar until the appropriate radiographs can be obtained. A careful neurologic examination is necessary for infants with suspected spinal cord injuries. Complete spinal cord injury will lead to **spinal shock** with early areflexia. Severe cervical spinal cord injuries will usually lead to paradoxical respiration in patients who are breathing spontaneously. Paradoxical respiration occurs when the diaphragm functions because the phrenic nerves from C3, C4, and C5 are functioning normally but the intercostal musculature innervated by the thoracic spinal cord is paralyzed. In this situation, inspiration fails to expand of the chest wall but distends the abdomen.

The *mildest injury* to the spinal cord is transient quadriparesis evident for seconds or minutes with complete recovery in 24 hr. This injury follows a concussion of the cord.

A transverse injury in the high cervical cord level (C1-C2) causes respiratory arrest and death in the absence of ventilatory support. *Fracture dislocations at the C5-C6 level* resulting in spinal cord injuries are characterized by flaccid quadriparesis, loss of sphincter function, and a sensory level corresponding to the upper sternum. Fractures or dislocations in the low thoracic (T12-L1) region may produce the **conus medullaris syndrome,** which includes a loss of urinary and rectal sphincter control, flaccid weakness, and sensory disturbances of the legs. A **central cord lesion** may result from contusion and hemorrhage and typically involves the upper extremities to a greater degree than the legs. There are lower motor neuron signs in the upper extremities and upper motor neuron signs in the legs, bladder dysfunction, and loss of sensation caudal to the lesion. There may be considerable recovery, particularly in the lower extremities.

Thoracolumbar injuries are usually fracture–dislocations such as occur in severe motor vehicle accidents when children are wearing lap belts but not shoulder harnesses. These injuries lead to a conus medullaris syndrome. These patients exhibit a loss of bowel and bladder function and lower motor neuron injuries involving the innervation of the lower extremities.

CLEARING THE CERVICAL SPINE IN CHILDREN

The management of children following major trauma is challenging. Clearing the cervical spine in children carries some of the same issues as it does in comatose adults in that with small children you cannot count on their cooperation with positioning for radiographs and complaints of pain are difficult to assess. There has been an increasing emphasis on the use of MRI for the evaluation of potential cervical spine instability but in small children this study requires sedation and, in most centers, the presence of an anesthesiologist. Despite the radiation dose, it is clear that the CT scan is the most important study with 100% sensitivity and 95% specificity. A multiply injured child is likely to be in the scanner having other anatomic studies done in any case and no other study has been shown to be better for detection of unstable cervical spine injury. This test detects all significant injuries to the cervical spine and has very few false-positives as opposed to MRI scanning, which overcalls the injury 1 in 4 times.

TREATMENT

The initial management of spine and spinal cord injuries in children is similar to that in adults. The cervical spine should be immobilized in the field by the emergency medical technicians. In cases of acute spinal cord injury, some data support the acute infusion of a bolus of high-dose (30 mg/kg) methylprednisolone followed by a 23 hr infusion (5.4 mg/kg/hr). The data for this treatment in children are controversial.

Surgical management of unstable spinal injuries must be tailored to the patient's age. For occipitocervical dislocations, early surgery with fusion from the occiput to C2 or C3 should be performed, even in babies older than 6 mo. Fixation of the subaxial spine must be tailored to the size of the pedicles and other osseus structures of the developing axial skeleton.

PREVENTION

The most important aspect of the care of spinal cord injuries in children relates to injury prevention. In this regard, the use of appropriate child restraints in automobiles is the most important precaution. In older children and adolescents, rules against spear tackling in football and the "Feet First, First Time Program" from the Think First Foundation aimed at adolescents diving into swimming pools and natural water areas are important ways to help prevent severe cervical spinal cord injuries.

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606.6 Transverse Myelitis

Harold L. Rekate

Transverse myelitis (TM) is a condition characterized by rapid development of both motor and sensory deficits at any level of the spinal cord. TM presents acutely as either partial or complete cord involvement and is defined as evidence of spinal cord inflammation by an MRI-documented enhancing lesion, or CSF pleocytosis (>10 cells), or increased immunoglobulin G index. The progression is rapid and the time to maximal disability is more than 4 hr and fewer than 21 days. It has multiple causes and tends to occur in 2 distinct contexts. Small children, 3 yr of age and younger, develop spinal cord dysfunction over hours to a few days. They have a history of an infectious disease, usually of viral origin, or of an immunization within the few weeks preceding the development of their neurologic difficulties. The clinical loss of function is often severe and may seem complete. Although a slow recovery (weeks to months) is common in these cases, it is likely to be incomplete. The likelihood of independent ambulation in these small children is approximately 40%. The pathologic findings of perivascular infiltration with mononuclear cells imply an infectious or inflammatory basis. Overt necrosis of spinal cord may rarely be seen.

In older children, the syndrome is somewhat different. Although the onset is also rapid with a nadir in neurologic function occurring between 2 days and 2 wk, recovery is more rapid and more likely to be complete. Pathologic or imaging examination shows acute demyelination.

CLINICAL MANIFESTATIONS

TM is often preceded within the previous 1-3 wk by a mild nonspecific illness, minimal trauma, or perhaps an immunization. In both forms the patient shows or complains of discomfort or overt pain in the neck or back, depending on the level of the lesion. The most common involved segments are in the thoracic region. Depending on its severity, the condition progresses to numbness, anesthesia, ataxia, areflexia, and motor weakness in the truncal and appendicular musculature at or distal to the lesion. Paralysis begins as flaccidity (paraparesis, tetraparesis), but over a few weeks spasticity develops and is evident by hyperreflexia and clonus. Rarely is the weakness unilateral. Urinary retention is an early finding; incontinence occurs later in the course. Most have sensory loss manifest as anesthesia, paresthesia, or allodynia. Other findings may include priapism and vision loss (neuromyelitis optica), as well as spinal shock and subsequent autonomic dysreflexia.

The differential diagnosis includes demyelinating disorders, overt meningitis, spinal cord infarction, or mass lesions such as bony distortion, abscess, and spine and spinal cord tumors (Table 606-1).

DIAGNOSTIC EVALUATION

MRI with and without contrast enhancement is essential to rule out a mass lesion requiring neurosurgical intervention. In both conditions, T1-weighted images of the spine at the anatomic level of involvement may be normal or may show distention of the spinal cord. In the infantile form, T2-weighted images show high signal intensity that extends over multiple segments. In the adolescent form, the high signal intensity may be limited to 1 or 2 segments. A limited degree of contrast enhancement after the administration of gadolinium is expected, especially in the infantile form, and denotes an inflammatory condition (Fig. 606-10). MRI of the brain is also indicated and shows evidence of other foci of demyelination in at least 30% of patients; in these patients and those with encephalopathy, acute disseminated encephalomyelitis must be considered (Fig. 606-11).

After a mass lesion associated with spinal cord compression or complete subarachnoid column block from spinal cord swelling have been ruled out, a lumbar puncture is indicated. In both forms of disease, the number of mononuclear cells is usually elevated. The level of CSF protein maybe elevated or normal. CSF should be analyzed for myelin basic protein and immunoglobulin levels, which are usually elevated in TM. The presence of inflammatory cells is essential for the diagnosis of TM.

Because one of the most important possibilities for this condition is neuromyelitis optica (NMO; Devic syndrome) the serum of all patients should be analyzed for the NMO antibody. This test is positive in most patients with NMO (see Chapter 600.2). NMO is associated with bilateral optic neuritis and recurrent or long segment TM (≥3 segments). NMO may involve any spinal segment in addition to the brainstem or conus medullaris and cauda equina (myeloradiculitis). As in adults with

Table 606-1 Clinical and Radiologic Mimics of Transverse Myelitis

EXTRAAXIAL COMPRESSION DISEASE
1. Vertebral spine disorders
   a. Trauma
      i. Blunt
      ii. Penetrating
      iii. Surfing
   b. Atlantoaxial subluxation
      i. Trisomy 21
      ii. Mucopolysaccharidosis type IV
      iii. Grisel syndrome
   c. Destructive lesions
      i. Tuberculosis
      ii. Lymphoma
      iii. Langerhans cell histiocytosis
   d. Scheuermann disease
2. Epidural disease
   a. Tumor
      i. Neuroblastoma
      ii. Wilms tumor
      iii. Ewing sarcoma
   b. Abscess
      i. Associated dermal sinus, vertebral body infection
   c. Hematoma
3. Arachnoiditis
   a. Tuberculosis
   b. Cryptococcosis
   c. Carcinomatous infiltration
4. Spinal nerve root inflammation
   a. Guillain-Barré syndrome

SPINAL CORD DISORDERS
1. Congenital malformation
   a. Neurenteric cysts
   b. Spinal cord tethering
2. Infection
   a. Nonpolio enteroviruses
   b. West Nile virus
   c. Human T-lymphocyte virus 1
   d. Neurocysticercosis
3. Vascular disorders
   a. Arteriovenous malformation
   b. Cavernomas
   c. Cobb syndrome
   d. Fibrocartilaginous embolization
   e. Spinal cord infarction
4. Vasculitis
   a. Systemic lupus erythematosus
   b. Behçet disease
5. Nutritional disorders
   a. Vitamin B_{12} deficiency (Subacute combined degeneration)
6. Toxic injury
   a. Chemotherapy (e.g., methotrexate)
   b. Radiation
7. Immune mediated
   a. Acute disseminated encephalomyelitis
   b. Neuromyelitis optica
   c. Multiple sclerosis

Modified from Thomas T, Branson HM: Childhood transverse myelitis and its mimics. Neuroimaging Clin N Am *23:267–278, 2013, Box 11.*

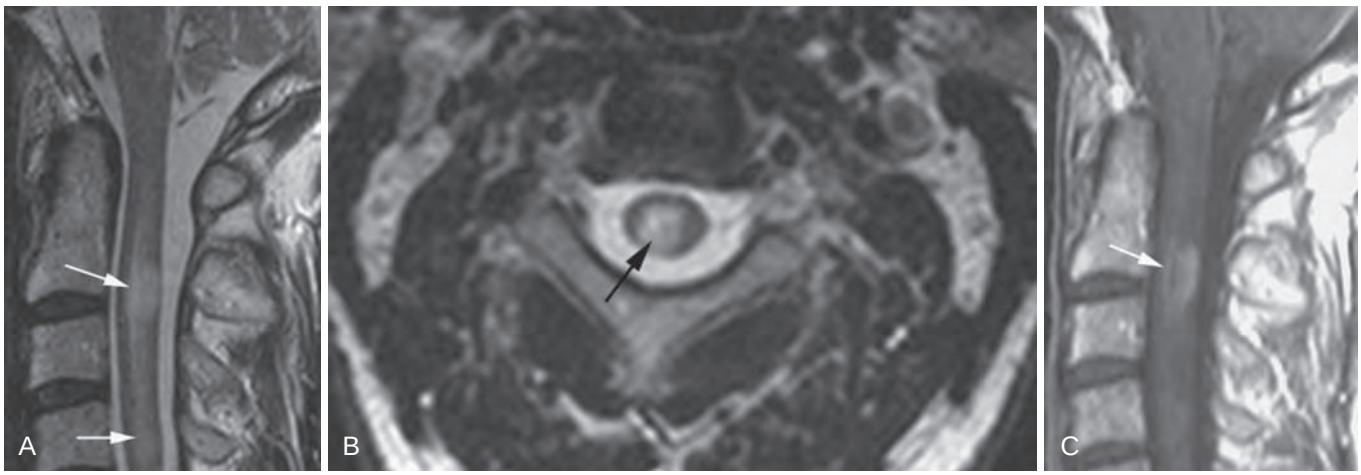


Figure 606-10 Transverse myelitis. **A,** Sagittal T2-weighted image demonstrates a longitudinal hyperintense spinal cord lesion spanning three vertebral segments *(arrows)*. **B,** On an axial T2-weighted image, the lesion involves more than two-thirds of the cord's cross-sectional area *(arrow)*. **C,** Sagittal T1-weighted postcontrast image shows an enhancing area within the lesion *(arrow)*. *(From Ajtai B, Lindzen E, Masdeu JC: Structural imaging: magnetic resonance imaging and computed tomography. In Daroff RB, Fenichel GM, Jankovic J, Mazziotta JC, editors:* Bradley's neurology in clinical practice, *ed 6. Philadelphia, 2012, WB Saunders,* Fig. 33A.96.*)*



Figure 606-11 Acute disseminated encephalomyelitis. Sagittal T2-weighted image shows a diffuse hyperintense lesion spanning the length of the cervical cord *(arrows)*. Note the enlarged caliber of the cord, which is a result of swelling. *(From Ajtai B, Lindzen E, Masdeu JC: Structural imaging: magnetic resonance imaging and computed tomography. In Daroff RB, Fenichel GM, Jankovic J, Mazziotta JC, editors:* Bradley's neurology in clinical practice, *ed 6. Philadelphia, 2012, WB Saunders,* Fig. 33A.95.*)*

TM, older children with the condition should have serum studies sent for autoimmune disorders, especially systemic lupus erythematosus.

TREATMENT

There are no standards for the treatment of TM. Available evidence suggests that modulation of the immune response may be effective in decreasing the severity and duration of the condition. The use of high-dose steroids, particularly methylprednisolone, is the initial approach to treatment of childhood forms of TM. If there is a poor response to high-dose steroids, other therapeutic approaches include intravenous immunoglobulin, plasma exchanges, rituximab, and cyclophosphamide.

Follow-up of children with TM often reveals poor ambulation, continued bowel or bladder symptoms and dysesthesias.

Bibliography is available at Expert Consult.

606.7 Spinal Arteriovenous Malformations

Harold L. Rekate

Arteriovenous malformations of the spinal cord are rare lesions in children. Only about 60 patients younger than age 18 yr are treated in the United States each year. These lesions are complex. Despite their rarity there are multiple subtypes, which require different treatment strategies. Patients commonly present with back or neck pain, depending on the segments of the spinal cord involved, and they may experience the insidious onset of motor and sensory disturbances. Sudden onset of paraplegia secondary to hemorrhage has been reported. Occasionally, patients present with subarachnoid hemorrhage without overt neurologic deficits, similar to the presentation associated with cerebral aneurysms. In some cases, bruits are audible upon auscultation over the bony spine.

DIAGNOSTIC EVALUATION

When a spinal arteriovenous malformation is suspected, MRI of the spinal cord is first needed to make the diagnosis and to obtain a general idea of the location of the lesion. MR angiography or CT angiography may provide further information, but formal catheter angiography of the spinal cord is needed to obtain an adequate understanding of the complex anatomy of the lesion and to plan the intervention.

TREATMENT

Open microsurgery had been the mainstay of treatment for spinal cord arteriovenous fistulas and arteriovenous malformations. With the rapid development of interventional techniques, the percentage of patients undergoing microsurgery has decreased from 70% to approximately 30%. Stereotactic radiosurgery may be used adjunctively. Treatment of these complex lesions requires the commitment of an organized neurovascular treatment program.

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Neuromuscular Disorders

PART XXVIII

Chapter 607

Evaluation and Investigation

Harvey B. Sarnat

The term **neuromuscular disease** defines disorders of the motor unit and excludes influences on muscular function from the brain, such as spasticity. The motor unit has 4 components: a motor neuron in the brainstem or ventral horn of the spinal cord; its axon, which together with other axons forms the peripheral nerve; the neuromuscular junction; and all muscle fibers innervated by a single motor neuron. The size of the motor unit varies among different muscles and with the precision of muscular function required. In large muscles, such as the glutei and quadriceps femoris, hundreds of muscle fibers are innervated by a single motor neuron; in small, finely tuned muscles, such as the stapedius or the extraocular muscles, a 1 : 1 ratio can prevail. The motor unit is influenced by suprasegmental or upper motor neuron control that alters properties of muscle tone, precision of movement, reciprocal inhibition of antagonistic muscles during movement, and sequencing of muscle contractions to achieve smooth, coordinated movements. Suprasegmental impulses also augment or inhibit the monosynaptic stretch reflex; the corticospinal tract is inhibitory upon this reflex.

Diseases of the motor unit are common in children. These neuromuscular diseases may be genetically determined, congenital or acquired, acute or chronic, and progressive or static. Because specific therapy is available for many diseases and because of genetic and prognostic implications, precise diagnosis is important; laboratory confirmation is required for most diseases because of overlapping clinical manifestations.

Many chromosomal loci are identified with specific neuromuscular diseases as a result of genetic linkage studies and the isolation and cloning of a few specific genes. In some cases, such as Duchenne muscular dystrophy, the genetic defect is a deletion of nucleotide sequences and is associated with a defective protein product, dystrophin. In other cases, such as myotonic muscular dystrophy, the genetic defect is an expansion or repetition, rather than a deletion, in a codon (a set of 3 consecutive nucleotide repeats that encodes for a single amino acid), with many copies of a particular codon (in this example they are also associated with abnormal messenger RNA). Some diseases manifest as autosomal dominant and autosomal recessive traits in different pedigrees; these distinct mendelian genotypes can result from different genetic mutations on different chromosomes (nemaline myopathy) or from small differences in the same gene at the same chromosomal locus (myotonia congenita), despite many common phenotypic features and shared histopathologic findings in a muscle biopsy specimen. Among the several clinically defined mitochondrial myopathies, specific mitochondrial DNA deletions and transfer RNA point mutations are recognized. The inheritance patterns and chromosomal and mitochondrial loci of common neuromuscular diseases affecting infants and children are summarized in Table 608-1 in Chapter 608.

CLINICAL MANIFESTATIONS

Examination of the neuromuscular system includes an assessment of muscle bulk, tone, and strength. Tone and strength should not be confused: **Passive tone** is range of motion around a joint; **active tone** is physiologic resistance to movement. Head lag when an infant is pulled to a sitting position from supine is a sign of weakness, not of low tone. Hypotonia may be associated with normal strength or with weakness; enlarged muscles may be weak or strong; thin, wasted muscles may be weak or have unexpectedly normal strength. The distribution of these components is of diagnostic importance. In general, myopathies follow a proximal distribution of weakness and muscle wasting (with the notable exception of myotonic muscular dystrophy); neuropathies are generally distal in distribution (with the notable exception of juvenile spinal muscular atrophy; Table 607-1). Involvement of the face, tongue, palate, and extraocular muscles provides an important distinction in the differential diagnosis. **Tendon stretch reflexes** are generally lost in neuropathies and in motor neuron diseases and are diminished but preserved in myopathies (Table 607-1). A few specific clinical features are important in the diagnosis of some neuromuscular diseases. **Fasciculations** of muscle, which are often best seen in the tongue, are a sign of denervation. Sensory abnormalities indicate neuropathy. Fatigable weakness is characteristic of neuromuscular junctional disorders. Myotonia is specific for a few myopathies.

Some features do not distinguish myopathy from neuropathy. Muscle pain or **myalgias** are associated with acute disease of either myopathic or neurogenic origin. Acute dermatomyositis and acute polyneuropathy (Guillain-Barré syndrome) are characterized by myalgias. Muscular dystrophies and spinal muscular atrophies are not associated with muscle pain. Myalgias also occur in several metabolic diseases of muscle and in ischemic myopathy, including vascular diseases such as dermatomyositis. Myalgias denote the acuity, rather than the nature, of the process, so that progressive but chronic diseases, such as muscular dystrophy and spinal muscular atrophy, are not painful but acute stages of inflammatory myopathies and acute denervation of muscle often do present with muscular pain and tenderness to palpation. **Contractures** of muscles, whether present at birth or developing later in the course of an illness, occur in both myopathic and neurogenic diseases.

Infant boys who are weak in late fetal life and in the neonatal period often have **undescended testes**. The testes are actively pulled into the scrotum from the anterior abdominal wall by a pair of cords that consist of smooth and striated muscle called the gubernacula. The gubernacula are weakened in many congenital neuromuscular diseases, including spinal muscular atrophy, myotonic muscular dystrophy, and many congenital myopathies.

The thorax of infants with congenital neuromuscular disease often has a funnel shape, and the ribs are thin and radiolucent as a result of intercostal muscle weakness during intrauterine growth. This phenomenon is characteristically found in infantile spinal muscular atrophy but also occurs in myotubular myopathy, neonatal myotonic dystrophy, and other disorders (Fig. 607-1). Because of the small muscle mass, birthweight may be low for gestational age.

Generalized hypotonia and motor developmental delay are the most common presenting manifestations of neuromuscular disease in infants and young children (Table 607-2). These features can also be expressions of neurologic disease, endocrine and systemic metabolic diseases, and Down syndrome, or they may be nonspecific neuromuscular expressions of malnutrition or chronic systemic illness (Table 607-3). A prenatal history of decreased fetal movements and intrauterine growth retardation is often found in patients who are symptomatic at birth. Developmental disorders tend to be of slow onset and are progressive. Acute flaccid paralysis in older infants and children has a different differential diagnosis (Table 607-4).

LABORATORY FINDINGS

Serum Enzymes

Several lysosomal enzymes are released by damaged or degenerating muscle fibers and may be measured in serum. The most useful of these enzymes is **creatine kinase (CK)**, which is found in only 3 organs and may be separated into corresponding isozymes: MM for skeletal muscle, MB for cardiac muscle, and BB for brain. Serum CK determination is not a universal screening test for neuromuscular disease because many diseases of the motor unit are not associated with elevated enzymes. The CK level is characteristically elevated in certain diseases, such as Duchenne muscular dystrophy, and the magnitude of increase is characteristic for particular diseases.

Table 607-1 Distinguishing Features of Disorders of the Motor System

LOCUS OF LESION	WEAKNESS				DEEP TENDON REFLEXES	ELECTRO-MYOGRAPHY	MUSCLE BIOPSY	OTHER
	Face	Arms	Legs	Proximal–Distal				
Central	0	+	+	≥	Normal or ↑	Normal	Normal	Seizures, hemiparesis, and delayed development
Ventral horn cell	Late	++++	++++	≥	0	Fasciculations and fibrillations	Denervation pattern	Fasciculations (tongue)
Peripheral nerve	0	+++	+++	<	↓	Fibrillations	Denervation pattern	Sensory deficit, elevated cerebrospinal fluid protein, depressed nerve biopsy
Neuromuscular junction	+++	+++	+++	=	Normal	Decremental response (myasthenia); incremental response and BSAP (botulism)	Normal	Response to neostigmine or edrophonium (myasthenia); constipation and fixed pupils (botulism)
Muscle	Variable (+ to ++++)	++	+	>	↓	Short duration, small-amplitude motor unit potentials and myopathic polyphasic potentials	Myopathic pattern*	Elevated muscle enzyme levels (variable)

*Can also show unique features, such as in central core disease, nemaline myopathy, myotubular myopathy, and congenital fiber type disproportion.
+ to ++++, varying degrees of severity; BSAP, brief duration, small amplitude, overly abundant motor unit potentials.
From Volpe J: Neurology of the newborn, *ed 4, Philadelphia, 2001, WB Saunders, p. 706.*

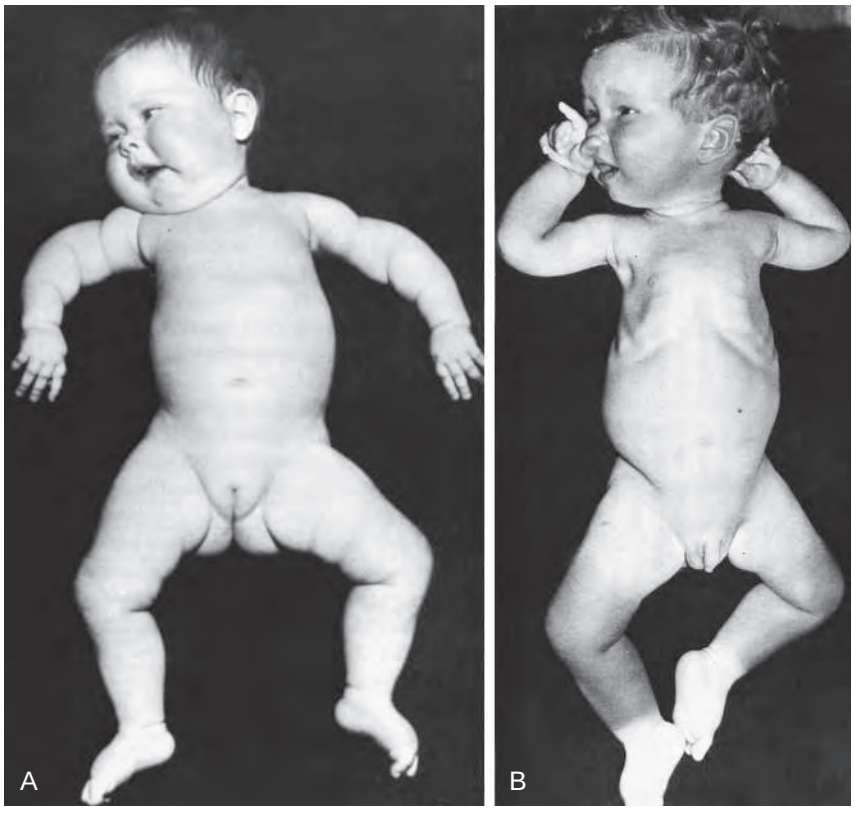


Figure 607-1 Type 1 spinal muscular atrophy (Werdnig-Hoffmann disease). Characteristic postures in 6 wk old **(A)** and 1 yr old **(B)** infants with severe weakness and hypotonia from birth. Note the frogleg posture of the lower limbs and internal rotation ("jug handle") **(A)** or external rotation **(B)** at the shoulders. Note also intercostal recession, especially evident in **B,** and normal facial expressions. *(From Volpe J:* Neurology of the newborn, *ed 4, Philadelphia, 2001, WB Saunders, p. 645.)*

Table 607-2 Pattern of Weakness and Localization in the Floppy Infant

ANATOMIC REGION OF HYPOTONIA	CORRESPONDING DISORDERS	PATTERN OF WEAKNESS AND INVOLVEMENT
Central nervous system	Chromosomal disorders Inborn errors of metabolism Cerebral dysgenesis Cerebral, spinal cord trauma	Central hypotonia Axial hypotonia more prominent Hyperactive reflexes
Motor neuron	Spinal muscular atrophy	Generalized weakness; often spares the diaphragm, facial muscles, pelvis, and sphincters
Nerve	Peripheral neuropathies	Distal muscle groups involved Weakness with wasting
Neuromuscular junction	Myasthenia syndromes Infantile botulism	Bulbar, oculomotor muscles exhibit greater degree of involvement
Muscle	Congenital myopathies Metabolic myopathies Congenital muscular dystrophy Congenital myotonic dystrophy	Weakness is prominent Proximal musculature Hypoactive reflexes Joint contractures

From Prasad AN, Prasad C: The floppy infant: contribution of genetic and metabolic disorders, Brain Dev *27:457–476, 2003.*

Molecular Genetic Markers

Many DNA markers of hereditary myopathies, including the muscular dystrophies, and neuropathies are available from leukocytes in blood samples. If the clinical manifestations suggest a particular disease, these tests can provide a definitive diagnosis and not subject the child to more-invasive procedures, such as muscle biopsy. Other molecular markers are available only in muscle biopsy tissue.

Nerve Conduction Velocity

Motor and sensory nerve conduction velocity may be measured electrophysiologically by using surface electrodes. Neuropathies of various types are detected by decreased conduction. The site of a traumatic nerve injury may also be localized. The nerve conduction value at birth is about half of the mature value achieved by age 2 yr. Tables are available for normal values at various ages in infancy, including for preterm infants. Because the nerve conduction velocity study measures only the fastest conducting fibers in a nerve, 80% of the total nerve fibers must be involved before slowing in conduction is detected.

Electromyography

Electromyography (EMG) requires insertion of a needle into the belly of a muscle and recording of the electric potentials in various states of contraction. It is less useful in pediatrics than in adult medicine, in part because of technical difficulties in recording these potentials in young children and in part because the best results require the patient's cooperation for full relaxation and maximal voluntary contraction of a muscle. Many children are too frightened to provide such cooperation. Characteristic EMG patterns distinguish denervation from myopathic involvement. The specific type of myopathy is not usually definitively diagnosed, but certain specialized myopathic conditions, such as myotonia, may be demonstrated. An EMG can transiently raise the serum CK level.

EMG combined with repetitive electrical stimulation of a motor nerve supplying a muscle to produce tetany is useful in demonstrating myasthenic decremental responses. Small muscles, such as the abductor digiti quinti of the hypothenar eminence, are used for such studies. Additional specialized tests, such as single myofiber EMG, may provide supplementary evidence in selected cases, but are performed only in large neuromuscular centers.

Imaging of Muscle and Central Nervous System

Ultrasonography, CT scans, and, more often, MRI are used to image muscle in many neuromuscular diseases. Although these methods are not always definitively diagnostic, in experienced hands, they provide a supplementary means of following the progression of disease over time. MRI is quite useful in identifying inflammatory myopathies of immune (dermatomyositis) or infectious (viral, bacterial, parasitic) origin. MRI is the study of choice to image the spinal cord, if a tumor or other structural lesion of the spinal cord is suspected as the cause of muscular dysfunction, and nerve roots and plexus (e.g., brachial plexus). Brain MRI is indicated in some myopathies, such as the congenital muscular dystrophies, in which cerebral malformations often accompany the myopathy because the mutated gene responsible is expressed in both muscle and the developing brain.

Muscle Biopsy

The muscle biopsy is traditionally the most important and specific diagnostic study of most neuromuscular disorders, if the definitive diagnosis of a hereditary disease is not provided by molecular genetic testing in blood. Not only are neurogenic and myopathic processes distinguished, but also the type of myopathy and specific enzymatic deficiencies may be determined. The vastus lateralis (quadriceps femoris) is the muscle that is most commonly sampled. The deltoid muscle should be avoided in most cases because it normally has a 60-80% predominance of type I fibers so that the distribution patterns of fiber types are difficult to recognize. Muscle biopsy is a simple outpatient procedure that may be performed under local anesthesia with or without femoral nerve block. Needle biopsies are preferred in some centers but are not percutaneous and require an incision in the skin similar to open biopsy; numerous samples must be taken to conduct an adequate examination of the tissue, and they provide inferior specimens. The volume of tissue from a needle biopsy is usually not adequate for all required studies, including supplementary biochemical studies, such as mitochondrial respiratory chain enzymes; a small, clean, open biopsy is therefore advantageous.

Histochemical studies of frozen sections of the muscle are obligatory in all pediatric muscle biopsies because many congenital and metabolic myopathies cannot be diagnosed from paraffin sections using conventional histologic stains. Immunohistochemistry is a useful supplement in some cases, such as for demonstrating dystrophin in suspected Duchenne muscular dystrophy or merosin in congenital muscular dystrophy. A portion of the biopsy specimen should be fixed for potential electron microscopy, but ultrastructure has additional diagnostic value only in selected cases. Interpretation of muscle biopsy samples is complex and should be performed by an experienced pathologist. A portion of frozen muscle tissue should also be routinely saved for possible biochemical analysis (mitochondrial cytopathies, carnitine palmitoyltransferase, acid maltase).

Immunocytochemical reactivities can be applied to formalin-fixed, paraffin-embedded sections and do not require frozen sections. Some reactivities, such as slow and fast myosin, can distinguish fiber types and hence substitute for myofibrillar adenosine triphosphatase histochemical stains in frozen sections. An increasing number of sarcolemmal regional proteins can be demonstrated that are specific for

Table 607-3 Differential Diagnosis of Infantile Hypotonia

Cerebral hypotonia
- Benign congenital hypotonia
- Chromosome disorders
- Prader-Willi syndrome
- Trisomy
- Chronic nonprogressive encephalopathy
- Cerebral malformation
- Perinatal distress
- Postnatal disorders
- Peroxisomal disorders
- Cerebrohepatorenal syndrome (Zellweger syndrome)
- Neonatal adrenoleukodystrophy
- Other genetic defects
- Familial dysautonomia
- Oculocerebrorenal syndrome (Lowe syndrome)
- Other metabolic defects
- Acid maltase deficiency (see "Metabolic Myopathies")
- Infantile G_M gangliosidosis

Spinal cord disorders

Spinal muscular atrophies
- Acute infantile
  - Autosomal dominant
  - Autosomal recessive
- Cytochrome-c oxidase deficiency
- X-linked
- Chronic infantile
  - Autosomal dominant
  - Autosomal recessive
- Congenital cervical spinal muscular atrophy
- Infantile neuronal degeneration
- Neurogenic arthrogryposis

Polyneuropathies
- Congenital hypomyelinating neuropathy
- Giant axonal neuropathy
- Hereditary motor-sensory neuropathies

Disorders of neuromuscular transmission
- Familial infantile myasthenia
- Infantile botulism
- Transitory myasthenia gravis

Fiber-type disproportion myopathies
- Central core disease
- Congenital fiber-type disproportion myopathy
- Myotubular (centronuclear) myopathy
- Acute
- Chronic
- Nemaline (nemaline rod) myopathy
- Autosomal dominant
- Autosomal recessive

Metabolic myopathies
- Acid maltase deficiency (Pompe disease)
- Cytochrome-c oxidase deficiency
- Other mitochondrial disorders
- Muscular dystrophies
- Bethlem myopathy
- Congenital dystrophinopathy
- Congenital muscular dystrophy
- Merosin deficiency primary
- Merosin deficiency secondary
- Merosin positive
- Congenital myotonic dystrophy

From Fenichel GM: The hypotonic infant. In Fenichel GM, editor: Clinical pediatric neurology: a signs and symptoms approach, *ed 5, Philadelphia, 2005, Saunders, p. 150.*

each of the various muscular dystrophies and include the dystrophins, merosin, sarcoglycans, and dystroglycans. Ryanodine receptors, important in myasthenia gravis and in malignant hyperthermia, also now can be demonstrated. In addition, immunocytochemical reactivities can distinguish the various types of inflammatory cells in autoimmune myopathies, including T and B lymphocytes and macrophages.

Table 607-4 Differential Diagnosis of Acute Flaccid Paralysis

Brainstem stroke

Brainstem encephalitis

Acute anterior poliomyelitis
- Caused by poliovirus
- Caused by other neurotropic viruses

Acute myelopathy
- Space-occupying lesions
- Acute transverse myelitis

Peripheral neuropathy
- Guillain-Barré syndrome
- Post–rabies vaccine neuropathy
- Diphtheritic neuropathy
- Heavy metals, biologic toxins, or drug intoxication
- Acute intermittent porphyria
- Vasculitic neuropathy
- Critical illness neuropathy
- Lymphomatous neuropathy

Disorders of neuromuscular transmission
- Myasthenia gravis
- Biologic or industrial toxins
- Tic paralysis

Disorders of muscle
- Hypokalemia
- Hypophosphatemia
- Inflammatory myopathy
- Acute rhabdomyolysis
- Trichinosis
- Familial periodic paralyses (normokalemic, hypokalemic, hyperkalemic)

From Hughes RAC, Camblath DR: Guillain-Barré syndrome, Lancet *366:1653–1666, 2005.*

Nerve Biopsy

The most commonly sampled nerve is the sural nerve, a pure sensory nerve that supplies a small area of skin on the lateral surface of the foot. Whole or fascicular biopsy specimens of this nerve may be taken. When the sural nerve is severed behind the lateral malleolus of the ankle, regeneration of the nerve occurs in more than 90% of cases, so that permanent sensory loss is not experienced. The sural nerve is often involved in many neuropathies whose clinical manifestations are predominantly motor.

Electron microscopy is performed on most nerve biopsy specimens because many morphologic alterations cannot be appreciated at the resolution of a light microscope. Teased fiber preparations are sometimes useful in demonstrating segmental demyelination, axonal swellings, and other specific abnormalities, but these time-consuming procedures are not done routinely. Special stains may be applied to ordinary frozen or paraffin sections of nerve biopsy material to demonstrate myelin, axoplasm, and metabolic products.

The molecular genetic identification of the specific mutation in many of the hereditary motor and sensory neuropathies, determined from blood samples, has rendered the nerve biopsy much less often performed than in the past, but it retains a great value in selected cases for which the etiology remains elusive despite genetic and electrophysiological testing.

Cardiac Assessment

Cardiac evaluation is important if myopathy is suspected because of involvement of the heart in muscular dystrophies and in inflammatory and metabolic myopathies. Electrocardiography often detects early cardiomyopathy or conduction defects that are clinically asymptomatic. At times, a more complete cardiac work-up, including echocardiography and consultation with a pediatric cardiologist, is indicated. Serial pulmonary function tests also should be performed in muscular dystrophies and in other chronic or progressive diseases of the motor unit.

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Chapter 608

Developmental Disorders of Muscle

Harvey B. Sarnat

A heterogeneous group of congenital neuromuscular disorders is known as the **congenital myopathies** (Tables 608-1 and 608-2). Most of these disorders have subcellular abnormalities that can be demonstrated only by muscle biopsy, by means of histochemistry and electron microscopy. In others, the muscle biopsy abnormality is not a subcellular anatomic defect but an aberration in the ratio and sizes of specific myofiber types. A genetic basis is demonstrated in many of the congenital myopathies, and molecular genetic testing from blood samples may confirm the diagnosis without muscle biopsy.

Most congenital myopathies are nonprogressive conditions, but some patients show slow clinical deterioration accompanied by additional changes in their muscle histology. In some congenital myopathies, such as severe neonatal nemaline myopathy, the clinical expression can be life-threatening because of dysphagia and respiratory and/or cardiac insufficiency. *Cardiomyopathy develops in some patients with congenital myopathies* (Table 608-3). Most of the diseases in the category of congenital myopathies are hereditary; others are sporadic. Although clinical features, including phenotype, can raise a strong suspicion of a congenital myopathy, the definitive diagnosis is determined by the histopathologic findings in the muscle biopsy specimen. In conditions for which the defective gene has been identified, the diagnosis may be established by the specific molecular analysis of the suspected gene expressed in lymphocytes. The morphologic and histochemical abnormalities differ considerably from those of the muscular dystrophies, spinal muscular atrophies, and neuropathies. Many are reminiscent of the embryologic development of muscle, thus suggesting possible defects in the genetic regulation of muscle development.

Congenital myopathies often show closer genetic relationships than previously appreciated between entities that have quite distinct pathologic phenotypes in the muscle biopsy and also distinctiveness in clinical expression with a degree of overlap. For example, mutation of the *tropomyosin-3* (*TPM3*) gene is one of the well-documented etiologies of nemaline myopathy, but identical genetic mutations of this gene are more recently also shown to be capable of causing isolated congenital fiber-type disproportion without nemaline rods, cap myopathy, centronuclear ("myotubular") myopathy, and central core/minicore disease.

MYOGENIC REGULATORY GENES AND GENETIC LOCI OF INHERITED DISEASES OF MUSCLE

A family of 4 myogenic regulatory genes shares encoding transcription factors of "basic helix-loop-helix" proteins associated with common DNA nucleotide sequences. These genes direct the differentiation of striated muscle from any undifferentiated mesodermal cell. The earliest basic helix-loop-helix gene to program the differentiation of myoblasts is myogenic factor 5 *(MYF5).* The second gene, *myogenin,* promotes

Text continued on p. 2970

Table 608-1 Classification of Muscular Dystrophies

	INHERITANCE	OMIM NUMBER	LOCUS	GENE SYMBOL	PROTEIN	MAIN LOCALIZATION
Duchenne or Becker muscular dystrophy	X-R	310200 (Duchenne); 300376 (Becker)	Xq21·2	*DMD*	Dystrophin	Sarcolemma-associated protein
LIMB-GIRDLE MUSCULAR DYSTROPHY						
Type 1A	AD	159000	5q31	*MYOT*	Myotilin	Sarcomere-associated protein (Z disc)
Type 1B	AD	159001	1q21·2	*LMNA*	Lamin A/C	Nuclear lamina-associated protein
Type 1C	AD	607780	3p25	*CAV3*	Caveolin-3	Sarcolemma-associated protein
Type 1D	AD	603511	7q	*DNAJB6*	Co-chaperone DNAJB6	Sarcomere-associated protein (Z disc)
Type 1E	AD	602067	6q23	*DES*	Desmin	Intermediate filament protein
Type 1F	AD	608423	7q32	Unknown	Unknown	Unknown
Type 1G	AD	609115	4p21	Unknown	Unknown	Unknown
Type 1H	AD	613530	3p23–p25	Unknown	Unknown	Unknown
Type 2A	AR	253600	15q15·1	*CAPN3*	Calpain-3	Myofibril-associated proteins
Type 2B	AR	253601	2p13	*DYSF*	Dysferlin	Sarcolemma-associated protein
Type 2C	AR	253700	13q12	*SGCG*	γ-Sarcoglycan	Sarcolemma-associated protein
Type 2D	AR	608099	17q12–q21·33	*SGCA*	α-Sarcoglycan	Sarcolemma-associated protein
Type 2E	AR	604286	4q12	*SGCB*	β-Sarcoglycan	Sarcolemma-associated protein
Type 2F	AR	601287	5q33	*SGCD*	δ-Sarcoglycan	Sarcolemma-associated protein

Table 608-1 Classification of Muscular Dystrophies—cont'd

	INHERITANCE	OMIM NUMBER	LOCUS	GENE SYMBOL	PROTEIN	MAIN LOCALIZATION
Type 2G	AR	601954	17q12	*TCAP*	Titin cap (telethonin)	Sarcomere-associated protein (Z disc)
Type 2H	AR	254110	9q31–q34	*TRIM32*	Tripartite motif-containing 32 (ubiquitin ligase)	Sarcomeric-associated protein (Z disc)
Type 2I	AR	607155	19q13·3	*FKRP*	Fukutin-related protein	Putative glycosyltransferase enzymes
Type 2J	AR	608807	2q31	*TTN*	Titin	Sarcomeric protein
Type 2K	AR	609308	9q34	*POMT1*	Protein-1-O-mannosyltransferase 1	Glycosyltransferase enzymes
Type 2L	AR	611307	11p14·3	*ANO5*	Anoctamin 5	Transmembrane protein, possible sarcoplasmic reticulum
Type 2M	AR	611588	9q31	*FKTN*	Fukutin	Putative glycosyltransferase enzymes
Type 2N	AR	613158	14q24	*POMT2*	Protein-O-mannosyltransferase 2	Glycosyltransferase enzymes
Type 2O	AR	613157	1p34	*POMGNT1*	Protein-O-linked mannose β 1,2-N-aminyltransferase 1	Glycosyltransferase enzymes
Type 2P	AR	613818	3p21	*DAG1*	Dystrophin-associated glycoprotein 1	Sarcomeric-associated protein
Type 2Q	AR	613723	8q24	*PLEC1*	Plectin 1	Sarcolemma-associated protein (Z disc)
FACIOSCAPULOHUMERAL MUSCULAR DYSTROPHY						
Type 1	AD	158900	4q35	Unknown	DUX4 and chromatin rearrangement	Nuclear
Type 2	AD	158901	18	Unknown	SMCHD1	Structural maintenance of chromosome's flexible hinge domain containing 1
EMERY-DREIFUSS MUSCULAR DYSTROPHY						
X-linked type 1	X-R	310300	Xq28	*EMD*	Emerin	Nuclear membrane protein
X-linked type 2	X-R	300696	Xq27·2	*FHL1*	Four and a half LIM domain 1	Sarcomere and sarcolemma
Autosomal dominant	AD	2181350	1q21·2	*LMNA*	Lamin A/C	Nuclear membrane protein
Autosomal recessive	AR	604929	1q21·2	*LMNA*	Lamin A/C	Nuclear membrane protein
With nesprin-1 defect	AD	612998	6q25	*SYNE1*	Spectrin repeat containing, nuclear envelope 1 (nesprin-1)	Nuclear membrane protein
With nesprin-2 defect	AD	5612999	4q23	*SYNE2*	Spectrin repeat containing, nuclear envelope 2 (nesprin-2)	Nuclear membrane protein
Congenital muscular dystrophy with merosin deficiency (MDC1A)	AR	607855	6q2	*LAMA2*	Laminin α_2 chain of merosin	Extracellular matrix proteins
Congenital muscular dystrophy	AR	604801	1q42	Unknown	Unknown	Unknown
Congenital muscular dystrophy and abnormal glycosylation of dystroglycan (MDC1C)	AR	606612	19q13	*FKRP*	Fukutin-related protein	Putative glycosyltransferase enzymes
Congenital muscular dystrophy and abnormal glycosylation of dystroglycan (MDC1D)	AR	608840	22q12	*LARGE*	Like-glycosyl transferase	Putative glycosyltransferase enzymes
Fukuyama congenital muscular dystrophy	AR	253800	9q31–q33	*FCMD*	Fukutin	Putative glycosyltransferase enzymes

Continued

Table 608-1 Classification of Muscular Dystrophies—cont'd

	INHERITANCE	OMIM NUMBER	LOCUS	GENE SYMBOL	PROTEIN	MAIN LOCALIZATION
WALKER–WARBURG SYNDROME						
With fukutin defect	AR	236670	9q31–q33	*FCMD*	Fukutin	Putative glycosyltransferase enzymes
With protein-O-mannosyltransferase 1 defect	AR	236670	9q34	*POMT1*	Protein-1-O-mannosyltransferase 1	Glycosyltransferase enzymes
With protein-O-mannosyltransferase 2 defect	AR	236670	14q24	*POMT2*	Protein-O-mannosyltransferase 2	Glycosyltransferase enzymes
With protein-O-linked mannose β 1,2-N-aminyltransferase 1 defect	AR	236670	1p34	*POMGNT1*	Protein-O-linked mannose β 1,2-N-aminyltransferase 1	Glycosyltransferase enzymes
With fukutin-related protein defect	AR	236670	19q13	*FKRP*	Fukutin-related protein	Putative glycosyltransferase enzymes
MUSCLE-EYE-BRAIN DISEASE						
With protein-O-linked mannose β 1,2-N-aminyltransferase 1 defect	AR	253280	1p34	*POMGNT1*	Protein-O-linked mannose β 1,2-N-aminyltransferase 1	Glycosyltransferase enzymes
With fukutin-related protein defect	AR	253280	19q13	*FKRP*	Fukutin-related protein	Putative glycosyltransferase enzymes
With protein-O-mannosyltransferase 2 defect	AR	253280	14q24	*POMT2*	Protein-O-mannosyltransferase 2	Glycosyltransferase enzymes
Congenital muscular dystrophy caused by glycosylation disorder	AR	NA	9q34·1	*DPM2*	Dolichyl-phosphate mannosyltransferase polypeptide 2	Glycosyltransferase enzymes
Congenital muscular dystrophy caused by glycosylation disorder	AR	NA	1q21·3	*DPM3*	Dolichyl-phosphate mannosyltransferase polypeptide 3	Glycosyltransferase enzymes
Congenital muscular dystrophy with mitochondrial structural abnormalities	mtDNA	602541	22q13	*CHKB*	Choline kinase	Sarcolemmal and mitochondrial membrane
Congenital muscular dystrophy with rigid spine syndrome	AR	602771	1p36	*SEPN1*	Selenoprotein N1	Endoplasmic reticulum protein
ULLRICH SYNDROME						
With collagen type VI subunit α_1 defect	AR	254090	21q22·3	*COL6A1*	Collagen type VI, subunit α_1	Extracellular matrix proteins
With collagen type VI subunit α_2 defect	AR	254090	21q22·3	*COL6A2*	Collagen type VI, subunit α_2	Extracellular matrix proteins
With collagen type VI subunit α_3 defect	AR	254090	2q37	*COL6A3*	Collagen type VI, subunit α_3	Extracellular matrix proteins
Congenital muscular dystrophy with integrin α_7 defect	AR	613204	12q13	*ITGA7*	Integrin α_7	External sarcolemmal protein
Congenital muscular dystrophy with integrin α_9 defect	AR	NA	3p21·3	*ITGA9*	Integrin α_9	External sarcolemmal protein
Muscular dystrophy with generalized lipodystrophy	AR	NA	17q21–q23	*PTRF*	Polymerase I and transcript release factor (cavin-1)	T tubules and sarcolemma
Oculopharyngeal muscular dystrophy	AD or AR	164300	14q11·2	*PABPN1*	Polyadenylate-binding protein nuclear 1	Unknown

AD, autosomal dominant; AR, autosomal recessive; NA, not assigned; OMIM, Online Mendelian Inheritance in Man; X-R, X-linked recessive.
From Mercuri E, Muntoni F: Muscular dystrophies. Lancet *381:845–858, 2013, Table 1.*

Table 608-2 Clinical Signs of Muscular Dystrophy

	MOTOR FUNCTION	DISTRIBUTION OF WEAKNESS	RIGID SPINE	CARDIOMYOPATHY	RESPIRATORY IMPAIRMENT	DISEASE COURSE	INCREASED CK	OTHER SIGNS
CONGENITAL-ONSET MUSCULAR DYSTROPHY								
Congenital muscular dystrophy with merosin deficiency	Independent ambulation generally not achieved in patients with absent merosin	Upper limbs > lower limbs	–	Not frequent	++	Slowly progressive	++	White matter changes on brain MRI
Congenital muscular dystrophy and abnormal glycosylation of dystroglycan (Walker-Warburg syndrome, muscle-eye-brain disease, congenital muscular dystrophy type 1C, etc.)	Independent ambulation generally not achieved	Upper limbs > lower limbs	–	Not frequent	+	Slowly progressive	++	Frequent structural brain changes
Congenital muscular dystrophy with rigid spine syndrome type 1 (SEPN1)	Ambulation achieved	Axial muscles > limbs	++	–	Early respiratory failure	Progression of respiratory signs > motor signs	N or +	Scoliosis
Ullrich syndrome	Ambulation achieved in ~50% but lost by middle teens	Proximal and axial	++	–	Early respiratory failure	Progression of respiratory and motor signs	N or +	Distal laxity
FROM EARLY-ONSET TO CHILDHOOD-ONSET MUSCULAR DYSTROPHY								
Duchenne muscular dystrophy	Independent ambulation achieved, but lost before age of 13 yr	Proximal > distal (pattern A)	–	++	++	Progression of motor, cardiac, and respiratory signs	++	Mental retardation in 30%
Emery-Dreifuss muscular dystrophy with lamin AC deficiency (type 2)	Ambulation achieved in all cases except for rare cases with congenital onset	Scapuloperoneal (pattern B)	++	++	In adulthood in the typical form, but also in childhood (congenital variants)	Slowly progressive	+ (+)	Frequent association with Dunningham-type lipodystrophy
Limb-girdle muscular dystrophy with lamin AC deficiency (type 1B)	Independent ambulation achieved, variable progression	Proximal > distal (pattern A)	+	++	In adulthood	Progression of cardiac signs > motor signs	+ (+)	None
Limb-girdle muscular dystrophy with calpain deficiency (type 2A)	Ambulation achieved	Proximal > distal (pattern A)	+	–	Not frequent	Slow progression	++	None

Continued

Table 608-2 Clinical Signs of Muscular Dystrophy—cont'd

	MOTOR FUNCTION	DISTRIBUTION OF WEAKNESS	RIGID SPINE	CARDIOMYOPATHY	RESPIRATORY IMPAIRMENT	DISEASE COURSE	INCREASED CK	OTHER SIGNS
CHILDHOOD-ONSET AND ADULTHOOD-ONSET MUSCULAR DYSTROPHY								
Becker muscular dystrophy	Independent ambulation achieved, variable progression	Proximal > distal (pattern A)	–	++	Not frequent	Progressive with substantial variability	++	None
Limb-girdle muscular dystrophy with sarcoglycan deficiency (types 2C, 2D, 2E, 2F)	Independent ambulation achieved, generally lost in the 2nd decade	Proximal > distal (pattern A)	–	++	++	Progression of motor, cardiac, and respiratory signs	++	None
Limb-girdle muscular dystrophy with abnormal glycosylation of dystroglycan (types 2I, 2K, 2L, 2M, 2N, 2O)	Independent ambulation achieved, variable progression	Proximal > distal (pattern A)	–	++	+(+)	Progressive	++	Mental retardation reported in some cases
Limb-girdle muscular dystrophy with dysferlin deficiency (type 2B)	Independent ambulation always achieved	Both pattern A and pattern E	–	–	–	Progressive in adulthood	++	None
Limb-girdle muscular dystrophy with telethonin deficiency (type 2G)	Independent ambulation achieved, generally lost in the 4th decade	Proximal > distal (pattern A); in some pattern B	–	+	+	Progressive in adulthood	+ (+)	None
Limb-girdle muscular dystrophy with titin deficiency (type 2J)	Independent ambulation achieved	Proximal > distal (pattern A) but also pattern E	–	–	–	Roughly half lose ambulation in adulthood	++	None
Facioscapulohumeral dystrophy	Independent ambulation achieved, variable progression	Pattern D	–	–	Uncommon and mild	Slowly progressive	N or +	Neurosensory hearing loss and retinal degeneration
Emery-Dreifuss muscular dystrophy with merin deficiency (type 1)	Independent ambulation achieved, variable progression	Scapuloperoneal (pattern B)	+	++	Not frequent	Progression of cardiac signs > motor signs	+ (+)	None
ADULT-ONSET MUSCULAR DYSTROPHY								
Limb-girdle muscular dystrophy with anoctamin deficiency (type 2L)	Onset in adulthood, 8:1 ratio of men to women	Mainly lower limbs pattern A, rarely pattern E	–	–	–	Slowly progressive in adulthood	++	None
Limb-girdle muscular dystrophy type 1A (myotilin)	Independent ambulation achieved	Proximal > distal (pattern A)	–	–	–	Generally slowly progressive in adulthood	+	Dysarthria in some cases
Limb-girdle muscular dystrophy with caveolin deficiency (type 1C)	Independent ambulation achieved; rippling might be seen before weakness	Proximal and distal	–	+	–	Slowly progressive, variable	++	Cramps, rippling, percussion-induced repetitive contractions

–, Absent; +, mild; ++, severe; +(+), variable; CK, creatine kinase; N, normal.
From Mercuri E, Muntoni F: Muscular dystrophies. Lancet *381:845–858, 2013, Table 2.*

Table 608-3 Cardiac Involvement in Muscular Dystrophies

	ONSET AND FIRST SIGNS	PROGRESSION	CARDIAC DEATH	SURVEILLANCE
Duchenne muscular dystrophy	Dilated cardiomyopathy with reduced left-ventricular ejection fraction after 10 yr of age	Dilated cardiomyopathy in almost all patients by 18 yr of age. Ventricular dysrhythmias occur in older patients	Congestive heart failure or sudden death in 20% of patients, although the contribution of heart to death of ventilated patients is now well established	Echocardiography every 2 yr in the 1st decade of life and annually after 10 yr of age (or more frequently if abnormalities are identified)
Becker muscular dystrophy	Dilated cardiomyopathy, generally after 10 yr of age	Present in 40% of patients older than 18 yr and more than 80% of those older than 40 yr. Most patients develop dilated cardiomyopathy followed by ventricular arrhythmias	Death from congestive heart failure and arrhythmias is estimated to occur in up to 50% of cases. Cardiac transplants reported	Echocardiography at least every 5 yr
Myotonic dystrophy	Cardiac abnormalities can occur as early as the 2nd decade of life	Conduction deficits occur in about 65% of adult patients	20-30% of patients; mean 54 yr of age. Sudden death is mainly caused by conduction blocks, but ventricular tachyarrhythmias are also a possible cause of death	ECG yearly. Holter monitoring is recommended in patients with ECG abnormalities to detect asymptomatic conduction blocks and arrhythmias
EMERY-DREIFUSS MUSCULAR DYSTROPHY				
X-linked recessive Emery-Dreifuss muscular dystrophy (type 1)	Conduction disturbances generally in the 2nd decade	Ventricular myocardium might become involved, leading to mild ventricular dilation and low-to-normal systolic function	Sudden death is by far the most common cause of death and can be very unpredictable	ECG and yearly Holter monitoring are indicated. Pacemaker implantation should be considered if sinus node or atrioventricular node disease develops. Defibrillator might be needed in some patients
Emery-Dreifuss muscular dystrophy 2 and limb-girdle muscular dystrophy 1B	Conduction disease and cardiac failure	Dysrhythmias (sinus bradycardia, atrioventricular conduction block, or atrial arrhythmias) present in 92% of patients older than 30 yr	Sudden death reported also in patients with pacemaker. Rare death with defibrillator also reported. Cardiac failure. Cardiac transplants reported	ECG and yearly Holter monitoring are indicated. Defibrillator implantation should be considered as pacemaker does not have a substantial effect on mortality
LIMB-GIRDLE MUSCULAR DYSTROPHY				
Sarcoglycanopathies	ECG and/or echocardiographic abnormalities reported in 20-30% of patients (especially β and δ variants; less common in α variant)	Severe dilated cardiomyopathy and lethal ventricular arrhythmias might occur in patients with Duchenne muscular dystrophy–like dystrophy	Typically by cardiac failure. Cardiac transplants reported	No evidence-based standards of care exist, but experts have made recommendations
Limb-girdle muscular dystrophy 2I	Cardiac involvement reported in 29-62% of limb-girdle muscular dystrophy 2I. Dilated cardiomyopathy may start in teenage yr	Symptomatic cardiac failure over time, at a mean age of 38 yr (range: 18-58 yr)	Cardiac failure. Cardiac transplants reported	No evidence-based standards of care exist, but experts have made recommendations
Limb-girdle muscular dystrophy 1E	Dilated, restrictive, hypertrophic cardiomyopathies and arrhythmias. Cardiac involvement can precede muscle weakness in some patients	Major cardiac signs, such as atrioventricular block, can be the presenting symptom or occur within a decade of onset of muscle weakness	Life-threatening cardiac complications in roughly 50% of patients, at a mean age of 40 yr, including sudden death, end-stage heart failure, atrioventricular block, and syncope	No evidence-based standards of care exist, but experts have made recommendations

Continued

Table 608-3 Cardiac Involvement in Muscular Dystrophies—cont'd

	ONSET AND FIRST SIGNS	PROGRESSION	CARDIAC DEATH	SURVEILLANCE
CONGENITAL MUSCULAR DYSTROPHY				
Congenital muscular dystrophy merosin muscular dystrophy type C1A	Occasional reports of reduced left ventricular systolic function	Not well characterized	Rare by cardiac failure	No evidence-based standards of care exist, but experts have made recommendations
Fukuyama congenital muscular dystrophy	Systolic left-ventricular dysfunction may develop in the 2nd decade	Symptomatic cardiac failure over time	Death from congestive heart failure might occur by the age of 20 yr	No evidence-based standards of care exist, but experts have made recommendations
Muscular dystrophy type C1C	Dilated cardiomyopathy reported in young children	Not well characterized	Not reported	No evidence-based standards of care exist, but experts have made recommendations
Facioscapulohumeral muscular dystrophy	Uncommon	Not well characterized	Not reported	No evidence-based standards of care exist, but experts have made recommendations

ECG, electrocardiogram.
From Mercuri E, Muntoni F: Muscular dystrophies. Lancet *381:845–858, 2013, Table 3.*

fusion of myoblasts to form myotubes. *Herculin* (also known as *MYF6*) and *MYOD1* are the other 2 myogenic genes. *Myf5* cannot support myogenic differentiation without myogenin, *MyoD,* and *MYF6.* Each of these 4 genes can activate the expression of at least 1 other and, under certain circumstances, can autoactivate as well. Another recently discovered gene known as **myomaker** also facilitates myoblast fusion. The expression of *MYF5* and of *herculin* is transient in early ontogenesis but returns later in fetal life and persists into adult life.

The human locus of the *MYOD1* gene is on chromosome 11, very near to the domain associated with embryonal rhabdomyosarcoma. The genes *Myf5* and *herculin* are on chromosome 12, and *myogenin* is on chromosome 1.

The myogenic genes are activated during muscle regeneration, recapitulating the developmental process; *MyoD* in particular is required for myogenic stem cell (satellite cell) activation in adult muscle. *PAX3, PAX7,* and *WNT3a* genes also play important roles in myogenesis and interact with each of the 4 basic genes mentioned above. Another gene, *myostatin,* is a negative regulator of muscle development by preventing myocytes from differentiating. The precise integrative roles of the myogenic genes in developmental myopathies are not yet fully defined.

The myogenic genes are important not only for fetal myogenesis but also for regeneration of muscle at any age, particularly in degenerative diseases such as muscular dystrophies and autoimmune inflammatory myopathies and in injuries of muscle secondary to trauma or to toxins. Satellite cells in mature muscle that mediate regeneration have the same somitic origin as embryonic muscle progenitor cells, but the genes that regulate them differ. *Pax3* and *Pax7* mediate the migration of primitive myoblast progenitors from the myotomes of the somites to their peripheral muscle sites in the embryo, but only 1 of 2 *Pax7* genes continues to act postnatally for satellite cell survival. Then it, too, no longer is required after the juvenile period for muscle satellite (i.e., stem) cells to become activated for muscle regeneration.

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608.1 Myotubular Myopathy (Centronuclear Myopathy)

Harvey B. Sarnat

The term **myotubular myopathy** is a misnomer because it implies maturational arrest of fetal muscle during the myotubular stage of development at 8-15 wk of gestation. It was based on the morphologic appearance of myofibers as a row of central nuclei and mitochondria within a core of cytoplasm, with contractile myofibrils forming a cylinder around this core (Fig. 608-1). These morphologically abnormal myofibers are not true fetal myotubes, however; hence the more neutral and descriptive term **centronuclear myopathy** is preferred.

PATHOGENESIS

The common pathogenesis involves loss of myotubularin protein, leading to structural and functional abnormalities in the organization of T-tubules and sarcoplasmic reticulum and defective excitation-contraction coupling.

CLINICAL MANIFESTATIONS

Fetal movements can decrease in late gestation. Polyhydramnios is a common complication because of pharyngeal weakness of the fetus and inability to swallow amniotic fluid.

At birth, affected infants have a thin muscle mass involving axial, limb girdle, and distal muscles; severe generalized hypotonia; and diffuse weakness. Respiratory efforts may be ineffective, requiring ventilatory support. Gavage feeding may be required because of weakness of the muscles of sucking and deglutition. The testes are often undescended. Facial muscles may be weak, but infants do not have the characteristic facies of myotonic dystrophy. Ptosis may be a prominent feature. Ophthalmoplegia is observed in a few cases. The palate may be high. The tongue is thin, but fasciculations are not seen. Tendon stretch reflexes are weak or absent.

Myotubular myopathy is not associated with cardiomyopathy (mature cardiac muscle fibers normally have central nuclei), but one report describes complete atrioventricular block without cardiomyopathy in a patient with confirmed X-linked myotubular myopathy. Congenital anomalies of the central nervous system or of other systems are not associated. A single patient with progressive dementia was reported, who had a mutation removing the start signal of exon 2. Patients with much milder symptoms or a much later age of onset with mutations in the same gene are now known. Some of these are manifesting carriers.

LABORATORY FINDINGS

Serum levels of creatine kinase (CK) are normal. Electromyography does not show evidence of denervation; results are usually normal or show minimal nonspecific myopathic features in early infancy. Nerve conduction velocity may be slow but is usually normal. The

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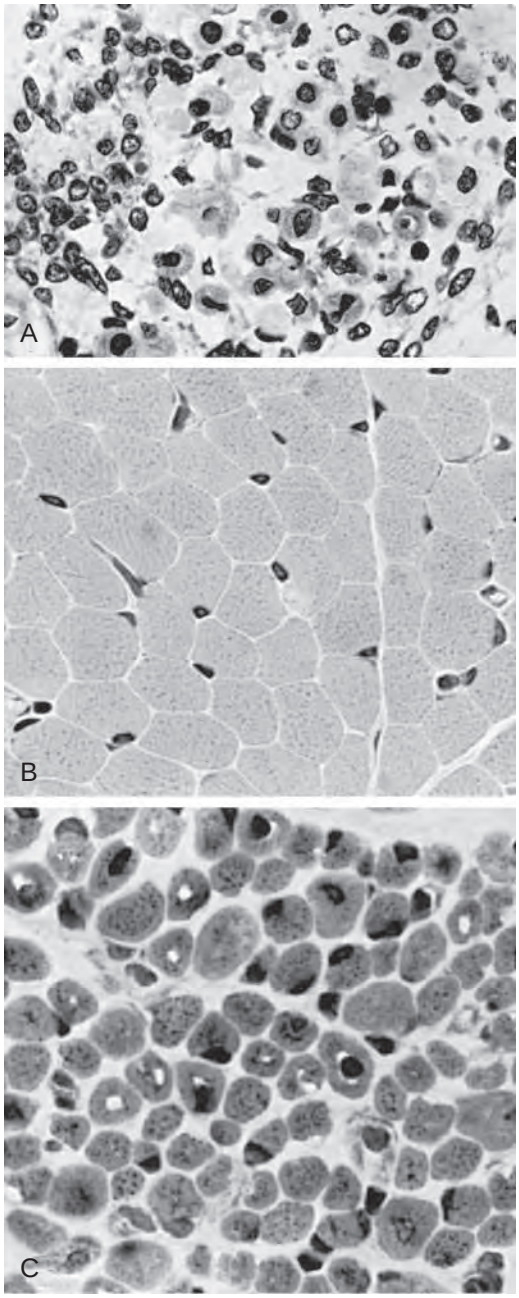


Figure 608-1 Cross section of muscle from a 14 wk old human fetus **(A),** a normal full-term neonate **(B),** and a term neonate with X-linked recessive myotubular myopathy **(C).** Myofibers have large central nuclei in the fetus and in myotubular myopathy patient, and nuclei are at the periphery of the muscle fiber in the term neonate as in the adult (hematoxylin and eosin, ×500).

electrocardiogram appears normal. Chest radiographs show no cardiomegaly; the ribs may be thin.

DIAGNOSIS

If the diagnosis is strongly suspected from the clinical presentation, especially if this diagnosis was confirmed in a sibling, genetic tests can be performed in the neonatal period. In most cases the diagnosis is not so evident, but the muscle biopsy findings are diagnostic at birth, even in premature infants. More than 90% of muscle fibers are small and have centrally placed, large vesicular nuclei in a single row. Spaces between nuclei are filled with sarcoplasm containing mitochondria. Histochemical stains for oxidative enzymatic activity and glycogen reveal a central distribution as in fetal myotubes. The cylinder of myofibrils shows mature histochemical differentiation with adenosine triphosphatase stains. The connective tissue of muscle spindles, blood vessels, intramuscular nerves, and motor end plates is mature. Ultrastructural features other than those that define the disease are also mature. Electron microscopy shows disorganized triads and focal loss of myofilaments. Vimentin and desmin show strong immunoreactivity in muscle fibers in congenital centronuclear myopathy and no demonstrable activity in normal term neonatal muscle. The molecular genetic marker in blood is available also for early prenatal diagnosis if suspicion is strong because of family history. Table 608-4 distinguishes centronuclear myopathy from other congenital myopathies.

GENETICS

At least 5 genes are involved in this disorder and account for approximately 80% of patients. These include mutations in myotubularin (*MTM1* gene) with X-linked severe manifestations; dynamin 2 (*DNM2*) with autosomal dominant or sporadic occurrence; amphiphysin 2 (*BIN1*) and titin (*TTN*) mutations with autosomal recessive inheritance and ryanodine receptor 1 (*RYR1*), with autosomal recessive or sporadic occurrence.

X-linked recessive inheritance is the most common trait in this disease affecting boys. The mothers of affected infants are clinically asymptomatic, but their muscle biopsy specimens show minor alterations. Genetic linkage on the X chromosome has been localized to the Xq28 site, a locus different from the Xp21 gene of Duchenne and Becker muscular dystrophies. A deletion in the responsible *MTM1* gene has been identified. It encodes a protein called myotubularin. This gene belongs to a family of similar genes encoding enzymatically active and inactive forms of phosphatidylinositol-3-phosphatases that form dimers. *MTM1*, dynamin-2, and amphiphysin all are localized to the T-tubule wall in triads. This crucial region is where the action potential releases a signal to the ryanodine receptor to release calcium. The pathogenesis is in the regulation of enzymatic activity and binding to other proteins induced by dimer interactions. Although only a single *MTM1* gene is involved, 5 distinct point mutations and many different alleles, as well as large duplications, can produce the same clinical disease. Mutations in the dynamin-2 protein result in an autosomal dominant form of centronuclear myopathy and may account for up to half of all patients with centronuclear myopathy, but these cases usually are mild and might not manifest clinically until adult life as diffuse, slowly progressive weakness and generalized muscular pseudohypertrophy.

Other **rarer centronuclear myopathies** also are known; some are autosomal recessive and affect both sexes and others are sporadic and of unknown genetic origin. The recessive forms are sometimes divided into an early-onset form with or without ophthalmoplegia and a late-onset form without ophthalmoplegia.

TREATMENT

Only supportive and palliative treatment is presently available. Progressive scoliosis may be treated by long posterior fusion. Genetic and neuropathologic studies of X-linked centronuclear ("myotubular") myopathy have led to effective gene therapy in mice and in dogs, so that even after a single dose the animals are more ambulatory and have much improved weakness. Gene replacement therapy in this disease is now being studied in humans.

PROGNOSIS

Approximately 75% of severely affected neonates with the X-linked disease die within the 1st few wk or mo of life. Survivors do not experience a progressive course but have major physical handicaps, rarely walk, and remain severely hypotonic. Late-onset and especially autosomal dominant forms have a much better prognosis, often with mild static weakness.

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Table 608-4 Specific Congenital Myopathies: Distinguishing Clinical Features

MYOPATHY	NEONATAL HYPOTONIA AND WEAKNESS	SEVERE FORM WITH NEONATAL DEATH	FACIAL WEAKNESS	PTOSIS	EXTRAOCULAR MUSCULAR WEAKNESS
Central core disease	+	0	±	0	0
Nemaline myopathy	+	+	+	0	0
Myotubular myopathy (centronuclear myopathy)	+	+	+	+	+
Congenital fiber-type disproportion	+	±	±	0	+

+, Often a prominent feature; ±, variably a prominent feature; 0, not a prominent feature.
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608.2 Congenital Muscle Fiber-Type Disproportion

Harvey B. Sarnat

Congenital muscle fiber-type disproportion (CMFTD) occurs as an isolated congenital myopathy but also develops in association with various unrelated disorders that include nemaline rod disease, Krabbe disease (globoid cell leukodystrophy) early in the course before expression of the neuropathy, cerebellar hypoplasia and certain other brain malformations, fetal alcohol syndrome, some glycogenoses, multiple sulfatase deficiency, Lowe syndrome, rigid spine myopathy, and some infantile cases of myotonic muscular dystrophy. CMFTD should, therefore, be regarded as a syndrome, unless a specific genetic mutation is confirmed.

PATHOGENESIS

The association of CMFTD with cerebellar hypoplasia suggests that the pathogenesis may be an abnormal suprasegmental influence on the developing motor unit during the stage of histochemical differentiation of muscle between 20 and 28 wk of gestation. Muscle fiber types and growth are determined by innervation and are mutable even in adults. Although CMFTD does not actually correspond with any normal stage of development, it appears to be an embryologic disturbance of fiber type differentiation and growth.

CLINICAL MANIFESTATIONS

As an isolated condition not associated with other diseases, CMFTD is a nonprogressive disorder present at birth. Patients have generalized hypotonia and weakness, but the weakness is usually not severe and respiratory distress and dysphagia are rare. Contractures are present at birth in 25% of patients. Poor head control and developmental delay for gross motor skills are common in infancy. Walking is usually delayed until 18-24 mo but is eventually achieved. Because of the hypotonia, subluxation of the hips can occur. Muscle bulk is reduced. The muscle wasting and hypotonia are proportionately greater than the weakness, and the child may be stronger than expected during examination. Cardiomyopathy is a rare complication.

The facies of children with CMFTD often raise suspicion, especially if the child is referred for assessment of developmental delay and hypotonia. The head is dolichocephalic, and facial weakness is present. The palate is usually high arched. Thin muscles of the trunk and extremities give a thin, wasted appearance. The phenotype is very similar to that of nemaline myopathy that also includes CMFTD as part of the pathologic picture. Patients do not complain of myalgias. The clinical course is nonprogressive.

LABORATORY FINDINGS

Serum CK, electrocardiogram, electromyography, and nerve conduction velocity results are normal in simple CMFTD. If other diseases are associated, laboratory investigation of those conditions discloses the specific features.

DIAGNOSIS

CMFTD is diagnosed by muscle biopsy that shows disproportion in size and relative ratios of histochemical fiber types: Type I fibers are uniformly small, and type II fibers are hypertrophic; type I fibers are more numerous than type II fibers. Degeneration of myofibers and other primary myopathic features are absent. The biopsy is diagnostic at birth. Table 608-2 lists the features that distinguish CMFTD from other congenital myopathies.

GENETICS

Many cases of simple CMFTD are sporadic, although autosomal recessive inheritance is well documented in some families and an autosomal dominant trait is suspected in others. The genetic basis is heterogeneous in hereditary forms; a mutation in the insulin receptor gene at 19p13.2 is reported. Translocation t(10;17) was seen in 1 family. X-linked transmission with linkage to Xp23.12-p11.4 and Xq13.1-q22.1 also is described. In 3 unrelated families with CMFTD, a heterozygous missense mutation of the skeletal muscle α-actin gene (*ACTA1*) was demonstrated, but this genetic defect represents a minority; mutations in *TPM3* are a more common genetic finding. As with X-linked myotubular myopathy, large duplications in the *TPM3* gene can cause CMFTD. In CMFTD associated with cerebellar hypoplasia, the genetic effect is on cerebellar development and the muscular expression is secondary.

TREATMENT

No drug therapy is available. Physiotherapy may be helpful for some patients in strengthening muscles that do not receive sufficient exercise in daily activities. Mild congenital contractures often respond well to gentle range-of-motion exercises and rarely require plaster casting or surgery.

Bibliography is available at Expert Consult.

608.3 Nemaline Rod Myopathy

Harvey B. Sarnat

Nemaline rods (derived from the Greek *nema*, meaning "thread") are rod-shaped, inclusion-like abnormal structures within muscle fibers. They are difficult to demonstrate histologically with conventional hematoxylin-and-eosin stain, but are easily seen with special stains. They are not foreign inclusion bodies but rather consist of excessive Z-band material with a similar ultrastructure (Fig. 608-2). Chemically, the rods are composed of actin, α-actinin, tropomyosin-3, and the protein nebulin. Nemaline rod formation may be an unusual reaction of muscle fibers to injury because these rod structures have rarely been found in other diseases. They are most abundant in the congenital myopathy known as *nemaline rod disease.* Most rods are within the myofibrils, but intranuclear rods are occasionally demonstrated by electron microscopy. Intranuclear rods occur mainly in neonates with

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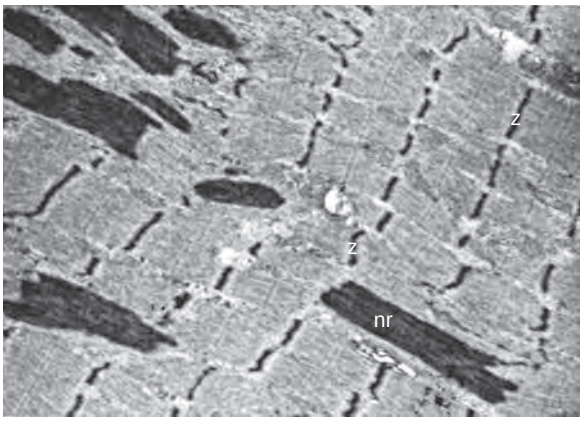


Figure 608-2 Electron micrograph of the muscle from a patient shown in Figure 608-4. Nemaline rods *(nr)* are seen within many myofibrils. They are identical in composition to the normal Z bands *(z)* (×6,000).



Figure 608-3 Back of a 13 yr old girl with the juvenile form of nemaline rod disease. The paraspinal muscles are very thin, and winging of the scapulas is evident. The muscle mass of the extremities is also greatly reduced proximally and distally.

severe weakness; they usually indicate *ACTA1* mutations and may coexist with the more usual cytoplasmic rods. Nemaline myopathy caused by *ACTA1* mutation is one of a spectrum of "actinopathies."

Mutations in tropomyosin-2 (*TPM2*) can cause a congenital myopathy related to nemaline rod myopathy, designated **cap myopathy**, in which accumulations of distorted myofilaments are focally present on the periphery of fibers. They may coexist with myofibrillar nemaline rods. Somatic mosaicism is demonstrated in *TPM2*-related nemaline myopathy with cap structures.

CLINICAL MANIFESTATIONS

Neonatal, infantile, and juvenile forms of the disease are known. The neonatal form is severe and usually fatal because of respiratory failure since birth. In the infantile form, generalized hypotonia and weakness, which can include bulbar-innervated and respiratory muscles, and a very thin muscle mass are characteristic (Fig. 608-3).



Figure 608-4 Infantile form of nemaline rod disease in a 6 yr old boy. Facial weakness and generalized muscle wasting are severe. The head is dolichocephalic. The mouth is usually open because the masseters are too weak to lift the mandible against gravity for more than a few seconds.

The head is dolichocephalic, and the palate high arched or even cleft. Muscles of the jaw may be too weak to hold it closed (Fig. 608-4). Decreased fetal movements are reported by the mother, and neonates suffer from hypoxia and dysphagia; arthrogryposis may be present. Infants with severe neonatal and infantile nemaline myopathy have facies and phenotype that are nearly indistinguishable from those of neonatal myotonic dystrophy, but their mothers have normal facies. The juvenile form is the mildest and is not associated with respiratory failure, but the phenotype, including facial involvement, is similar.

LABORATORY FINDINGS

Serum CK level is normal or mildly elevated. The muscle biopsy is diagnostic. In addition to the characteristic nemaline rods, it also shows CMFTD or at least fiber type I predominance. In some patients, uniform type I fibers are seen with few or no type II fibers. Focal myofibrillar degeneration and an increase in lysosomal enzymes have been found in a few severe cases associated with progressive symptoms. Intranuclear nemaline rods, demonstrated by electron microscopy, correlate with the most severe neonatal manifestations. Because nemaline bodies can occur in other myopathies, their presence in the muscle biopsy is not pathognomonic in the absence of the supportive clinical manifestations. Adult-onset cases may be associated with monoclonal gammopathy.

GENETICS

Autosomal dominant and autosomal recessive forms of nemaline rod disease occur, and an X-linked dominant form in girls also can occur. Nemaline myopathy can be caused by mutation in at least 7 genes, including α-actin, α-tropomyosin, β-tropomyosin, troponin-T, nebulin, cofilin-2, and Kelch-like family member *(KLML40)*. The latter causes severe neonatal autosomal recessive nemaline myopathy. The proteins encoded for by all these genes are related to the thin filaments of myofibrils. Dominant nemaline myopathy is most often caused by mutations in *ACTA-1* or α-tropomyosin (*TPM3* at the 1q21-q23 locus); recessive mutations most frequently result from nebulin mutations (2q21.2-q22 locus), which account for about half the cases of nemaline myopathy and are particularly prevalent in Ashkenazi Jews. Some

mutations in the α-actin gene give rise to a severe neonatal myopathy with masses of exclusively thin filaments, with or without rods. Mutations in tropomyosin-2 can cause a congenital myopathy with nonspecific findings. In α-actin defects both autosomal dominant and recessive varieties occur at the same 1q42.1 locus. The autosomal dominantly inherited defect of β-tropomyosin at 9q13 and the α-tropomyosin defects are rare and account for only 3% of patients with nemaline myopathy. An autosomal recessive troponin-T defect is at locus 19q13 and has been found only in the Amish population, in whom the incidence of nemaline myopathy is as high as 1 in 500, whereas in Australia in non-Amish ethnic groups it is estimated at 1 in 500,000.

TREATMENT AND PROGNOSIS

Therapy is supportive. Survivors are confined to an electric wheelchair and are usually unable to overcome gravity. Both proximal and distal muscles are involved. Congenital arthrogryposis can occur and predicts a poor prognosis. Gastrostomy may be needed for chronic dysphagia. In the juvenile form, patients are ambulatory and are able to perform most tasks of daily living. Weakness is not usually progressive, but some patients have more difficulty over time or enter a phase of progressive weakness. Cardiomyopathy is an uncommon complication. Death usually results from respiratory insufficiency, with or without superimposed pneumonia.

Bibliography is available at Expert Consult.

608.4 Central Core, Minicore, and Multicore Myopathies

Harvey B. Sarnat

Central core disease most often manifests itself in children with slow motor development who are hypotonic and have mild weakness especially in the hip girdle; congenital dislocation or dysplasia of the hips may be diagnosed in the neonatal period. In older children, central core disease is an important differential diagnosis of progressive thoracolumbar scoliosis. Central core myopathies are transmitted as either an autosomal dominant or recessive trait and are caused by the same abnormal gene at the 19q13.1 locus. This gene programs the ryanodine receptor *(RYR1)*, a tetrameric receptor that contains a non–voltage-gated calcium channel; it is prevalent in the sarcoplasmic reticulum and especially at the junction of the T-tubule with the cisternae of the sarcoplasmic reticulum. It contains the channel by which calcium is released among the myofilaments. Mutations in the *RYR1* gene are also the cause of **malignant hyperthermia**.

Infantile hypotonia, proximal weakness, muscle wasting, and involvement of facial muscles and neck flexors are the typical features in both the dominant and recessive forms. Contractures of the knees, hips, and other joints are common, and kyphoscoliosis and pes cavus often develop, even without much axial or distal muscle weakness. There is a high incidence of cardiac abnormalities. The course is not progressive, except for the contractures. In one variant, external ophthalmoplegia also is present. Rare cases of minicore myopathy also show hypertrophic cardiomyopathy associated with short-chain acyl-coenzyme A dehydrogenase deficiency.

The disease is characterized pathologically by central cores within muscle fibers in which only amorphous, granular cytoplasm is found with an absence of myofibrils and organelles. Histochemical stains show a lack of enzymatic activities of all types within these cores, as well as absence of contractile proteins (actin and myosin) that form the thin and thick myofilaments. Variants of central cores, called *minicores* and *multicores*, are described in some families.

Minicores or multicores are small areas, usually multiple within muscle fibers, that lack mitochondria and show Z-disc streaming. They can be caused by mutations in the gene (*SEPN1*) for the selenoprotein N, localized to triads, but *RYR1* mutations also are reported. The distinction previously made between single and multiple cores in myofibers is now believed to be of little importance and they represent the same basic disease process.

The serum CK value is normal in central core disease except during crises of malignant hyperthermia, which can result in rhabdomyolysis or extensive acute myofiber necrosis (see Chapter 611.2). Central core disease is consistently associated with malignant hyperthermia, which can precede the diagnosis of central core disease. All patients should have special precautions with pretreatment with dantrolene before an anesthetic agent is administered.

Bibliography is available at Expert Consult.

608.5 Myofibrillar Myopathies

Harvey B. Sarnat

Most myofibrillar myopathies are not symptomatic in childhood, but occasionally older children and adolescents show early symptoms of nonspecific proximal and distal weakness. An infantile form also occurs and can cause mild neonatal hypotonia and weakness with disproportionately severe dysphagia and respiratory insufficiency, at times leading to early death. It is not progressive, however, and some patients show improvement in later infancy and early childhood, acquiring the ability to swallow by 3 yr of age. Cardiomyopathy is a complication in a minority.

The diagnosis is by muscle biopsy: some sarcomeres of myofibers have disorganization or dissolution of myofibrils adjacent to other areas of normal sarcomeres within the same fiber. These zones are associated with streaming of the Z bands and focally increased desmin intermediate filaments, myotilin, and αB-crystallin. Immunocytochemical and ultrastructural study of the muscle biopsy tissue is required. Mutation in the desmin gene is implicated as a contributory factor in the etiology of both adult-onset and childhood myofibrillar myopathies, but the primary defect is a mutation in, not just an upregulation of, the αB-crystallin molecule. An associated secondary mitochondrial defect is detected in some patients.

A unique autosomal recessive myopathy in Cree native infants is characterized by severe generalized muscular hypertonia that is not relieved by neuromuscular blockade and hence is myopathic in origin. Most die in infancy of respiratory insufficiency as a result of diaphragmatic involvement. The muscle biopsy shows findings similar to many other myofibrillar myopathies (Fig. 608-5); a novel αB-crystallin gene mutation is the cause.

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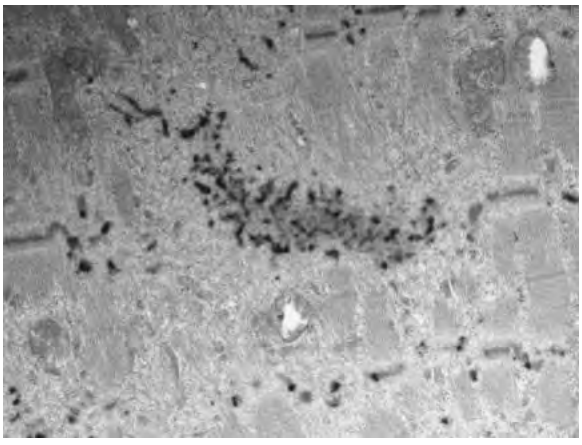


Figure 608-5 Electron micrograph of quadriceps femoris muscle biopsy of a 1 mo old native girl with Cree myofibrillar myopathy. Within the same myofiber, some sarcomeres are well formed and others exhibit disarray of the thick and thin myofilaments and fragmentation of Z bands. Mitochondria appear normal (×21,400).

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608.6 Brain Malformations and Muscle Development

Harvey B. Sarnat

Infants with **cerebellar hypoplasia** are hypotonic and developmentally delayed, especially in gross motor skills. Muscle biopsy is sometimes performed to exclude a congenital myopathy. A biopsy specimen can show delayed maturation of muscle, fiber-type predominance, or CMFTD. Other malformations of the brain may also be associated with abnormal histochemical patterns, but supratentorial lesions are less likely than brainstem or cerebellar lesions to alter muscle development. Abnormal descending impulses along bulbospinal pathways probably alter discharge patterns of lower motor neurons that determine the histochemical differentiation of muscle at 20-28 wk of gestation. The corticospinal tract does not participate because it is not yet functional during this period of fetal life.

In several congenital muscular dystrophies (see Chapter 609.6), including the Walker-Warburg syndrome, Fukuyama disease, and muscle-eye-brain disease of Santavuori, major cerebral malformations, such as pachygyria and lissencephaly, are present. It is clear that in at least some of these cases, the abnormal protein implicated in pathogenesis of the syndrome is expressed in both muscle and brain and is important for both stabilization of muscle and migration of central neurons.

Bibliography is available at Expert Consult.

608.7 Amyoplasia

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Congenital absence of individual muscles is common and is often asymmetric. A common aplasia is the *palmaris longus muscle* of the ventral forearm, which is absent in 30% of normal subjects and is fully compensated for by other flexors of the wrist. Unilateral absence of a *sternocleidomastoid muscle* is one cause of congenital torticollis. Absence of 1 *pectoralis major muscle* is part of the **Poland anomalad**.

When innervation does not develop, as in the lower limbs in severe cases of *myelomeningocele*, muscles can fail to develop. In *sacral agenesis*, the abnormal somites that fail to form bony vertebrae can also fail to form muscles from the same defective mesodermal plate, a disorder of induction resulting in segmental amyoplasia. Skeletal muscles of the extremities fail to differentiate from embryonic myomeres if the long bones do not form. Absence of 1 long bone, such as the radius, is associated with variable aplasia or hypoplasia of associated muscles, such as the flexor carpi radialis. End-stage neurogenic atrophy of muscle is sometimes called **amyoplasia**, but this use is semantically incorrect.

Generalized amyoplasia usually results in fetal death, and liveborn neonates rarely survive. A mutation in 1 of the myogenic genes is the suspected etiology because of genetic knockout studies in mice, but it has not been proven in humans.

608.8 Muscular Dysgenesis (Proteus Syndrome Myopathy)

Harvey B. Sarnat

Proteus syndrome is a disturbance of cellular growth involving ectodermal and mesodermal tissues, representing a cellular mosaicism. The genetic defect is a mutation in the *AKT1* gene, of the same genetic family as *AKT3*, which causes hemimegalencephaly; indeed many cases of Proteus syndrome also have hemimegalencephaly. These genes participate in the mammalian target of rapamycin pathway. Proteus syndrome also manifests as asymmetric overgrowth of the extremities, verrucous cutaneous lesions, angiomas of various types, thickening of bones, and excessive growth of muscles without weakness. Severe seizures, beginning in neonates, are uncommon. Histologically, the muscle demonstrates a unique *muscular dysgenesis*. Abnormal zones are adjacent to zones of normal muscle formation and do not follow anatomic boundaries.

Bibliography is available at Expert Consult.

608.9 Benign Congenital Hypotonia

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Benign congenital hypotonia is not a disease, but it is a descriptive term for infants or children with nonprogressive hypotonia of unknown origin. The hypotonia is not usually associated with weakness or developmental delay, although some children acquire gross motor skills more slowly than normal. Tendon stretch reflexes are normal or hypoactive. There are no cranial nerve abnormalities, and intelligence is normal.

The **diagnosis** is one of exclusion (see Table 607-2 in Chapter 607) after results of laboratory studies, including muscle biopsy and imaging of the brain with special attention to the cerebellum, are normal. Muscle biopsy is deferred in some mild cases to follow the clinical evolution over time, but the diagnosis in these infants is more provisional. No known molecular genetic basis for this syndrome has been identified. Table 607-3 in Chapter 607 lists the differential diagnosis.

The **prognosis** is generally good; no specific therapy is required. Contractures do not develop. Physical therapy might help achieve motor milestones (walking) sooner than expected. Hypotonia persists into adult life. The disorder is not always as "benign" as its name implies because a common complication is recurrent dislocation of joints, especially the shoulders. Excessive motility of the spine can result in stretch injury, compression, or vascular compromise of nerve roots or of the spinal cord. These are particular hazards for patients who perform gymnastics or who become circus performers because of agility of joints without weakness or pain.

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608.10 Arthrogryposis

Harvey B. Sarnat

Arthrogryposis multiplex congenita is not a disease but is a descriptive term that signifies multiple congenital contractures and is heterogeneous in etiology (see Chapter 682).

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Chapter 609

Muscular Dystrophies

Harvey B. Sarnat

The term *dystrophy* means abnormal growth, derived from the Greek *trophe,* meaning "nourishment." A muscular dystrophy is distinguished from all other neuromuscular diseases by 4 obligatory criteria: It is a primary myopathy, it has a genetic basis, the course is progressive, and degeneration and death of muscle fibers occur at some stage in the

disease. This definition excludes neurogenic diseases such as spinal muscular atrophy, nonhereditary myopathies such as dermatomyositis, nonprogressive, and nonnecrotizing congenital myopathies such as congenital muscle fiber-type disproportion, and nonprogressive inherited metabolic myopathies. Some metabolic myopathies can fulfill the definition of a progressive muscular dystrophy but are not traditionally classified as dystrophies (muscle carnitine deficiency).

All muscular dystrophies might eventually be reclassified as metabolic myopathies once the biochemical defects are better defined. Muscular dystrophies are a group of unrelated diseases, each transmitted by a different genetic trait and each differing in its clinical course and expression. Some are severe diseases at birth that lead to early death; others follow very slow progressive courses over many decades, may be compatible with normal longevity, and might not even become symptomatic until late adult life. Some categories of dystrophies, such as limb-girdle muscular dystrophy (LGMD), are not homogeneous diseases but rather syndromes encompassing several distinct myopathies. Relationships among the various muscular dystrophies are resolved by molecular genetics rather than by similarities or differences in clinical and histopathologic features.

609.1 Duchenne and Becker Muscular Dystrophies

Harvey B. Sarnat

Duchenne muscular dystrophy (DMD) is the most common hereditary neuromuscular disease affecting all races and ethnic groups. Its characteristic clinical features are progressive weakness, intellectual impairment, hypertrophy of the calves, and proliferation of connective tissue in muscle. The incidence is 1 in 3,600 liveborn infant boys. This disease is inherited as an X-linked recessive trait. The abnormal gene is at the Xp21 locus and is one of the largest genes. **Becker muscular dystrophy** (BMD) is a disease that is fundamentally similar to DMD, with a genetic defect at the same locus, but clinically it follows a milder and more protracted course.

CLINICAL MANIFESTATIONS

Infant boys are rarely symptomatic at birth or in early infancy, although some are mildly hypotonic. Early gross motor skills, such as rolling over, sitting, and standing, are usually achieved at the appropriate ages or may be mildly delayed. Poor head control in infancy may be the first sign of weakness. Distinctive facies are not an early feature because facial muscle weakness is a late event; in later childhood, a "transverse" or horizontal smile may be seen. Walking is often accomplished at the normal age of approximately 12 mo, but hip girdle weakness may be seen in subtle form as early as the 2nd yr. Toddlers might assume a lordotic posture when standing to compensate for gluteal weakness. An early Gowers sign is often evident by age 3 yr and is fully expressed by age 5 or 6 yr (see Fig. 590-5 in Chapter 590). A Trendelenburg gait, or hip waddle, appears at this time. Common presentations in toddlers include delayed walking, falling, toe walking, and trouble running or walking upstairs, developmental delay, and, less often, malignant hyperthermia after anesthesia.

The length of time a patient remains ambulatory varies greatly. Some patients are confined to a wheelchair by 7 yr of age; most patients continue to walk with increasing difficulty until age 10 yr without orthopedic intervention. With orthotic bracing, physiotherapy, and sometimes minor surgery (Achilles tendon lengthening), most are able to walk until age 12 yr. Ambulation is important not only for postponing the psychologic depression that accompanies the loss of an aspect of personal independence but also because scoliosis usually does not become a major complication as long as a patient remains ambulatory, even for as little as 1 hr per day; scoliosis often becomes rapidly progressive after confinement to a wheelchair.

The relentless progression of **weakness** continues into the 2nd decade. The function of distal muscles is usually relatively well enough preserved, allowing the child to continue to use eating utensils, a pencil, and a computer keyboard. Respiratory muscle involvement is expressed as a weak and ineffective cough, frequent pulmonary infections, and decreasing respiratory reserve. Pharyngeal weakness can lead to episodes of aspiration, nasal regurgitation of liquids, and an airy or nasal voice quality. The function of the extraocular muscles remains well preserved. Incontinence due to anal and urethral sphincter weakness is an uncommon and very late event.

Contractures most often involve the ankles, knees, hips, and elbows. **Scoliosis** is common. The thoracic deformity further compromises pulmonary capacity and compresses the heart. Scoliosis usually progresses more rapidly after the child becomes nonambulatory and may be uncomfortable or painful. Enlargement of the calves (pseudohypertrophy) and wasting of thigh muscles are classic features. The enlargement is caused by hypertrophy of some muscle fibers, infiltration of muscle by fat, and proliferation of collagen. After the calves, the next most common site of muscular hypertrophy is the tongue, followed by muscles of the forearm. Fasciculations of the tongue do not occur. The voluntary sphincter muscles rarely become involved.

Unless ankle contractures are severe, ankle deep tendon reflexes remain well preserved until terminal stages. The knee deep tendon reflexes may be present until about 6 yr of age but are less brisk than the ankle jerks and are eventually lost. In the upper extremities, the brachioradialis reflex is usually stronger than the biceps or triceps brachii reflexes.

Cardiomyopathy, including persistent tachycardia and myocardial failure, is seen in 50-80% of patients with this disease. The severity of cardiac involvement does not necessarily correlate with the degree of skeletal muscle weakness. Some patients die early of severe cardiomyopathy while still ambulatory; others in terminal stages of the disease have well-compensated cardiac function. Smooth muscle dysfunction, particularly of the gastrointestinal tract, is a minor, but often overlooked, feature.

Intellectual impairment occurs in all patients, although only 20-30% have an IQ <70. The majority have learning disabilities that still allow them to function in a regular classroom, particularly with remedial help. A few patients are profoundly intellectually impaired, but there is no correlation with the severity of the myopathy. Epilepsy is slightly more common than in the general pediatric population. Autism-like behavior may develop but is uncommon. Dystrophin is expressed in brain and retina, as well as in striated and cardiac muscle, though the level is lower in brain than in muscle. This distribution might explain some of the central nervous system manifestations. Abnormalities in cortical architecture and of dendritic arborization may be detected neuropathologically; cerebral atrophy is demonstrated by MRI late in the clinical course. The degenerative changes and fibrosis of muscle constitute a painless process. Myalgias and muscle spasms do not occur. Calcinosis of muscle is rare.

Death occurs usually at about 18-20 yr of age. The causes of death are respiratory failure during sleep, intractable heart failure, pneumonia, or, occasionally, aspiration and airway obstruction.

In **BMD,** boys remain ambulatory until late adolescence or early adult life. Calf pseudohypertrophy, cardiomyopathy, and elevated serum levels of creatine kinase (CK) are similar to those of patients with DMD. Learning disabilities are less common. The onset of weakness is later in BMD than in DMD. Death often occurs in the mid to late 20s; fewer than half of patients are still alive by age 40 yr; these survivors are severely disabled.

LABORATORY FINDINGS

The serum CK level is consistently greatly elevated in DMD, even in presymptomatic stages, including at birth. The usual serum concentration is 15,000-35,000 IU/L (normal <160 IU/L). A normal serum CK level is incompatible with the diagnosis of DMD, although in terminal stages of the disease, the serum CK value may be considerably lower than it was a few years earlier because there is less muscle to degenerate. Other lysosomal enzymes present in muscle, such as aldolase and aspartate aminotransferase, are also increased but are less specific.

Cardiac assessment by echocardiography, electrocardiography (ECG), and radiography of the chest is essential and should be repeated

periodically. After the diagnosis is established, patients should be referred to a pediatric cardiologist for long-term cardiac care.

Electromyography (EMG) shows characteristic myopathic features but is not specific for DMD. No evidence of denervation is found. Motor and sensory nerve conduction velocities are normal.

DIAGNOSIS

Polymerase chain reaction (PCR) for the dystrophin gene mutation is the primary test, if the clinical features and serum CK are consistent with the diagnosis. If the blood PCR is diagnostic, muscle biopsy may be deferred, but if it is normal and clinical suspicion is high, the more specific dystrophin immunocytochemistry performed on muscle biopsy sections detects the 30% of cases that do not show a PCR abnormality. Immunohistochemical staining of frozen sections of muscle biopsy tissue detects differences in the rod domain, the carboxyl-terminus (that attaches to the sarcolemma), and the aminoterminus (that attaches to the actin myofilaments) of the large dystrophin molecule, and may be prognostic of the clinical course as Duchenne or Becker disease. More-severe weakness occurs with truncation of the dystrophin molecule at the carboxyl-terminus than at the aminoterminus. The diagnosis should be confirmed by blood PCR or muscle biopsy in every case. Dystroglycans and other sarcolemmal regional proteins, such as merosin and sarcoglycans, also can be measured because they may be secondarily decreased.

The **muscle biopsy** is diagnostic and shows characteristic changes (Figs. 609-1 and 609-2). Myopathic changes include endomysial connective tissue proliferation, scattered degenerating and regenerating myofibers, foci of mononuclear inflammatory cell infiltrates as a reaction to muscle fiber necrosis, mild architectural changes in still-functional muscle fibers, and many dense fibers. These hypercontracted fibers probably result from segmental necrosis at another level, allowing calcium to enter the site of breakdown of the sarcolemmal membrane and trigger a contraction of the whole length of the muscle fiber. Calcifications within myofibers are correlated with secondary β-dystroglycan deficiency.

The decision about whether muscle biopsy should be performed to establish the diagnosis sometimes presents problems. If there is a family history of the disease, particularly in the case of an involved brother whose diagnosis has been confirmed, a patient with typical

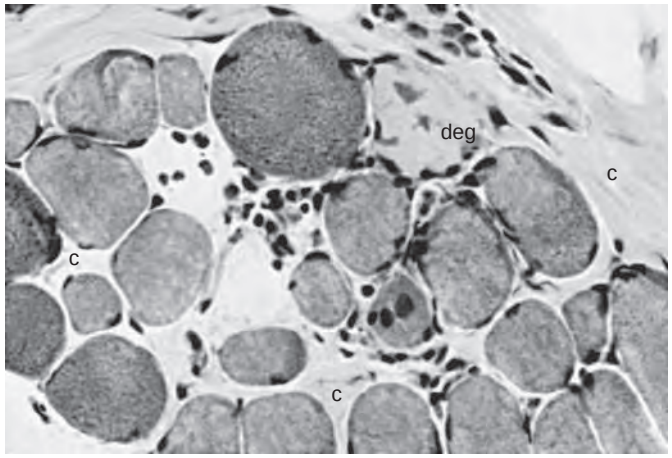


Figure 609-1 Muscle biopsy of a 4 yr old boy with Duchenne muscular dystrophy. Both atrophic and hypertrophic muscle fibers are seen, and some fibers are degenerating *(deg)*. Connective tissue *(c)* between muscle fibers is increased (hematoxylin and eosin, ×400).

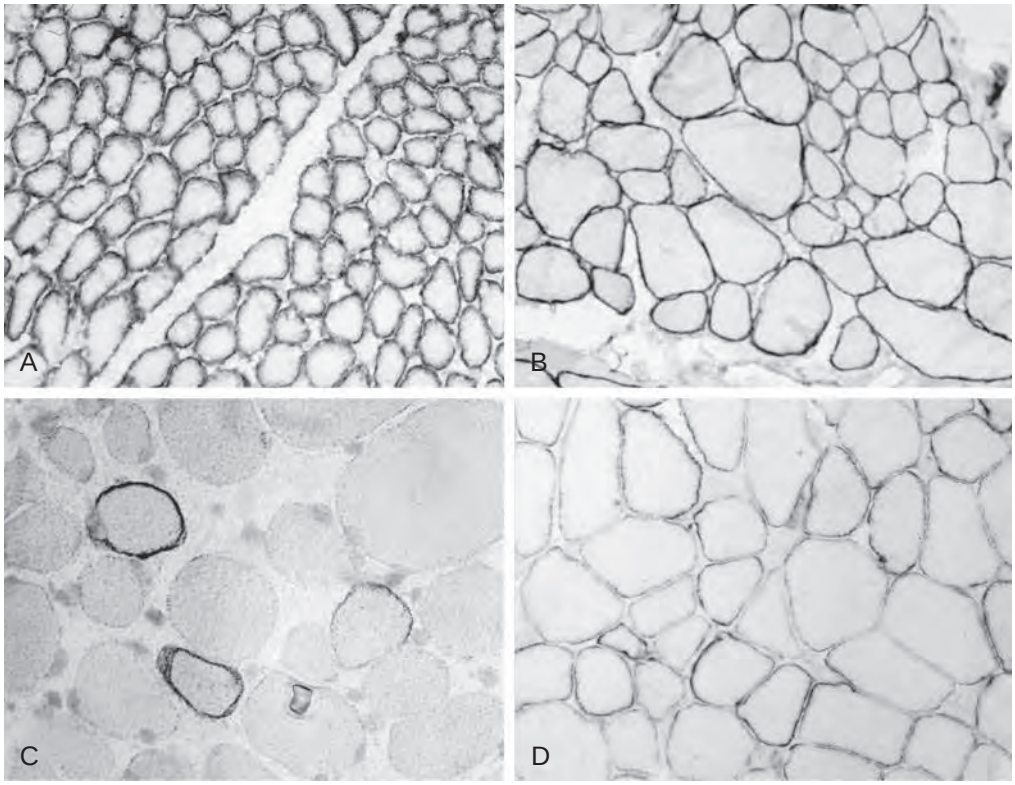


Figure 609-2 Dystrophin is demonstrated by immunohistochemical reactivity in the muscle biopsies of a normal term male neonate **(A),** a 10 yr old boy with limb-girdle muscular dystrophy **(B),** a 6 yr old boy with Duchenne muscular dystrophy **(C),** and a 10 yr old boy with Becker muscular dystrophy **(D).** In the normal condition, and also in non–X-linked muscular dystrophies in which dystrophin is not affected, the sarcolemmal membrane of every fiber is strongly stained, including atrophic and hypertrophic fibers. In Duchenne dystrophy, most myofibers express no detectable dystrophin, but a few scattered fibers known as revertant fibers show near-normal immunoreactivity. In Becker muscular dystrophy, the abnormal dystrophin molecule is thin, with pale staining of the sarcolemma, in which reactivity varies not only between myofibers but also along the circumference of individual fibers (×250).

clinical features of DMD and high concentrations of serum CK probably does not need to undergo biopsy. The result of the PCR might also influence whether to perform a muscle biopsy. A first case in a family, even if the clinical features are typical, should have the diagnosis confirmed to ensure that another myopathy is not masquerading as DMD. The most common muscles sampled are the vastus lateralis (quadriceps femoris) and the gastrocnemius.

GENETIC ETIOLOGY AND PATHOGENESIS

Despite the X-linked recessive inheritance in DMD, approximately 30% of cases are new mutations, and the mother is not a carrier. The female carrier state usually shows no muscle weakness or any clinical expression of the disease, but affected girls are occasionally encountered, usually having much milder weakness than boys. These symptomatic girls are explained by the Lyon hypothesis in which the normal X chromosome becomes inactivated and the one with the gene deletion is active (see Chapter 80). The full clinical picture of DMD has occurred in several girls with Turner syndrome in whom the single X chromosome must have had the Xp21 gene deletion.

The asymptomatic carrier state of DMD is associated with elevated serum CK values in 80% of cases. The level of increase is usually in the magnitude of hundreds or a few thousand but does not have the extreme values noted in affected males. Prepubertal girls who are carriers of the dystrophy also have increased serum CK values, with highest levels at 8-12 yr of age. Approximately 20% of carriers have normal serum CK values. If the mother of an affected boy has normal CK levels, it is unlikely that her daughter can be identified as a carrier by measuring CK. Muscle biopsy of suspected female carriers can detect an additional 10% in whom serum CK is not elevated; a specific genetic diagnosis using PCR on peripheral blood is definitive. Some female carriers suffer cardiomyopathy without weakness of striated muscles.

A 427-kDa cytoskeletal protein known as *dystrophin* is encoded by the gene at the Xp21.2 locus. This gene contains 79 exons of coding sequence and 2.5 Mb of DNA, 10 times larger than the next largest gene yet identified. This subsarcolemmal protein attaches to the sarcolemmal membrane overlying the A and M bands of the myofibrils and consists of 4 distinct regions or domains: the aminoterminus contains 250 amino acids and is related to the *N*-actin binding site of α-actinin; the second domain is the largest, with 2,800 amino acids, and contains many repeats, giving it a characteristic rod shape; a third, cysteine-rich domain is related to the carboxyl-terminus of α-actinin; and the final carboxyl-terminal domain of 400 amino acids is unique to dystrophin and to a dystrophin-related protein encoded by chromosome 6. "Dystrophin deficiency" at the sarcolemma disrupts the membrane cytoskeleton and leads to loss secondarily of other components of the cytoskeleton.

The molecular defects in the dystrophinopathies vary and include intragenic deletions, duplications, or point mutations of nucleotides. Approximately 65% of patients have deletions; approximately 10% exhibit duplications while approximately 10% have point mutations or smaller rearrangements. The site or size of the intragenic abnormality does not always correlate well with the phenotypic severity; in both Duchenne and Becker forms the mutations are mainly near the middle of the gene, involving deletions of exons 46-51. Phenotypic or clinical variations are explained by the alteration of the translational reading frame of messenger RNA (mRNA), which results in unstable, truncated dystrophin molecules and severe, classic DMD; mutations that preserve the reading frame still permit translation of coding sequences further downstream on the gene and produce a semifunctional dystrophin, expressed clinically as BMD. An even milder form of adult-onset disease, formerly known as **quadriceps myopathy,** is also caused by an abnormal dystrophin molecule. The clinical spectrum of the dystrophinopathies not only includes the classic Duchenne and Becker forms but also ranges from a severe neonatal muscular dystrophy to asymptomatic children with persistent elevation of serum CK levels >1,000 IU/L.

Analysis of the dystrophin protein requires a muscle biopsy and is demonstrated by Western blot analysis or in tissue sections by immunohistochemical methods using either fluorescence or light microscopy of antidystrophin antisera (see Fig. 609-2). In classic DMD, levels of <3% of normal are found; in BMD, the molecular weight of dystrophin is reduced to 20-90% of normal in 80% of patients, but in 15% of patients the dystrophin is of normal size but reduced in quantity, and 5% of patients have an abnormally large protein caused by excessive duplications or repeats of codons. Selective immunoreactivity of different parts of the dystrophin molecule in sections of muscle biopsy material distinguishes the Duchenne and Becker forms (Fig. 609-3). The demonstration of deletions and duplications also can be made from blood samples by the more rapid PCR, which identifies as many as 98% of deletions by amplifying 18 exons but cannot detect duplications. The diagnosis can thus be confirmed at the molecular genetic level from either the muscle biopsy material or from peripheral blood, although as many as 30% of boys with DMD or BMD have a false-normal blood PCR; all cases of dystrophinopathy are detected by muscle biopsy.

The same methods of DNA analysis from blood samples may be applied for carrier detection in female relatives at risk, such as sisters and cousins, and to determine whether the mother is a carrier or whether a new mutation occurred in the embryo. Prenatal diagnosis is possible as early as the 12th wk of gestation by sampling chorionic villi for DNA analysis by Southern blot or PCR and is confirmed in aborted fetuses with DMD by immunohistochemistry for dystrophin in muscle.

TREATMENT

There is no medical cure for this disease. Much can be done to treat complications and to improve the quality of life of affected children. **Cardiac decompensation** often responds initially well to digoxin. **Pulmonary infections** should be promptly treated. Patients should avoid contact with children who have obvious respiratory or other contagious illnesses. Immunizations for influenza virus and other routine vaccinations are indicated.

Preservation of a good **nutritional state** is important. DMD is not a vitamin-deficiency disease, and excessive doses of vitamins should be avoided. Adequate calcium intake is important to minimize osteoporosis in boys confined to a wheelchair, and fluoride supplements may also be given, particularly if the local drinking water is not fluoridated. Because sedentary children burn fewer calories than active children and because depression is an additional factor, these children tend to eat excessively and gain weight. Obesity makes a patient with myopathy even less functional because part of the limited reserve muscle strength is dissipated in lifting the weight of excess subcutaneous adipose tissue. Dietary restrictions with supervision may be needed.

Physiotherapy delays but does not always prevent contractures. At times, contractures are actually useful in functional rehabilitation. If contractures prevent extension of the elbow beyond 90 degrees and the muscles of the upper limb no longer are strong enough to overcome gravity, the elbow contractures are functionally beneficial in fixing an otherwise flail arm and in allowing the patient to eat and write. Surgical correction of the elbow contracture may be technically feasible, but the result may be deleterious. Physiotherapy contributes little to muscle strengthening because patients usually are already using their entire reserve for daily function, and exercise cannot further strengthen involved muscles. Excessive exercise can actually accelerate the process of muscle fiber degeneration.

Special vigilance should be maintained in watching for progressive scoliosis, which should be treated early by orthopedists using external braces or corsets and occasionally by surgeons. Scoliosis often becomes rapidly progressive once the patient is confined to a wheelchair.

Another recommended treatment of patients with DMD involves the use of prednisone, prednisolone, deflazacort, or other steroids. Glucocorticoids decrease the rate of apoptosis or programmed cell death of myotubes during ontogenesis and can decelerate the myofiber necrosis in muscular dystrophy. Strength usually improves initially, but the long-term complications of chronic steroid therapy, including

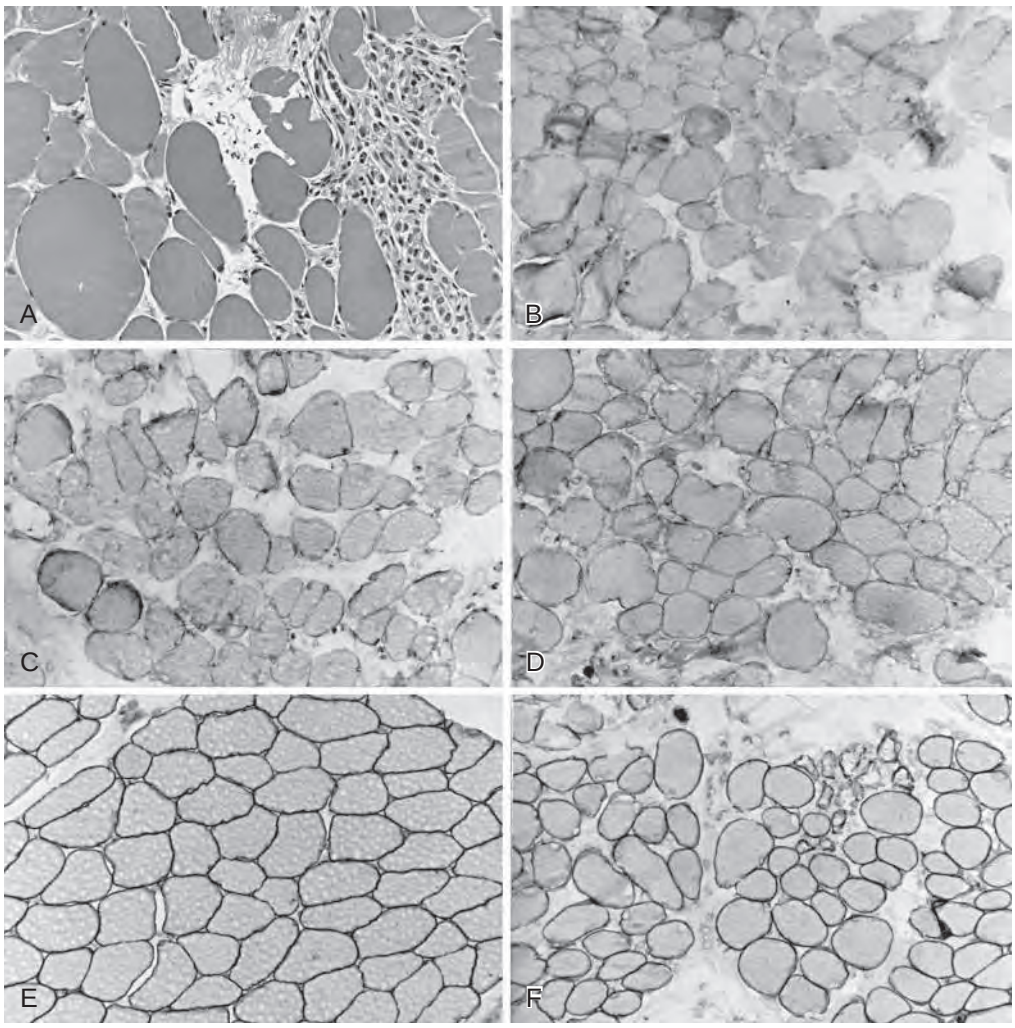


Figure 609-3 Quadriceps femoris muscle biopsy specimens from a 4 yr old boy with Becker muscular dystrophy. **A,** Myofibers vary greatly in size, with both atrophic and hypertrophic forms; at the right is a zone of degeneration and necrosis infiltrated by macrophages, similar to Duchenne muscular dystrophy (hematoxylin and eosin, ×250). Immunoreactivity using antibodies against the dystrophin molecule in the rod domain **(B),** carboxyl-terminus **(C),** and aminoterminus **(D)** all show deficient but not totally absent dystrophin expression; most fibers of all sizes retain some dystrophin in parts of the sarcolemma but not around the entire circumference in cross section. Alternatively, the prominence of dystrophin is less, appearing weak, when compared with the simultaneously incubated normal control from another child of similar age **(E). F,** Merosin expression is normal in this patient with Becker dystrophy, in both large and small myofibers, and is lacking only in frankly necrotic fibers. Compare with classic Duchenne muscular dystrophy illustrated in Figure 609-2C and with Figure 609-6.

considerable weight gain and osteoporosis, can offset this advantage or even result in greater weakness than might have occurred in the natural course of the disease. Nevertheless, some patients with DMD treated early with steroids appear to have an improved long-term prognosis in muscle and myocardial outcome, as well as short-term improvement in muscle strength, and steroids can help keep patients ambulatory for more years than expected without treatment. One protocol gives prednisone (0.75 mg/kg/day) for the 1st 10 days of each month to avoid chronic complications. Deflazacort, administered as 0.9 mg/kg/day, may be more effective than prednisone. Fluorinated steroids, such as dexamethasone or triamcinolone, should be avoided because they induce myopathy by altering the myotube abundance of ceramide. The American Academy of Neurology and the Child Neurology Society recommend administering corticosteroids during the ambulatory stage of the disease.

Another potential treatment still under investigation is intravenous or subcutaneous injection of antisense oligonucleotide drugs that induce exon skipping during mRNA splicing in patients with susceptible mutations (~15% of patients) to restore the open reading frame in the DMD gene. Drisapersen and eteplirsen are exon 51 skipping antisense oligonucleotides that bind RNA and skip (bridge) over the defective exon, thus producing a shorter but potentially functional dystrophin protein. The shortened protein has been demonstrated to appear in muscle biopsies after treatment with these agents.

Bibliography is available at Expert Consult.

609.2 Emery-Dreifuss Muscular Dystrophy

Harvey B. Sarnat

Emery-Dreifuss muscular dystrophy, also known as **scapuloperoneal or scapulohumeral muscular dystrophy,** is a rare X-linked recessive dystrophy. The usual locus of its associated genetic abnormality is on the long arm within the large Xq28 region that includes other mutations that cause myotubular myopathy, neonatal adrenoleukodystrophy, and the Bloch-Sulzberger type of incontinentia pigmenti; it is far from the gene for DMD on the short arm of the X chromosome. Another, rarer form of Emery-Dreifuss dystrophy is transmitted as an autosomal dominant trait and is localized at 1q. This form can manifest quite late, in adolescence or early adult life, although the muscular and cardiac symptoms and signs are similar, and sudden death from ventricular fibrillation is a risk.

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Clinical manifestations begin at between 5 and 15 yr of age, but many patients survive to late adult life because of the slow progression of the disease's course. A rarer severe infantile presentation also is documented. Muscles do not exhibit pseudohypertrophy. Contractures of elbows and ankles develop early, and muscle becomes wasted in a scapulohumeroperoneal distribution. Facial weakness does not occur; this disease is thus distinguished clinically from autosomal dominant scapulohumeral and scapuloperoneal syndromes of neurogenic origin. Myotonia is absent. Intellectual function is normal. Dilated cardiomyopathy is severe and is often the cause of death, more commonly from conduction defects such as atrial fibrillation/flutter and sudden ventricular fibrillation than from intractable myocardial failure. Stroke is another complication, secondary to the cardiac arrhythmia. The serum CK value is only mildly to moderately elevated, further distinguishing this disease from other X-linked recessive muscular dystrophies.

Nonspecific myofiber necrosis and endomysial fibrosis are seen in the muscle biopsy. Many centronuclear fibers and selective histochemical type I muscle fiber atrophy can cause confusion with myotonic dystrophy.

GENETICS

The defective gene in the X-linked form is called *EMD* or *EDMD* and encodes a protein, emerin. Unlike other dystrophies in which the defective gene is expressed at the sarcolemmal membrane, emerin is expressed at the inner nuclear membrane; this protein stabilizes the nuclear membrane against the mechanical stresses that occur during muscular contraction. It interacts with *Nesprin-1* and *Nesprin-2* genes, also critical for nuclear membrane integrity. Complete deletion of *EDMD* occurs in approximately 25% of cases and results from an inversion in the Xq28 region; total absence of emerin is demonstrated by both Western blotting and immunoreactivity in tissue sections. Another gene, *LMNA*, at the 1q21 locus, is linked to the nuclear envelope and encodes lamins A and C, sometimes termed *laminopathy*. This genetic mutation causes an identical clinical phenotype to EMD defects, except that both sexes are affected and it is transmitted as either an autosomal dominant or recessive trait. Most *EDMD* deletions are null mutations, whereas most *LMNA* alterations are mainly missense mutations with a minority being nonsense or out-of-frame mutations. Desmin protein also may be mutated and seen to be abnormally expressed in the muscle biopsy. Homozygous nonsense mutations in these *lamin A/C* genes are lethal owing to cardiomyopathy and conduction disturbances.

DIAGNOSIS AND INVESTIGATIONS

In suspected cases, emerin deficiency may be demonstrated not only in the muscle biopsy by immunoreactivity and Western blotting techniques but also in a variety of other tissues, including circulating lymphocytes in peripheral blood, exfoliative buccal mucosal cells, and skin fibroblasts. Emerin is absent in varying proportions in female carriers. Genetic testing of the specific genes also is available. Patients should all have careful cardiac evaluation, including electrocardiogram and echocardiogram. Serum CK should be measured because it may be moderately elevated; though nonspecific, it provides a baseline for comparison with future measurements. Muscle MRI of the glutei and lower extremities may be helpful, particularly in *LMNA* mutations. EMG is not definitively diagnostic, but it provides a serial means of following the progression of the myopathy. Muscle biopsy is diagnostic from the onset of symptoms. In the differential diagnosis, an Emery-Dreifuss–like syndrome with joint contractures, mild weakness, and later-onset cardiac symptoms is caused by *FHL1* mutations of myofibrillar myopathy, but reducing bodies are absent.

Treatment should be supportive, with special attention to cardiac conduction defects, and can require medications or a pacemaker. Implantable cardioverter-defibrillators are now available and have prevented sudden death in some patients with Emery-Dreifuss muscular dystrophy.

Bibliography is available at Expert Consult.

609.3 Myotonic Muscular Dystrophy

Harvey B. Sarnat

Myotonic dystrophy (Steinert disease) is the second most common muscular dystrophy in North America, Europe, and Australia, having an incidence varying from 1 in 100,000 to 1 in 300,000 in the general population. It is inherited as an autosomal dominant trait. Classic myotonic dystrophy (type 1) (DM1) is caused by a CTG trinucleotide expansion on chromosome 19q13.3 in the 3′ untranslated region of *DMPK*, the gene that encodes a serine-threonine protein kinase. Type 2 (DM2) is associated with unstable CCTG tetranucleotide repeat expansion on chromosome 3q21 of an intron of the zinc finger 9 protein gene. A third, late form (DM3) is identified, at locus 15q21-q24.

Myotonic dystrophy is an example of a genetic defect causing dysfunction in multiple organ systems. Not only is striated muscle severely affected, but smooth muscle of the alimentary tract and uterus is also involved, cardiac function is altered, and patients have multiple and variable endocrinopathies, immunologic deficiencies, cataracts, dysmorphic facies, increased risk for malignancies, intellectual impairment, and other neurologic abnormalities.

CLINICAL MANIFESTATIONS

DM1 becomes symptomatic at any age, but DM2 is rarely expressed in infancy or early childhood. In the usual clinical course, **excluding the severe neonatal** form, DM1 infants can appear almost normal at birth, or facial wasting and hypotonia can already be early expressions of the disease. The facial appearance is characteristic, consisting of an inverted V-shaped upper lip, thin cheeks, and scalloped, concave temporalis muscles (Fig. 609-4). The head may be narrow, and the palate is high and arched because the weak temporal and pterygoid muscles in late fetal life do not exert sufficient lateral forces on the developing head and face.

Weakness is mild in the 1st few yr. Progressive wasting of distal muscles becomes increasingly evident, particularly involving intrinsic muscles of the hands. The thenar and hypothenar eminences are flattened, and the atrophic dorsal interossei leave deep grooves between the fingers. The dorsal forearm muscles and anterior compartment muscles of the lower legs also become wasted. The tongue is thin and atrophic. Wasting of the sternocleidomastoids gives the neck a long, thin, cylindrical contour. Proximal muscles also eventually undergo atrophy, and scapular winging appears. Difficulty with climbing stairs



Figure 609-4 Facial weakness, inverted V–shaped upper lip, and loss of muscle mass in the temporal fossae are characteristic of myotonic muscular dystrophy, even in infancy, as seen in this 8 mo old girl.

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and Gowers sign are progressive. Tendon stretch reflexes are usually preserved.

The distal distribution of muscle wasting in myotonic dystrophy is an *exception* to the general rule of myopathies having proximal and neuropathies having distal distribution patterns. The muscular atrophy and weakness in myotonic dystrophy are slowly progressive throughout childhood and adolescence and continue into adulthood. It is rare for patients with myotonic dystrophy to lose the ability to walk even in late adult life, although splints or bracing may be required to stabilize the ankles.

Myotonia, a characteristic feature shared by few other myopathies, does not occur in infancy and is usually not clinically or even electromyographically evident until about age 5 yr. Exceptional patients develop it as early as age 3 yr. Myotonia is a very slow relaxation of muscle after contraction, regardless of whether that contraction was voluntary or was induced by a stretch reflex or electrical stimulation. During physical examination, myotonia may be demonstrated by asking the patient to make tight fists and then to quickly open the hands (grip myotonia; Fig. 609-5). It may be induced by striking the thenar eminence with a rubber percussion hammer (percussion myotonia), and it may be detected by watching the involuntary drawing of the thumb across the palm. Myotonia can also be demonstrated in the tongue by pressing the edge of a wooden tongue blade against its dorsal surface and by observing a deep furrow that disappears slowly. The severity of myotonia does not necessarily parallel the degree of weakness, and the weakest muscles often have only minimal myotonia. *Myotonia is not a painful muscle spasm*. Myalgias do not occur in myotonic dystrophy.

The **speech** of patients with myotonic dystrophy is often articulated poorly and is slurred because of the involvement of the muscles of the face, tongue, and pharynx. Difficulties with swallowing sometimes occur. Aspiration pneumonia is a risk in severely involved children. Incomplete external ophthalmoplegia sometimes results from extraocular muscle weakness.

Smooth muscle involvement of the **gastrointestinal tract** results in slow gastric emptying, poor peristalsis, and constipation. Some patients have encopresis associated with anal sphincter weakness. Women with myotonic dystrophy can have ineffective or abnormal uterine contractions during labor and delivery.

Cardiac involvement is usually manifested as heart block in the Purkinje conduction system and arrhythmias (and sudden death) rather than as cardiomyopathy, unlike most other muscular dystrophies. Atrial or ventricular tachyarrhythmias have also resulted in sudden death in adults and older children.

Endocrine abnormalities involve many glands and appear at any time during the course of the disease so that endocrine status must be reevaluated annually. Hypothyroidism is common; hyperthyroidism occurs rarely. Adrenocortical insufficiency can lead to an addisonian crisis even in infancy. Diabetes mellitus is common in patients with myotonic dystrophy; some children have a disorder of insulin release rather than defective insulin production. Onset of puberty may be precocious or, more often, delayed. Testicular atrophy and testosterone deficiency are common in adults and are responsible for a high incidence of male infertility. Ovarian atrophy is rare. Frontal baldness is also characteristic in male patients and often begins in adolescence.

Immunologic deficiencies are common in myotonic dystrophy. The plasma immunoglobulin G level is often low.

Cataracts often occur in myotonic dystrophy. They may be congenital, or they can begin at any time during childhood or adult life. Early cataracts are detected only by slit-lamp examination; periodic examination by an ophthalmologist is recommended. Visual evoked potentials are often abnormal in children with myotonic dystrophy and are unrelated to cataracts. They are not usually accompanied by visual impairment.

About half of the patients with myotonic dystrophy are **intellectually impaired,** but severe intellectual impairment is unusual. The remainder are of average or occasionally above-average intelligence. Epilepsy is not common. Cognitive impairment might result from accumulations of mutant *DMPK* mRNA and aberrant alternative splicing in cerebral cortical neurons. A higher than expected incidence of autism occurs in children with DM1.

A severe **congenital form** of myotonic dystrophy appears in a minority of involved infants born to mothers with symptomatic myotonic dystrophy. All patients with this severe congenital disease to date have had the DM1 form. Clubfoot deformities alone or more extensive congenital contractures of many joints can involve all extremities (arthrogryposis multiplex congenita) and even include the cervical spine. Generalized hypotonia and weakness are present at birth. Facial wasting is prominent. Infants can require gavage feeding or ventilator support for respiratory muscle weakness or apnea. Those requiring ventilation for <30 days often survive, and those with prolonged ventilation have an infant mortality of 25%. Children ventilated for <30 days have better motor, language, and daily activity skills than those requiring prolonged ventilation. One or both leaves of the diaphragm may be nonfunctional. The abdomen becomes distended with gas in the stomach and intestine because of poor peristalsis from smooth muscle weakness. The distention further compromises respiration. Inability to empty the rectum can compound the problem.



Figure 609-5 The patient was asked to squeeze with both of his hands for several seconds and then suddenly release his grasp, and several seconds passed before full relaxation was achieved, an exam finding known as grip myotonia. *(From Hughes BN, Hogue JS, Hsieh DT: Grip and percussion myotonia in myotonic dystrophy type 1,* J Pediatr *164:1234, 2014.)*

LABORATORY FINDINGS

The classic myotonic electromyogram is not found in infants but can appear in toddlers or children in the early school years. The levels of serum CK and other serum enzymes from muscle may be normal or only mildly elevated in the hundreds (never the thousands).

ECG should be performed annually in early childhood. Ultrasound imaging of the abdomen may be indicated in affected infants to determine diaphragmatic function. Radiographs of the chest and abdomen and contrast studies of gastrointestinal motility may be needed.

Endocrine assessment should be undertaken to determine thyroid and adrenal cortical function and to verify carbohydrate metabolism (glucose tolerance test). Immunoglobulins should be examined, and, if needed, more extensive immunologic studies should be performed.

DIAGNOSIS

The primary diagnostic test is a DNA analysis of blood to demonstrate the abnormal expansion of the CTG or CCTG repeat. Prenatal diagnosis also is feasible. The muscle biopsy specimen in older children shows many muscle fibers with central nuclei and selective atrophy of histochemical type I fibers, but degenerating fibers are usually few and widely scattered, and there is little or no fibrosis of muscle. Intrafusal fibers of muscle spindles are also abnormal. In young children with the common form of the disease, the biopsy specimen can even appear normal or at least not show myofiber necroses, which is a striking contrast with DMD. In the severe neonatal form of myotonic dystrophy, the muscle biopsy reveals maturational arrest in various stages of

development in some and congenital muscle fiber-type disproportion in others. It is likely that the sarcolemmal membrane of muscle fibers not only has abnormal properties of electrical polarization but is also incapable of responding to trophic influences of the motor neuron. Muscle biopsy is not usually required for diagnosis, which in typical cases can be based on the clinical manifestations, including family history. **Neonatal myotonic dystrophy** must be distinguished from amyoplasia, congenital muscular dystrophy with or without merosin expression, congenital myasthenia gravis, spinal muscular atrophy, and arthrogryposis secondary to oligohydramnios.

GENETICS

The genetic defect in myotonic muscular dystrophy is on chromosome 19 at the 19q13 locus. It consists of an expansion of the *DM* gene that encodes a serine-threonine kinase *(DMPK),* with numerous repeats of the CTG codon. Expansions range from 50 to >2,000, with the normal alleles of this gene ranging in size from 5-37; the larger the expansion, the more severe the clinical expression, with the largest expansions seen in the severe neonatal form. Rarely, the disease is associated with no detectable repeats, perhaps a spontaneous correction of a previous expansion but a phenomenon still incompletely understood. Another myotonic dystrophy (proximal myotonic myopathy) is a clinical entity linked to at least 2 different chromosomal loci than classic myotonic dystrophy but to 1 locus that shares a common unique pathogenesis in being mediated by a mutant mRNA. Defects in RNA splicing explain the insulin resistance in myotonic dystrophies as well as the myotonia.

Clinical and genetic expression can vary between siblings or between an affected parent and child. In the severe neonatal form of the disease, the mother is the transmitting parent in 94% of cases, a fact not explained by increased male infertility alone. Several cases of paternal transmission have been reported. Genetic analysis reveals that symptomatic neonates usually have many more repeats of the CTG codon than do patients with the more classic form of the disease, regardless of which parent is affected. Myotonic dystrophy often exhibits a pattern of **anticipation** in which each successive generation has a tendency to be more severely involved than the previous generation. Prenatal genetic diagnosis of myotonic dystrophy is available.

Treatment

There is no specific medical treatment, but the cardiac, endocrine, gastrointestinal, and ocular complications can often be treated. Physiotherapy and orthopedic treatment of contractures in the neonatal form of the disease may be beneficial. Myotonia may improve with exercise (warm-up phenomenon). Cardiac pacemaker implantation might be considered for heart block and antiarrhythmic drugs might be indicated but are needed only rarely in children.

Myotonia may be diminished, and function may be restored by drugs that raise the depolarization threshold of muscle membranes, such as mexiletine, phenytoin, carbamazepine, procainamide, and quinidine sulfate. These drugs also have cardiotropic effects; thus, cardiac evaluation is important before prescribing them. Phenytoin and carbamazepine are used in doses similar to their use as antiepileptics (see Chapter 593.6); serum concentrations of 10-20 μg/mL for phenytoin and 5-12 μg/mL for carbamazepine should be maintained. If a patient's disability is caused mainly by weakness rather than by myotonia, these drugs will be of no value.

OTHER MYOTONIC SYNDROMES

Most patients with myotonia have myotonic dystrophy. However, myotonia is not specific for this disease and occurs in several rarer conditions.

Myotonic chondrodystrophy (Schwartz-Jampel disease) is a rare congenital disease characterized by generalized muscle hypertrophy and weakness. Dysmorphic phenotypical features and the radiographic appearance of long bones are reminiscent of Morquio disease (see Chapter 88), but abnormal mucopolysaccharides are not found. Dwarfism, joint abnormalities, and blepharophimosis are present. Several patients have been the products of consanguinity, suggesting autosomal recessive inheritance. The muscle protein perlecan, encoded by the *SJS1* gene, a large heparan sulfate proteoglycan of basement membranes and cartilage, is defective in some cases of Schwartz-Jampel disease and explains both the muscular hyperexcitability and the chondrodysplasia.

EMG reveals continuous electrical activity in muscle fibers closely resembling or identical to myotonia. Muscle biopsy reveals nonspecific

Table 609-1 Channelopathies and Related Disorders

DISORDER	PATTERN OF CLINICAL FEATURES	INHERITANCE	CHROMOSOME	GENE
CHLORIDE CHANNELOPATHIES				
Myotonia Congenita				
Thomsen disease	Myotonia	Autosomal dominant	7q35	*CLC1*
Becker disease	Myotonia and weakness	Autosomal recessive	7q35	*CLC1*
SODIUM CHANNELOPATHIES				
Paramyotonia congenita	Paramyotonia	Autosomal dominant	17q13.1-13.3	*SCNA4A*
Hyperkalemic periodic paralysis	Periodic paralysis with myotonia and paramyotonia	Autosomal dominant	17q13.1-13.3	*CNA4A*
Hypokalemic periodic paralysis	Periodic paralysis	Autosomal dominant	17q13.1-13.3	*SCNA4A*
POTASSIUM-AGGRAVATED MYOTONIAS				
Myotonia fluctuans	Myotonia	Autosomal dominant	17q13.1-13.3	*SCNA4A*
Myotonia permanens	Myotonia	Autosomal dominant	17q13.1-13.3	*SCNA4A*
Acetazolamide-responsive myotonia	Myotonia	Autosomal dominant	17q13.1-13.3	*SCNA4A*
CALCIUM CHANNELOPATHIES				
Hypokalemic periodic paralysis	Periodic paralysis	Autosomal dominant	1q31-32	Dihydropyridine receptor
Schwartz-Jampel syndrome (chondrodystrophic myotonia)	Myotonia; dysmorphic	Autosomal recessive	1q34.1-36.1	*Perlecan*
Rippling muscle disease	Muscle mounding, stiffness	Autosomal dominant	1q41	*Caveolin-3*
Anderson syndrome	Periodic paralysis, cardiac arrhythmia, distinctive facies	Autosomal dominant	17q23	*KCNJ2-Kir2.1*
Brody disease	Delayed relaxation, no electromyogram myotonia	Autosomal recessive	16p12	Calcium adenosine triphosphatase
Malignant hyperthermia	Anesthetic-induced delayed relaxation	Autosomal dominant	19q13.1	Ryanodine receptor

From Goldman L, Ausiello D: Cecil textbook of medicine, *ed 22, Philadelphia, 2004, WB Saunders.*

myopathic features, which are minimal in some cases and pronounced in others. The sarcotubular system is dilated.

Myotonia congenita (Thomsen disease) is a channelopathy (Table 609-1) and is characterized by weakness and generalized muscular hypertrophy so that affected children resemble bodybuilders. Myotonia is prominent and can develop at age 2-3 yr, earlier than in myotonic dystrophy. The disease is clinically stable and is apparently not progressive for many years. Muscle biopsy specimens show minimal pathologic changes, and the EMG demonstrates myotonia. Various families are described as showing either autosomal dominant (Thomsen disease) or recessive (Becker disease, not to be confused with BMD or DMD) inheritance. Rarely, myotonic dystrophy and myotonia congenita coexist in the same family. The autosomal dominant and autosomal recessive forms of myotonia congenita have been mapped to the same 7q35 locus. This gene is important for the integrity of chloride channels of the sarcolemmal and T-tubular membranes.

Paramyotonia is a temperature-related myotonia that is aggravated by cold and alleviated by warm external temperatures. Patients have difficulty when swimming in cold water or if they are dressed inadequately in cold weather. *Paramyotonia congenita* (Eulenburg disease) is a defect in a gene at the 17q13.1-13.3 locus, the identical locus identified in hyperkalemic periodic paralysis. By contrast with myotonia congenita, paramyotonia is a disorder of the voltage-gated sodium channel caused by a mutation in the α subunit. Myotonic dystrophy also is a sodium channelopathy (see Table 609-1).

In sodium channelopathies, exercise produces increasing myotonia, whereas in chloride channelopathies, exercise reduces the myotonia. This is easily tested during examination by asking patients to close the eyes forcefully and open them repeatedly; it becomes progressively more difficult in sodium channel disorders and progressively easier in chloride channel disorders.

Bibliography is available at Expert Consult.

609.4 Limb-Girdle Muscular Dystrophies

Harvey B. Sarnat

Limb-girdle muscular dystrophies (LGMDs) encompass a heterogeneous group of progressive hereditary muscular dystrophies that mainly affect muscles of the hip and shoulder girdles (Table 609-2). Distal muscles also eventually become atrophic and weak. Hypertrophy of the calves and ankle contractures develop in some forms, causing potential confusion with BMD. Sixteen genetic forms of LGMD are now described, each at a different chromosomal locus and expressing different protein defects. Some include diseases classified with other traditional groups, such as the lamin-A/C defects of the nuclear membrane (see Emery-Dreifuss muscular dystrophy, above), and some forms of congenital muscular dystrophy. LGMD1 denotes autosomal dominant inheritance and LGMD2 implies an autosomal recessive trait, but neither term defines the genetic etiology. LGMD2 is mainly a group of several sarcoglycanopathies, calpainopathy resulting from a mutation in the *calpain-3* gene (*CAPN3*), or dysferlinopathies that include Miyoshi myopathy, which usually does not become symptomatic until adult life.

The initial **clinical manifestations** rarely appear before middle or late childhood or may be delayed until early adult life. Low back pain may be a presenting complaint because of the lordotic posture resulting from gluteal muscle weakness. Confinement to a wheelchair usually becomes obligatory at about 30 yr of age. The rate of progression varies from one pedigree to another but is uniform within a kindred. Although weakness of neck flexors and extensors is universal, facial, lingual, and other bulbar-innervated muscles are rarely involved. As weakness and muscle wasting progress, tendon stretch reflexes become diminished. Cardiac involvement is unusual. Intellectual function is generally normal. The clinical **differential diagnosis** of LGMD includes juvenile spinal muscular atrophy (Kugelberg-Welander disease), myasthenia gravis, and metabolic myopathies.

The EMG and muscle biopsy show confirmatory evidence of muscular dystrophy, but none of the findings is specific enough to make the definitive **diagnosis** without additional clinical criteria. In some cases, α-sarcoglycan (formerly known as *adhalin*), a dystrophin-related glycoprotein of the sarcolemma, is deficient; this specific defect may be demonstrated in the muscle biopsy by immunocytochemistry, as may deficiency of 3 other forms of sarcoglycan as well. Increased serum CK level is usual, but the magnitude of elevation varies among families. The ECG is usually unaltered.

In one autosomal dominant form of LGMD, a genetic defect has been localized to the long arm of chromosome 5. In the autosomal recessive disease, it is on the long arm of chromosome 15. A mutated dystrophin-associated protein in the sarcoglycan complex (sarcoglycanopathy; LGMD types 2C, 2E, and 2F) is responsible for some cases of autosomal recessive LGMD. Most sarcoglycanopathies result from a mutation in α-sarcoglycan; other LGMDs resulting from deficiencies in β-, γ-, and δ-sarcoglycan also occur. In normal smooth muscle, α-sarcoglycan is replaced by ε-sarcoglycan, and the others are the same. A dystroglycan mutation also is implicated in some cases.

Another group of LGMDs (type 2B) are caused by allelic mutations of the dysferlin *(DYSF)* gene, another gene expressing a protein essential to structural integrity of the sarcolemma, though not associated with the dystrophin-glycoprotein complex. *DYSF* interacts with caveolin-3 or calpain-3, and *DYSF* deficiency may be secondary to defects in these other gene products. Primary calpain-3 defect (type 2A) is reported in Amish families and in families from French Reunion Island and from Brazil. Autosomal recessive (Miyoshi myopathy) and autosomal dominant traits are documented. Both are slowly progressive myopathies with onset in adolescence or young adult life and can affect distal as well as proximal muscles. Cardiomyopathy is rare. Chronically elevated serum CK in the thousands is found in dysferlinopathies. Ultrastructure shows a thickened basal lamina over defects in the sarcolemma and replacement of the sarcolemma by multiple

Table 609-2 Autosomal Recessive Limb-Girdle Muscular Dystrophies

TYPE	LOCATION	GENE PRODUCT	CLINICAL FEATURES
LGMD2A	15q	Calpain 3	Onset at 8-15 yr, progression variable
LGMD2B	2p13-16	Dysferlin	Onset at adolescence, mild weakness; gene site is the same as for Miyoshi myopathy
LGMD2C	13q12	Sarcoglycan	Duchenne-like, severe childhood autosomal recessive muscular dystrophy (SCARMD1)
LGMD2D	17q12	α-Sarcoglycan (adhalin)	Duchenne-like, severe childhood autosomal recessive muscular dystrophy (SCARMD2)
LGMD2E	4q12	β-Sarcoglycan	Phenotype between Duchenne and Becker muscular dystrophies
LGMD2F	5q33-34	Sarcoglycan	Slowly progressive, growth retardation

LGMD, limb-girdle muscular dystrophy.
From Fenichel GM: Clinical pediatric neurology: a signs and symptoms approach, *ed 5, Philadelphia, 2005, Elsevier Saunders, p. 176, Table 7-5.*

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layers of small vesicles. Regenerating myofibers outnumber degenerating myofibers. These disorders were formerly called *hyperCKemia* and *rippling muscle disease,* the latter sometimes confused with myotonia. An autosomal recessive mutation in the calcium-activated chloride channel anoctamin-5 can cause proximal LGMD2.

There is overlap of the group of LGMDs with the congenital muscular dystrophies, such as Walker-Warburg syndrome with *POMT*, Fukuyama muscular dystrophy with *FKRP* genetic defects, and Ullrich muscular dystrophy of collagen VI subunits.

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609.5 Facioscapulohumeral Muscular Dystrophy

Harvey B. Sarnat

Facioscapulohumeral muscular dystrophy, also known as **Landouzy-Dejerine disease,** is probably not a single disease entity but a group of diseases with similar clinical manifestations. Autosomal dominant inheritance is the rule; genetic anticipation is often found within several generations of a family, the succeeding more severely involved at an earlier age than the preceding. The frequency is 1 : 20,000 population. Though the clinical onset is generally in later childhood or adult life, early molecular defects arising during myogenesis are demonstrated in the human fetus. The genetic mechanism in autosomal dominant facioscapulohumeral dystrophy involves integral deletions of a 3.3-kb tandem repeat (D4Z4) in the subtelomeric region at the 4q35 locus. Several other genes clustered at the 4q35 locus are upregulated in fetuses with facioscapulohumeral dystrophy. D4Z4 acts as a lamins-dependent insulator exhibiting both enhancer-blocking and barrier activities and displaces the telomere toward the nuclear periphery. A 3.3-kb repeat array at the subtelomeric locus 10q26 is closely homologous, with chromosomal translocation or sequence conversion between these 2 regions, possibly predisposing to the DNA rearrangement causing facioscapulohumeral dystrophy. Approximately 10% of families with this phenotype do not map to the 4q35 locus.

CLINICAL MANIFESTATIONS

Facioscapulohumeral dystrophy shows the earliest and most severe weakness in facial and shoulder girdle muscles. The facial weakness differs from that of myotonic dystrophy; rather than an inverted V–shaped upper lip, the mouth in facioscapulohumeral dystrophy is rounded and appears puckered because the lips protrude. Inability to close the eyes completely in sleep is a common expression of upper facial weakness; some patients have extraocular muscle weakness, although ophthalmoplegia is rarely complete. Facioscapulohumeral dystrophy has been associated with Möbius syndrome on rare occasions. Pharyngeal and tongue weakness may be absent and is never as severe as the facial involvement. Hearing loss, which may be subclinical, and retinal vasculopathy (indistinguishable from Coats disease) are associated features, particularly in severe cases of facioscapulohumeral dystrophy with early-childhood onset.

Scapular winging is prominent, often even in infants. Flattening or even concavity of the deltoid contour is seen, and the biceps and triceps brachii muscles are wasted and weak. Muscles of the hip girdle and thighs also eventually lose strength and undergo atrophy, and Gowers sign and a Trendelenburg gait appear. Contractures of the extremities are rare. Finger and wrist weakness occasionally is the first symptom. Weakness of the anterior tibial and peroneal muscles can lead to footdrop; this complication usually occurs only in advanced cases with severe weakness. Lumbar lordosis and kyphoscoliosis are common complications of axial muscle involvement. Calf pseudohypertrophy is not a usual feature but is described rarely.

Facioscapulohumeral muscular dystrophy can also be a mild disease causing minimal disability. Clinical manifestations might not be expressed in childhood and are delayed into middle adult life. Unlike most other muscular dystrophies, asymmetry of weakness is common. About 30% of affected patients are asymptomatic or show only mild scapular winging and decreased tendon stretch reflexes, of which they were unaware until formal neurologic examination was performed.

LABORATORY FINDINGS

Serum levels of CK and other enzymes vary greatly, ranging from normal or near-normal to elevations of several thousand. An ECG should be performed, although the anticipated findings are usually normal. EMG reveals nonspecific myopathic muscle potentials. Diagnostic molecular testing in individual cases and within families is indicated for prediction.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

Molecular genetic diagnosis is the most specific confirmation if clinical suspicion is high, with or without a family history of the disease. Muscle biopsy distinguishes more than one form of facioscapulohumeral dystrophy, consistent with clinical evidence that several distinct diseases are embraced by the term *facioscapulohumeral dystrophy.* Muscle biopsy and EMG also distinguish the primary myopathy from a neurogenic disease with a similar distribution of muscular involvement. The general histopathologic findings in the muscle biopsy material are extensive proliferation of connective tissue between muscle fibers, extreme variation in fiber size with many hypertrophic as well as atrophic myofibers, and scattered degenerating and regenerating fibers. An "inflammatory" type of facioscapulohumeral muscular dystrophy is also distinguished, characterized by extensive lymphocytic infiltrates within muscle fascicles. Despite the resemblance of this form to inflammatory myopathies, such as polymyositis, there is no evidence of autoimmune disease, and steroids and immunosuppressive drugs do not alter the clinical course. A precise histopathologic diagnosis has important therapeutic implications. Mononuclear cell "inflammation" in a muscle biopsy sample of infants younger than 2 yr old is usually facioscapulohumeral dystrophy or, less often, a congenital muscular dystrophy.

TREATMENT

Physiotherapy is of no value in regaining strength or in retarding progressive weakness or muscle wasting. Footdrop and scoliosis may be treated by orthopedic measures. In selected cases, surgical wiring of the scapulas to the thoracic wall provides improved shoulder stability and abduction of the arm, but brachial plexopathy, frozen shoulder, and scapular fractures are reported complications. Cosmetic improvement of the facial muscles of expression may be achieved by reconstructive surgery, which grafts a fascia lata to the zygomatic muscle and to the zygomatic head of the quadratus labii superioris muscle. Exercise of facial muscles can help minimize secondary disuse atrophy. No effective pharmacologic or genetic treatment is presently available.

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609.6 Congenital Muscular Dystrophies

Harvey B. Sarnat

The term *congenital muscular dystrophy* is misleading because all muscular dystrophies are genetically determined. It is used to encompass several distinct diseases that have a common characteristic of severe involvement at birth but that, ironically, often follow a more benign clinical course than the early onset and the histopathological changes in the muscle biopsy would suggest. A distinguishing feature of the congenital dystrophies, by contrast with other muscular dystrophies, is a high association with brain malformations, particularly disorders of cortical development such as lissencephaly/pachygyria and polymicrogyria, often complicated by severe epilepsy. Autosomal recessive inheritance is the rule.

CLINICAL MANIFESTATIONS

In several distinct clinical and genetic diseases grouped under the umbrella term *congenital muscular dystrophies*, infants often have

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contractures or arthrogryposis at birth and are diffusely hypotonic. The muscle mass is thin in the trunk and extremities. Head control is poor. Facial muscles may be mildly involved, but ophthalmoplegia, pharyngeal weakness, and weak sucking are not common. A minority has severe dysphagia and requires gavage or gastrostomy. Tendon stretch reflexes may be hypoactive or absent. Arthrogryposis is common in all forms of congenital muscular dystrophy (see Chapter 608.10). Congenital contractures of the elbows have a high association with the **Ullrich type of congenital muscular dystrophy** owing to a defect in 1 or more of the 3 collagen VI genes, each at a different locus.

The congenital muscular dystrophies can be classified according to the type of protein altered by the specific genetic mutations. Diseases of extracellular matrix proteins include merosin deficiency (*LAMA2* mutation at locus 6q22-q23) and Ullrich disease (*COL6A1*, *-A2* and *-A3* mutations at 21q22 and 2q37 loci). A protein of the endoplasmic reticulum (*SEPN1* mutation at 1p35) is the basis of rigid spine syndrome. Abnormal glycosylation of α-dystroglycan causes Walker-Warburg syndrome (*POMT1* mutation at 9q34), muscle-eye-brain disease of Santavuori (*POMGnT1* mutation at 1p32), Fukuyama muscular dystrophy (*FCMD* mutation at 8q31-q33 and 9q31), and congenital muscular dystrophy with secondary merosin deficiency (*FKRP* mutation at 19q13). Glycosylation defects (dystroglycanopathies) result in defective neuroblast migration in the fetal brain and also can cause dilated cardiomyopathy. The dystroglycan molecule interacts with both proteins of the plasma (sarcolemmal) membrane and those of the extracellular matrix and basal lamina not only in muscle but also in brain, where defective dystroglycan and poor glycosylation result in gaps in the pial limiting membrane, a discontinuous glia limitans, causing cobblestone lissencephaly and glioneuronal heterotopia of overmigrated neural cells during formation of the cerebral cortex.

The **Fukuyama type** of congenital muscular dystrophy is the second most common muscular dystrophy in Japan (after DMD); it has also been reported in children of Dutch, German, Scandinavian, and Turkish ethnic backgrounds. In the Fukuyama variety, severe cardiomyopathy and malformations of the brain usually accompany the skeletal muscle involvement. Signs and symptoms related to these organs are prominent: cardiomegaly and heart failure, intellectual disability, seizures, microcephaly, and failure to thrive.

Central neurologic disease can accompany forms of congenital muscular dystrophy other than Fukuyama disease. Mental and neurologic status is the most variable feature; an apparently normal brain and normal intelligence do not preclude the diagnosis if other manifestations indicate this myopathy. The cerebral malformations that occur are not consistently of one type and vary from severe dysplasias (holoprosencephaly, lissencephaly) to milder conditions (agenesis of the corpus callosum, focal heterotopia of the cerebral cortex and subcortical white matter, cerebellar hypoplasia). Seizures are a frequent complication, as early as the neonatal period, and may include infantile spasms and other severe infantile epilepsies.

Congenital muscular dystrophy is a constant association with cerebral dysgenesis in the **Walker-Warburg syndrome** and in **muscle-eye-brain disease of Santavuori.** The neuropathologic findings are those of neuroblast migratory abnormalities in the cerebral cortex, cerebellum, and brainstem. Studies indicate considerably more genetic overlap between Walker-Warburg, Fukuyama, and muscle-eye-brain forms of congenital muscular dystrophy that explain mixed and transitional phenotypes, so that, for example, a *Fukutin*-related (*FKRP*) gene can cause a Walker-Warburg or muscle-eye-brain presentation, or *POMGnT1* also can produce phenotypes other than classic Walker-Warburg disease.

LABORATORY FINDINGS

Serum CK level is usually moderately elevated from several hundred to many thousand IU/L; only marginal increases are sometimes found. EMG shows nonspecific myopathic features. Investigation of all forms of congenital muscular dystrophy should include cardiac assessment and an imaging study of the brain. Muscle biopsy is essential for the diagnosis, but if there is a high degree of suspicion (e.g., a confirmed genetic defect in a sibling), specific genetic testing might avoid the muscle biopsy.

DIAGNOSIS

Muscle biopsy is diagnostic in the neonatal period or thereafter. An extensive proliferation of endomysial collagen envelops individual muscle fibers even at birth, also causing them to be rounded in cross-sectional contour by acting as a rigid sleeve, especially during contraction. The perimysial connective tissue and fat are also increased, and the fascicular organization of the muscle may be disrupted by the fibrosis. Tissue cultures of intramuscular fibroblasts exhibit increased collagen synthesis, but the structure of the collagen is normal. Muscle fibers vary in diameter, and many show central nuclei, myofibrillar splitting, and other cytoarchitectural alterations. Scattered degenerating and regenerating fibers are seen. No inflammation or abnormal inclusions are found.

Immunocytochemical reactivity for merosin (α_2 chain of laminin) at the sarcolemmal region is absent in approximately 40% of cases and normally expressed in the others (Figs. 609-6 and 609-7).

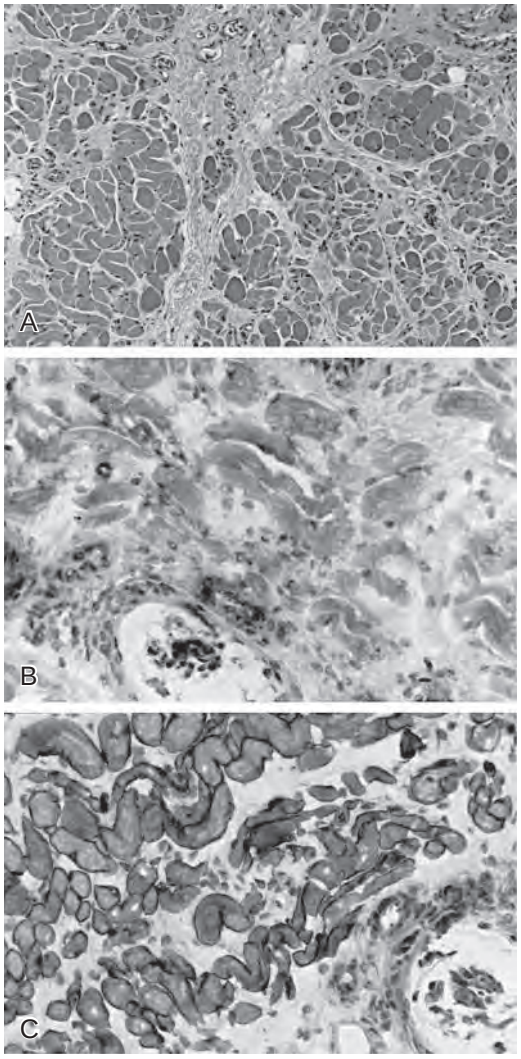


Figure 609-6 Quadriceps femoris muscle biopsy of a 6 mo old girl with congenital muscular dystrophy associated with merosin (α_2-laminin) deficiency. **A,** Histologically, the muscle is infiltrated by a great proliferation of collagenous connective tissue; myofibers vary in diameter, but necrotic fibers are rare. **B,** Immunocytochemical reactivity for merosin (α_2-laminin) is absent in all fibers, including the intrafusal myofibers of a muscle spindle seen at bottom. **C,** Dystrophin expression (rod domain) is normal. Compare with Figures 609-2, 609-3, and 609-7.

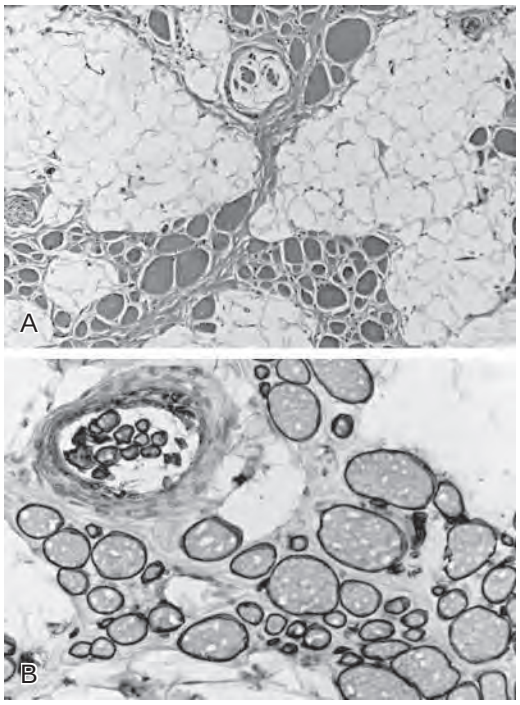


Figure 609-7 Quadriceps femoris muscle biopsy specimen of a 2 yr old girl with congenital muscular dystrophy. **A,** The fascicular architecture of the muscle is severely disrupted, and muscle is replaced by fat and connective tissue; the remaining small groups of myofibers of variable size are seen, including a muscle spindle at top. **B,** Merosin expression is normal in both extrafusal fibers of all sizes and in intrafusal spindle fibers. The severity of the myopathy does not relate to the presence or absence of merosin in congenital muscular dystrophy. Compare with Figure 609-6.

Merosin is a protein that binds the sarcolemmal membrane of the myofiber to the basal lamina or basement membrane. Merosin also is expressed in brain and in Schwann cells. The presence or absence of merosin does not always correlate with the severity of the myopathy or predict its course, but cases with merosin deficiency tend to have more severe cerebral involvement. Adhalin (α-dystroglycan) may be secondarily reduced in some cases. Collagen VI is selectively reduced or absent in Ullrich disease because of a mutation in the *COL6A* gene. Mitochondrial dysfunction may be another secondary defect.

TREATMENT

Only supportive therapy is available in general. Cyclosporine might correct the mitochondrial dysfunction and muscular apoptosis in collagen VI myopathy. Though no curative treatment is presently available for the congenital muscular dystrophies, a consensus statement on the standard of supportive care was issued at a special workshop in 2009 and published the following year. It covers aspects of various organ systems that could be involved, including neurologic, pulmonary, gastroenterologic, cardiac, orthopedic/rehabilitation, and palliative care.

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Chapter 610

Endocrine and Toxic Myopathies

Harvey B. Sarnat

THYROID MYOPATHIES

See also Chapters 563-568.

Thyrotoxicosis causes proximal weakness and wasting accompanied by myopathic electromyographic changes. Thyroxine binds to myofibrils and, if in excess, impairs contractile function. **Hyperthyroidism** can also induce myasthenia gravis and hypokalemic periodic paralysis, the latter mainly affecting East Asian males who have a genetic predisposition. Mutation in the gene *KCNJ18* may be responsible for altering the potassium channel Kir2.6 in up to one third of cases. Potassium supplementation and propranolol are useful in treating thyrotoxic periodic paralysis.

Hypothyroidism, whether congenital or acquired, consistently produces hypotonia and a proximal distribution of weakness. Although muscle wasting is most characteristic, one form of cretinism, the Kocher-Debré-Sémélaigne syndrome, is characterized by generalized pseudohypertrophy of weak muscles. Infants can have a Herculean appearance reminiscent of myotonia congenita. The serum creatine kinase (CK) level is elevated in hypothyroid myopathy and returns to normal after thyroid replacement therapy.

Results of muscle biopsy in hypothyroidism reveal acute myopathic changes, including myofiber necrosis and sometimes central cores. In hyperthyroidism, the muscle biopsy specimen shows only mild, nonspecific myopathic changes without necrosis of myofibers.

The clinical and pathologic features of hyperthyroid myopathy and hypothyroid myopathy resolve after appropriate treatment of the thyroid disorder. Many of the systemic symptoms of hyperthyroidism, including myopathic weakness and ophthalmoparesis, improve with the administration of β-blockers.

Most patients with primary **hyperparathyroidism** (see Chapter 573) develop weakness, fatigability, fasciculations, and muscle wasting that is reversible after removal of the parathyroid adenoma. The serum creatine kinase and muscle biopsy remain normal, but the electromyography can show nonspecific myopathic features. A minority of patients develop myotonia that could be confused with myotonic dystrophy.

STEROID-INDUCED MYOPATHY

Natural Cushing disease and iatrogenic Cushing syndrome from exogenous corticosteroid administration can cause painless, symmetric, progressive proximal weakness, increased serum creatine kinase levels, and a myopathic electromyogram and muscle biopsy specimen (see Chapter 577). Myosin filaments may be selectively lost. The 9α-fluorinated steroids, such as dexamethasone, betamethasone, and triamcinolone, are the most likely to produce *steroid myopathy.* Dexamethasone alters the abundance of ceramides in myotubes in developing muscle. In patients with dermatomyositis or other myopathies treated with steroids, it is sometimes difficult to distinguish refractoriness of the disease from steroid-induced weakness, especially after long-term steroid administration. Vitamin D is another factor altering muscle metabolism and particularly its sensitivity to insulin; vitamin D deficiency may be accentuated and contribute to steroid myopathy, especially in type 2 diabetic patients and insulin resistance.

All patients who have been taking steroids for long periods develop reversible type II myofiber atrophy; this is a *steroid effect* but is not steroid myopathy unless it progresses to become a necrotizing myopathy. At greatest risk in the pediatric age group are children requiring long-term steroid therapy for asthma, rheumatoid arthritis, dermatomyositis, lupus, and other autoimmune or inflammatory diseases or who are being treated for leukemia or other hematologic diseases.

Table 610-1 Toxic Myopathies

INFLAMMATORY Cimetidine D-Penicillamine Procainamide L-Tryptophan L-DOPA	**MALIGNANT HYPERTHERMIA** Halothane Ethylene Diethyl ether Methoxyflurane Ethyl chloride Trichloroethylene Gallamine Succinylcholine
NONINFLAMMATORY NECROTIZING OR VACUOLAR Cholesterol-lowering agents Chloroquine Colchicine Emetine ε-Aminocaproic acid Labetalol Cyclosporine and tacrolimus Isoretinoic acid (vitamin A analog) Vincristine Alcohol	**MITOCHONDRIAL** Zidovudine
RHABDOMYOLYSIS AND MYOGLOBINURIA Cholesterol-lowering drugs (especially statins) Alcohol Heroin Amphetamine Toluene Cocaine ε-Aminocaproic acid Pentazocine Phencyclidine	**MYOTONIA** 2,4-*d*-Chlorophenoxyacetic acid Anthracene-9-carboxycyclic acid Cholesterol-lowering drugs Chloroquine Cyclosporine
	MYOSIN LOSS Nondepolarizing neuromuscular blocking agents Intravenous glucocorticoids

From Goldman L, Ausiello D: Cecil textbook of medicine, *ed 22, Philadelphia, 2004, WB Saunders, p. 2399.*

In addition to steroids, the drugs listed in Table 610-1 can cause acute or chronic toxic myopathies. An incompletely understood entity known as critical illness myopathy is a progressive weakness of patients with extended illnesses who remain in the intensive care unit; it is associated pathologically with selective loss of thick (myosin) myofilaments; immobility and excessive steroid treatment are believed to be important factors. Various steroids are sometimes used chronically in the treatment of Duchenne muscular dystrophy; they may actually exaggerate the weakness because of steroid myopathy superimposed on the dystrophic process (see Chapter 609).

Hyperaldosteronism (Conn syndrome) is accompanied by episodic and reversible weakness similar to that of periodic paralysis. The proximal myopathy can become irreversible in chronic cases. Elevated creatine kinase levels and even myoglobinuria sometimes occur during acute attacks. Arterial hypertension is a frequent manifestation and, in children, aldosterone-secreting adenomas should be considered in the differential diagnosis of idiopathic hypertension. Hereditary primary aldosteronism is due to a mutation in one of the potassium channel genes *KCNJ5* and *GIRK4*.

Chronic growth hormone excess (sometimes illicitly acquired by adolescent athletes or seen in acromegaly) produces atrophy of some myofibers and hypertrophy of others, and scattered myofiber degeneration. Despite the augmented protein synthesis induced by growth hormone, it impairs myofibrillar adenosine triphosphatase activity and reduces sarcolemmal excitability, with resultant diminished, rather than increased, strength corresponding to the larger muscle mass. It has been used therapeutically in muscular dystrophy with both a positive effect and complications. *Ghrelin* is an intestinal hormone that activates a growth hormone secretagog receptor and stimulates growth hormone release. In addition to its effect as a "hunger hormone" that involves food intake and fat deposition, it also prevents muscular atrophy by inducing myodifferentiation and myoblast fusion.

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Chapter 611

Metabolic Myopathies

Harvey B. Sarnat

Table 611-1 describes the differential diagnosis of metabolic myopathies.

611.1 Periodic Paralyses (Potassium-Related) and Other Muscle Channelopathies

Harvey B. Sarnat

Episodic, reversible weakness or paralysis, known as **periodic paralysis,** is associated with transient alterations in serum potassium levels, usually hypokalemia but occasionally hyperkalemia. All familial forms of periodic paralysis are caused by mutations in genes encoding voltage-gated ion channels in muscle: sodium, calcium, and potassium. Mutations in the *CACNA1S* voltage-gated calcium (not potassium) channel are the etiology of hypokalemic periodic paralysis. Nonhereditary causes of periodic paralysis are caused by a diverse group of disorders that affect potassium balance (Table 611-2). During

Table 611-1 Metabolic and Mitochondrial Myopathies

GLYCOGEN METABOLISM DEFICIENCIES
Type II: α-1,4-Glucosidase (acid maltase)
Type III: Debranching
Type IV: Branching
Type V: Phosphorylase (McArdle disease)*
Type VII: Phosphofructokinase (Tarui disease)*
Type VIII: Phosphorylase B kinase*
Type IX: Phosphoglycerate kinase*
Type X: Phosphoglycerate mutase*
Type XI: Lactate dehydrogenase*
LIPID METABOLISM DEFICIENCIES
Carnitine palmitoyltransferase*
Primary systemic/muscle carnitine deficiency
Secondary carnitine deficiency
β-Oxidation defects
Medications (valproic acid)
PURINE METABOLISM DEFICIENCIES
Myoadenylate deaminase deficiency
MITOCHONDRIAL MYOPATHIES
Alpers-Huttenlocher syndrome
Chronic progressive external ophthalmoplegia
Kearns-Sayre syndrome
Pearson syndrome
Mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes (MELAS)
Mitochondrial neurogastrointestinal encephalomyopathy (MNGIE)
Myoclonic epilepsy with ragged red fibers (MERRF)
Leber hereditary optic neuropathy
Leigh syndrome
Infantile myopathy and lactic acidosis

*Deficiency can produce exercise intolerance and myoglobinuria.

From Chinnery PF: Muscle diseases. In Goldman L, Schafer AI, editors: Goldman's Cecil medicine, *ed 24, Philadelphia, 2012, Elsevier, Table 429-7, p. 2413.*

Table 611-2 Secondary Causes of Periodic Paralysis

HYPOKALEMIC
Thyrotoxic
Primary hyperaldosteronism (Conn syndrome)
Renal tubular acidosis (e.g., Fanconi syndrome)
Juxtaglomerular apparatus hyperplasia (Bartter syndrome)
Gastrointestinal potassium wastage
Villous adenoma
Laxative abuse
Pancreatic non–insulin-secreting tumors with diarrhea
Nontropical sprue
Barium intoxication
Potassium-depleting diuretics
Amphotericin B
Licorice
Corticosteroids
Toluene toxicity
p-Aminosalicylic acid
Carbenoxolone
HYPERKALEMIC
Addison disease
Hypoaldosteronism
Excessive potassium supplementation
Potassium-sparing diuretics
Chronic renal failure

From Chinnery PF: Muscle diseases. In Goldman L, Schafer AI, editors: Goldman's Cecil medicine, ed 24, Philadelphia, 2012, Elsevier, Table 429-8, p. 2415.

attacks, myofibers are electrically unexcitable, although the contractile apparatus can respond normally to calcium. The genetic disorder is inherited as an autosomal dominant trait. It is precipitated in some patients by a heavy carbohydrate meal, insulin, epinephrine including that induced by emotional stress, hyperaldosteronism or hyperthyroidism, administration of amphotericin B, or ingestion of licorice. The defective genes are at the 17q13.1-13.3 locus in **hyperkalemic periodic paralysis,** the same as in paramyotonia congenita, and at the 1q31-32 locus in **hypokalemic periodic paralysis.**

Attacks often begin in infancy, particularly in the hyperkalemic form, and the disease is nearly always symptomatic by 10 yr of age, affecting both sexes equally. Late childhood or adolescence is the more typical age of onset of the hypokalemic form, Andersen-Tawil syndrome, and paramyotonia congenita. Periodic paralysis is an episodic event; patients are unable to move after awakening and gradually recover muscle strength during the next few minutes or hours. All 4 extremities are involved. Muscles that remain active in sleep, such as the diaphragm, extraocular muscles (rapid eye movements), and cardiac muscle, are not affected. Patients are normal between attacks, but in adult life the attacks become more frequent, and the disorder causes progressive myopathy with permanent weakness even between attacks. The usual frequency of attacks in childhood is once a week. The differential diagnosis includes thyrotoxic periodic paralysis, myotonia congenita, and paramyotonia congenita. A triad of periodic paralysis, potentially fatal cardiac ventricular ectopy (caused by a defect in Kir2.1 channels for terminal repolarization), and characteristic physical features is known as **Andersen-Tawil syndrome.**

Alterations in serum potassium levels occur only during acute episodes and are accompanied by T-wave changes in the electrocardiogram. Hypokalemia may be caused by alterations in calcium gradients. The creatine kinase (CK) level may be mildly elevated at those times. Plasma phosphate levels often decrease during symptomatic periods. Muscle biopsy findings are often normal between attacks, but during an attack a vacuolar myopathy is demonstrated. Pathologic changes in the periodic paralyses are similar, whether the disease is the result of a sodium or a potassium channel defect, suggesting that the changes might result from the recurrent paralytic state rather than the specific channelopathy. The vacuoles are dilated sarcoplasmic reticulum and invaginations of the extracellular space into the cytoplasm, and they may be filled with glycogen. Muscle biopsy is not essential to diagnose periodic paralysis, however. Hypoglycemia does not occur. Loci for the majority of periodic paralyses have been demonstrated and the genes at least partially characterized, but many patients with the same clinical phenotype exhibit no mutations in the identified genes.

TREATMENT

Paralytic attacks of hypokalemic periodic paralysis are best treated by the oral administration of potassium or even fruit juices that contain potassium. A low sodium intake and the administration of acetazolamide, 125-250 mg bid or tid in school-age children, often is effective in abolishing attacks or at least reducing their frequency and severity. Spironolactone, in a dose of 100-200 mg/day PO in school-age children, may be beneficial as well.

OTHER MUSCLE CHANNELOPATHIES

Disorders of ion channels other than the well-documented potassium channelopathies also are recognized. A rare, severe **neonatal myotonia** is secondary to a mutation of the voltage-gated sodium-channel *SCN4A* gene; it is unrelated to neonatal myotonic dystrophy, myotonia congenita, or infantile myofibrillar myopathies. This same gene also is responsible for severe neonatal episodic laryngospasm. Mexiletine is effective treatment of the myotonia, but the long-term prognosis remains poor, with death by 2 yr of age. Sodium channel blockers, such as carbamazepine, phenytoin, and procainamide, are alternatives.

Neuromyotonia, a continuous muscle activity of neurogenic origin, may be caused by mutations in genes encoding or antibodies against potassium channels, but is rare in childhood. **Schwartz-Jampel disease**, resulting from, an autosomal recessive trait, involves severe muscle stiffness, myotonia, blepharospasm, and chondroplasia. It becomes symptomatic in the 1st yr of life and is slowly progressive until midadolescence, after which it is stable. It is no longer considered a variant of myotonic dystrophy and is caused by mutation in the *HSPG2* gene that encodes perlecan, the major heparin sulphate proteoglycan of basement membranes. Sodium channel blockers may be useful.

Bibliography is available at Expert Consult.

611.2 Malignant Hyperthermia

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See also Chapters 61 and 608.4.

This syndrome is usually inherited as an autosomal dominant trait. It occurs in all patients with central core disease but is not limited to that particular myopathy. The gene is at the 19q13.1 locus in both central core disease and malignant hyperthermia without this specific myopathy. At least 15 separate mutations in this gene are associated with malignant hyperthermia. The gene programs the ryanodine receptor, a tetrameric calcium release channel in the sarcoplasmic reticulum, in apposition to the voltage-gated calcium channel of the transverse tubule. It occurs rarely in Duchenne and other muscular dystrophies, in various other myopathies, in some children with scoliosis, and in an isolated syndrome not associated with other muscle disease. Affected children sometimes have peculiar facies. All ages are affected, including premature infants whose mothers underwent general anesthesia for cesarean section.

Acute episodes are precipitated by exposure to general anesthetics and occasionally to local anesthetic drugs. Patients suddenly develop extreme fever, rigidity of muscles, and metabolic and respiratory acidosis; the serum CK level rises to as high as 35,000 IU/L. Myoglobinuria can result in tubular necrosis and acute renal failure.

The muscle biopsy specimen obtained during an episode of malignant hyperthermia or shortly afterward is not indicated but shows widely scattered necrosis of muscle fibers known as **rhabdomyolysis**. Between attacks, the muscle biopsy specimen is normal unless there is an underlying chronic myopathy.

It is important to recognize patients at risk of malignant hyperthermia because the attacks may be prevented by administering dantrolene

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sodium before an anesthetic is given. Patients at risk, such as siblings, are identified by the caffeine contracture test: a portion of fresh muscle biopsy tissue in a saline bath is attached to a strain gauge and exposed to caffeine and other drugs; an abnormal spasm is diagnostic. The syndrome-associated receptor also may be demonstrated by immunochemistry in frozen sections of the muscle biopsy. The gene defect of the ryanodine receptor is present in 50% of patients; gene testing is available only for this genetic group. This receptor also may be seen in the muscle biopsy by immunoreactivity. Another candidate gene is at the 1q31 locus.

Apart from the genetic disorder of malignant hyperthermia, some drugs can induce acute rhabdomyolysis with myoglobinuria and potential renal failure, but this usually occurs in patients who are predisposed by some other metabolic disease (mitochondrial myopathies). Valproic acid can induce this process in children with mitochondrial cytopathies or with carnitine palmitoyltransferase deficiency.

611.3 Glycogenoses

Harvey B. Sarnat

See also Chapter 87.1.

Glycogenosis I (von Gierke disease) is not a true myopathy because the deficient liver enzyme glucose-6-phosphatase is not normally present in muscle. Nevertheless, children with this disease are hypotonic and mildly weak for unknown reasons.

Glycogenosis II (Pompe disease) is an autosomal recessively inherited deficiency of the glycolytic lysosomal enzyme α-glucosidase (formerly known as acid maltase) that cleaves the α-1,4 and α-1,6 glycosidic linkages. Of the 12 known glycogenoses, type II is the only one with a defective lysosomal enzyme. The defective gene is at locus 17q23, with more than 200 distinct mutations identified. Two clinical forms are described. The **infantile** form is a severe generalized myopathy and cardiomyopathy. Patients have cardiomegaly and hepatomegaly and are diffusely hypotonic and weak. The serum CK level is greatly elevated. A muscle biopsy specimen reveals a vacuolar myopathy with abnormal lysosomal enzymatic activities such as acid and alkaline phosphatases. Evidence of a secondary mitochondrial cytopathy is often demonstrated; it includes electron microscopic demonstration of paracrystallin structures within muscle mitochondria and low concentrations of respiratory chain enzymes. Death in infancy or early childhood is usual; however, enzyme replacement therapy has improved the outcome.

The **late childhood** or **adult** form is a much milder myopathy without cardiac or hepatic enlargement. It might not become clinically expressed until later childhood or early adult life but may be symptomatic as myopathic weakness and hypotonia even in early infancy. Even in late adult-onset acid maltase deficiency, >50% of the patients report difficulties with muscle strength dating from childhood. Ultrastructural evidence of secondary mitochondrial cytopathy also occurs, as with infantile Pompe disease. MRI of muscle may show distinctive changes that differ from other myopathies.

The serum CK level is greatly elevated, and the muscle biopsy findings are diagnostic even in the presymptomatic stage. The diagnosis of glycogenosis II is confirmed by quantitative assay of acid maltase activity in muscle or liver biopsy specimens. A rare variant of the milder form of acid maltase deficiency can show muscle acid maltase activity in the low normal range with only intermittent decreases to subnormal values; the muscle biopsy findings are similar although milder. In another form, **Danon disease,** transmitted as an X-linked recessive trait at the Xq24 locus, the primary deficiency is lysosomal membrane protein-2 (LAMP2) and results in hypertrophic cardiomyopathy, proximal myopathy, and intellectual disability.

Glycogenosis III (Cori-Forbes disease), a deficiency of debrancher enzyme (amylo-1,6-glucosidase), is more common than is usually diagnosed, and it is generally the least severe. Hypotonia, weakness, hepatomegaly, and fasting hypoglycemia in infancy are common, but these features often resolve spontaneously, and patients become asymptomatic in childhood and adult life. Others experience slowly progressive distal muscle wasting, hepatic cirrhosis, recurrent hypoglycemia, and heart failure. This more serious chronic course is particularly seen in the Inuit population. Minor myopathic findings including vacuolation of muscle fibers are found in the muscle biopsy specimen.

Glycogenosis IV (Andersen disease) is a deficiency of brancher enzyme, resulting in the formation of an abnormal glycogen molecule, amylopectin, in the liver, reticuloendothelial cells, and skeletal and cardiac muscle. Hypotonia, generalized weakness, muscle wasting, and contractures are the usual signs of myopathic involvement. Most patients die before age 4 yr because of hepatic or cardiac failure. A few children without neuromuscular manifestations have been described.

Glycogenosis V (McArdle disease) is caused by muscle glycogen phosphorylase deficiency inherited as an autosomal recessive trait at locus 11q13, encoded by the *PMGM* gene. Exercise intolerance is the cardinal clinical feature. Physical exertion results in cramps, weakness, and myoglobinuria, but strength is normal between attacks. The serum CK level is elevated only during exercise. A characteristic clinical feature is lack of the normal rise in serum lactate levels during ischemic exercise because of inability to convert pyruvate to lactate under anaerobic conditions in vivo. Myophosphorylase deficiency may be demonstrated histochemically and biochemically in the muscle biopsy tissue. Some patients have a defect in adenosine monophosphate–dependent muscle phosphorylase β-kinase, a phosphorylase enzyme activator. Muscle phosphorylase deficiency was the first neuromuscular disease to be diagnosed by MR spectroscopy, which shows that the intramuscular pH does not decrease with exercise and there is no depletion of adenosine triphosphatase but that the phosphocreatine concentration falls excessively. This noninvasive technique may be useful in some patients if the radiologist is experienced with the disease.

A rare **neonatal form of myophosphorylase deficiency** causes feeding difficulties in early infancy, may be severe enough to result in neonatal death, or can follow a course of slowly progressive weakness resembling a muscular dystrophy. The long-term prognosis is good. Patients must learn to moderate their physical activities, but they do not develop severe chronic myopathic handicaps or cardiac involvement.

Glycogenosis VII (Tarui disease) is muscle phosphofructokinase deficiency. Although this disease is rarer than glycogenosis V, the symptoms of exercise intolerance, clinical course, and inability to convert pyruvate to lactate are identical. The distinction is made by biochemical study of the muscle biopsy specimen. It is transmitted as an autosomal recessive trait at the 1cenq32 locus and some mutations are particularly prevalent in the Ashkenazi Jewish population.

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611.4 Mitochondrial Myopathies

Harvey B. Sarnat

See also Chapters 87.4 and 598.2.

Several diseases involving muscle, brain, and other organs are associated with structural and functional abnormalities of mitochondria, producing defects in aerobic cellular metabolism, the electron transport chain, and the Krebs cycle. Because mitochondria are found in all cells, except mature erythrocytes, the term **mitochondrial cytopathy** is used preferentially to emphasize the multisystemic nature of these diseases. The structural aberrations are best demonstrated by electron microscopy of the muscle biopsy sample, revealing a proliferation of abnormally shaped cristae, including stacked or whorled cristae and paracrystallin structures that occupy the space between cristae and are formed from CK. Muscle biopsies of neonates, infants, and toddlers show more severe involvement of endothelial cells of intramuscular capillaries than of myofibers, unlike the reverse in adults, but endothelial paracrystallin structures are globular rather than brick shaped as in myofibers. The endoplasmic reticulum becomes abnormally adherent to mitochondria. Similar endothelial mitochondrial alterations are seen in brain in Leigh and other infantile mitochondrial encephalopathies. Histochemical study of the muscle biopsy specimen reveals abnormal clumping of oxidative enzymatic activity and scattered myofibers, with

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loss of cytochrome-c oxidase activity and with increased neutral lipids within myofibers. Ragged red muscle fibers occur in some mitochondrial myopathies, particularly those with a combination of respiratory chain complexes I and IV deficiencies. Accumulations of this membranous material beneath the muscle fiber membrane are best demonstrated by special stains, such as modified Gomori trichrome.

These characteristic histochemical and ultrastructural changes are most consistently seen with point mutations in mitochondrial transfer RNA. The large mitochondrial DNA (mtDNA) deletions of 5 or 7.4 kb (the single mitochondrial chromosome has 16.5 kb) are associated with defects in mitochondrial respiratory oxidative enzyme complexes, if as few as 2% of the mitochondria are affected, but minimal or no morphologic or histochemical changes may be noted in the muscle biopsy specimen, even by electron microscopy; hence, quantitative biochemical studies of the muscle tissue are needed to confirm the diagnosis. Because most of the subunits of the respiratory chain complexes are encoded by nuclear DNA (nDNA) rather than mtDNA, mendelian autosomal inheritance is possible, rather than maternal transmission as with pure mtDNA point mutations. Complex II (succinate dehydrogenase) is the only enzyme complex in which all of its subunits are encoded by nDNA; hence it is histochemically reactive in all mitochondrial diseases with mtDNA point mutations. Serum lactate is elevated in some diseases, and cerebrospinal fluid lactate is more consistently elevated, even if serum concentrations are normal.

Several distinct mitochondrial diseases that primarily affect striated muscle or muscle and brain are identified. These can be divided into the ragged red fiber diseases and non–ragged fiber diseases. The ragged red fiber diseases include Kearns-Sayre, MELAS (*mi*tochondrial *e*ncephalopathy, *l*actic *a*cidosis, and *s*troke-like episodes) syndrome, MERRF (*m*yoclonic *e*pilepsy with *r*agged *r*ed *f*ibers) syndrome, and progressive external ophthalmoplegia syndromes, which are associated with a combined defect in respiratory chain complexes I and IV. The non–ragged fiber diseases include Leigh encephalopathy and Leber hereditary optic atrophy; they involve complex I or IV alone or, in children, the common combination of defective complexes III and V. **Kearns-Sayre syndrome** is characterized by the triad of progressive external ophthalmoplegia, pigmentary degeneration of the retina, and onset before age 20 yr. Heart block, cerebellar deficits, and high cerebrospinal fluid protein content are often associated. Visual evoked potentials are abnormal. Patients usually do not experience weakness of the trunk or extremities or dysphagia. Most cases are sporadic.

Chronic progressive external ophthalmoplegia may be isolated or accompanied by limb muscle weakness, dysphagia, and dysarthria. A few patients described as having *ophthalmoplegia plus* have additional central nervous system involvement. Autosomal dominant inheritance is found in some pedigrees, but most cases are sporadic.

MERRF and **MELAS syndromes** are other mitochondrial disorders affecting children. The latter is characterized by stunted growth, episodic vomiting, seizures, and recurring cerebral insults causing hemiparesis, hemianopia, or even cortical blindness, and dementia. The disease behaves as a degenerative disorder, and children die within a few years.

Other "degenerative" diseases of the central nervous system that also involve myopathy with mitochondrial abnormalities include **Leigh subacute necrotizing encephalopathy** (see Chapter 87.4) and **cerebrohepatorenal (Zellweger) disease, primarily a peroxisomal disease with secondary mitochondrial alterations** (see Chapter 86.2). Another recognized mitochondrial myopathy is **cytochrome-c oxidase deficiency. Oculopharyngeal muscular dystrophy** is also fundamentally a mitochondrial myopathy.

Mitochondrial depletion syndrome of early infancy is characterized by severely decreased oxidative enzymatic activities in most or all 5 of the complexes; in addition to diffuse muscle weakness, neonates and young infants can show multisystemic involvement and the syndrome occurs in several forms: myopathic; encephalomyopathic; hepatoencephalopathic; and intestinal encephalopathic. Cardiomyopathy and sometimes bullous skin lesions or generalized edema also can occur. **Alpers syndrome** is genetically homogeneous and is caused by mtDNA depletion and mutations in the *POLG1* gene. Several other genes are identified, mostly in later-onset forms; hence mitochondrial depletion is a syndrome and not a single disease. **Barth syndrome** is an X-linked recessive mitochondrial disorder characterized by cardiomyopathy, myopathy of striated muscle, growth retardation, neutropenia, and high serum and urinary concentrations of 3-methylglutaconic acid.

Many rare diseases with only a few case reports are suspected of being mitochondrial disorders. It is also now recognized that secondary mitochondrial defects occur in a wide range of nonmitochondrial diseases, including inflammatory autoimmune myopathies, Pompe disease, and some cerebral malformations, and also may be induced by certain drugs and toxins, so that interpretation of mitochondrial abnormalities as primary defects must be approached with caution.

mtDNA is distinct from the DNA of the cell nucleus and is inherited exclusively from the mother; mitochondria are present in the cytoplasm of the ovum but not in the head of the sperm, the only part that enters the ovum at fertilization. The rate of mutation of mtDNA is 10 times higher than that of nDNA. The mitochondrial respiratory enzyme complexes each have subunits encoded either in mtDNA or nDNA. Complex II (succinate dehydrogenase, a Krebs cycle enzyme) has 4 subunits, all encoded in nDNA; complex III (ubiquinol or cytochrome-b oxidase) has 9 subunits, only 1 of which is encoded by mtDNA and 8 of which are programmed by nDNA; complex IV (cytochrome-c oxidase) has 13 subunits, only 3 of which are encoded by mtDNA. For this reason, mitochondrial diseases of muscle may be transmitted as autosomal recessive traits rather than by strict maternal transmission, even though all mitochondria are inherited from the mother.

In Kearns-Sayre syndrome, a single large mtDNA deletion has been identified, but other genetic variants are known; in MERRF and MELAS syndromes of mitochondrial myopathy, point mutations occur in transfer RNA.

INVESTIGATIONS

Investigation for mitochondrial cytopathies begins with serum lactate. Lactic acid is not increased in all mitochondrial cytopathies, so that a normal result is not necessarily reassuring; cerebrospinal fluid lactate is increased in some cases in which serum lactate is normal, particularly if there are clinical signs of encephalopathy. Serum 3-methylglutaconic acid often is increased in mitochondrial cytopathies in general, demonstrated in more than 50 different genetic mutations, and hence is a good screening measurement; it rarely is increased in other metabolic diseases. This product also may be increased in urine. Hepatic enzymes (transaminases) should be measured in blood. Cardiac evaluation often is warranted. Molecular markers in blood for the common diseases with known mtDNA point mutations identify many of the mitochondrial cytopathies presenting in adult life or adolescence, but less frequently in children and least in young infants. MRI of the brain may reveal hyperintense lesions of the basal ganglia and MR spectroscopy can demonstrate an increased lactate peak. The muscle biopsy provides the best evidence of all mitochondrial myopathies and should include histochemistry for oxidative enzymes, electron microscopy, and quantitative biochemical assay of respiratory chain enzyme complexes and coenzyme-Q10; muscle tissue also can be analyzed for mtDNA. Many mitochondrial disorders also can affect the Schwann cells and axons of peripheral nerves and present clinically with neuropathy; hence motor and sensory nerve conduction velocities can be measured in selected patients; sural nerve biopsy is required only rarely if neuropathy is the predominant finding and the diagnosis is not evident from other studies.

TREATMENT

There is no effective treatment of mitochondrial cytopathies, but various "cocktails" are often used empirically to try to overcome the metabolic deficits. These include oral carnitine supplements, riboflavin, coenzyme-Q10, ascorbic acid (vitamin C), vitamin E, and other antioxidants. Although some anecdotal reports are encouraging, no controlled studies that prove efficacy have been published.

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611.5 Lipid Myopathies

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See Chapter 86.4.

Considered as metabolic organs, skeletal muscles are the most important sites in the body for long-chain fatty acid metabolism because of their large mass and their rich density of mitochondria where fatty acids are metabolized. They are the major source of energy for skeletal muscle during sustained exercise or fasting. Hereditary disorders of lipid metabolism that cause progressive myopathy are an important, relatively common, and often treatable group of muscle diseases. Increased lipid within myofibers is seen in the muscle biopsy of some mitochondrial myopathies and is a constant, rather than an unpredictable, feature of specific diseases. Among the ragged red fiber diseases, Kearns-Sayre syndrome always shows increased neutral lipid, whereas MERRF and MELAS syndromes do not, a useful diagnostic marker for the pathologist. Free fatty acids are converted to acyl-coenzyme A by fatty acyl-coenzyme A synthetases; the resulting long-chain fatty acids bind to carnitine and are transported into mitochondria where β-oxidation is carried out. Disorders of lipid fuel utilization and lipid storage disorders can be divided into defects of transport and oxidation of exogenous fatty acids within mitochondria and defects of endogenous triglyceride catabolism.

Muscle carnitine deficiency is an autosomal recessive disease caused by mutations in the *SLC22A5* gene, involving deficient transport of dietary carnitine across the intestinal mucosa. Carnitine is acquired from dietary sources but is also synthesized in the liver and kidneys from lysine and methionine; it is the obligatory carrier of long- and medium-chain fatty acids into muscle mitochondria.

The clinical course may be one of sudden exacerbations of weakness or can resemble a progressive muscular dystrophy with generalized proximal myopathy and sometimes facial, pharyngeal, and cardiac involvement. Symptoms usually begin in late childhood or adolescence or may be delayed until adult life. Progression is slow but can end in death.

Serum CK level is mildly elevated. Muscle biopsy material shows vacuoles filled with lipid within muscle fibers in addition to nonspecific changes suggestive of a muscular dystrophy. Mitochondria can appear normal or abnormal. Carnitine measured in muscle biopsy tissue is reduced, but the serum carnitine level is normal.

Treatment stops the progression of the disease and can even restore lost strength if the disease is not too advanced. It consists of special diets low in long-chain fatty acids. Steroids can enhance fatty acid transport. Specific therapy with L-carnitine taken orally in large doses overcomes the intestinal barrier in some patients. Some patients also improve when given supplementary riboflavin, and other patients seem to improve with propranolol.

Systemic carnitine deficiency is a disease of impaired renal and hepatic synthesis of carnitine rather than a primary myopathy. Patients with this autosomal recessive disease experience progressive proximal myopathy and show muscle biopsy changes similar to those of muscle carnitine deficiency; however, the onset of weakness is earlier and may be evident at birth. Endocardial fibroelastosis also can occur. Episodes of acute hepatic encephalopathy resembling Reye syndrome can occur. Hypoglycemia and metabolic acidosis complicate acute episodes. Cardiomyopathy may be the predominating feature in some cases and result in death.

Cerebral infarctions and myopathy occur in children, particularly when accompanied by hypoglycemia. Mean age at presentation is approximately 9 yr. Brain MRI shows distinctive changes related to multiple infarcts of various sizes.

The concentration of carnitine is reduced in serum as well as in muscle and liver. L-Carnitine deficiency can be corrected by oral administration of carnitine on a daily basis.

A similar clinical syndrome may be a complication of renal Fanconi syndrome because of excessive urinary loss of carnitine or loss during chronic hemodialysis.

Treatment with L-carnitine improves the maintenance of blood glucose and serum carnitine levels but does not reverse the ketosis or acidosis or improve exercise capacity.

Muscle carnitine palmitoyltransferase (CPT) deficiency manifests as episodes of rhabdomyolysis, coma, and elevated serum CK levels that may be indistinguishable from Reye syndrome. It is the most common identified cause of recurrent myoglobinuria in adults, but myoglobinuria is not a constant feature in all. CPT transfers long-chain fatty acid acyl-coenzyme A residues to carnitine on the outer mitochondrial membrane for transport into the mitochondria. Exercise intolerance and myoglobinuria resemble glycogenoses V and VII. The degree of exercise that triggers an attack varies among individuals, ranging from casual walking to strenuous exercise. Fasting hypoglycemia can occur. Some patients present only in late adolescence or adult life with myalgias. Genetic transmission is autosomal recessive and is caused by a defect on chromosome 1 at the 1p32 locus. Administration of valproic acid can precipitate acute rhabdomyolysis with myoglobinuria in patients with CPT deficiency; it should be avoided in the treatment of seizures or migraine if they occur. *Very long-chain acyl-coenzyme A dehydrogenase deficiency* has a similar clinical presentation but mainly with adult onset.

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611.6 Vitamin E Deficiency Myopathy

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In experimental animals, deficiency of vitamin E (α-tocopherol, an antioxidant also important in mitochondrial superoxide generation) produces a progressive myopathy closely resembling a muscular dystrophy. Myopathy and neuropathy are recognized in humans who lack adequate intake of this antioxidant. Patients with chronic malabsorption, those undergoing long-term dialysis, and premature infants who do not receive vitamin E supplements are particularly vulnerable. Treatment with high doses of vitamin E can reverse the deficiency. Myopathy caused by chronic hypervitaminosis E also occurs.

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Chapter 612

Disorders of Neuromuscular Transmission and of Motor Neurons

Harvey B. Sarnat

612.1 Myasthenia Gravis

Harvey B. Sarnat

AUTOIMMUNE MYASTHENIA GRAVIS

Myasthenia gravis is a chronic autoimmune disease of neuromuscular blockade, characterized clinically by rapid fatigability of striated muscle, particularly extraocular and palpebral muscles and those of swallowing. It must be distinguished from congenital myasthenic

syndrome, a genetic disorder of receptors on the postsynaptic membrane of the neuromuscular junction and toxin-induced myasthenia, such as botulism (see below). The release of acetylcholine (ACh) into the synaptic cleft by the axonal terminal is normal, but the postsynaptic muscle membrane (i.e., *sarcolemma*) or *motor end plate* is less responsive than normal. A decreased number of available ACh receptors is as a result of circulating receptor-binding antibodies in most cases of autoimmune myasthenia.

A rare **familial** myasthenia gravis is an autosomal recessive trait not associated with increased plasma anti-ACh antibodies. One familial form is a deficiency of motor end plate acetylcholinesterase (AChE). Most congenital (familial) forms are postsynaptic defects. Infants born to myasthenic mothers can have a **transient neonatal myasthenic syndrome** secondary to placentally transferred anti-ACh receptor antibodies, distinct from congenital myasthenic syndromes (Tables 612-1 and 612-2).

Clinical Manifestations

In juvenile autoimmune myasthenia gravis, unilateral or bilateral but usually asymmetrical ptosis and some degree of extraocular muscle weakness are the earliest and most constant signs. Extraocular weakness is not confined to muscles innervated by just 1 or 2 of the 3 corresponding brainstem nuclei and is progressive. Older children might complain of diplopia, and young children might hold open their eyes with their fingers or thumbs if the ptosis is severe

Table 612-1 Classification of the Congenital Myasthenic Syndromes

PRESYNAPTIC DEFECTS
- Paucity of synaptic vesicles and decreased quantal release
- Congenital myasthenic syndromes with episodic apnea (choline acetyltransferase deficiency)
- Lambert-Eaton syndrome–like form

SYNAPTIC DEFECTS
- End plate acetylcholinesterase deficiency

POSTSYNAPTIC DEFECTS
- Primary acetylcholine receptor deficiency
- Reduced receptor expression as a result of acetylcholine receptor mutations
- Reduced receptor expression because of rapsyn mutations
- Reduced receptor expression with plectin deficiency
- Primary acetylcholine receptor kinetic abnormality with or without acetylcholine receptor deficiency
- Slow-channel syndrome
- Fast-channel syndrome
- Sodium-channel mutations
- *Dok7* mutations

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Table 612-2 Distinctive Clinical and Electrodiagnostic Features of Congenital Myasthenic Syndromes

	Presynaptic		Synaptic	Postsynaptic			
	CHOLINE ACETYLTRANSFERASE DEFICIENCY	LEMS-LIKE FORM	AChE DEFICIENCY	PRIMARY AChR DEFICIENCY	SLOW-CHANNEL CMS	FAST-CHANNEL CMS	*DOK7* MUTATIONS
Autosomal dominant inheritance					X (most mutations)		
Episodic apnea triggered by stressors	X						
Neonatal hypotonia and respiratory insufficiency	X	X	X (in severe cases)	X (in severe cases)			
Skeletal deformities			X	X		X (in severe cases)	
Delayed pupillary light responses			X				
Prominent neck, wrist, and finger extensor weakness					X		
Repetitive CMAPs after single stimulus			X		X		
Progressive decrement with prolonged exercise or repetitive stimulation	X			X			
Marked increment (>200%) with high-frequency repetitive stimulation		X					
Decrement repairs with AChE inhibitors				X		X	
Clinical improvement with AChE inhibitors						X	
Clinical worsening with AChE inhibitors			X		X		X

AChE, acetylcholinesterase; AChR, acetylcholine receptor; CMAPs, compound muscle action potentials; CMS, congenital myasthenic syndrome; LEMS, Lambert-Eaton myasthenic syndrome.

From Muppidi S, Wolfe GI, Barhon RJ: Diseases of the neuromuscular junction. In Swaiman KF, Ashwal S, Ferriero DM, Schor NF, editors: Swaiman's pediatric neurology, *ed 5, Philadelphia, 2012, Elsevier, Table 91-3.*

enough to obstruct vision. Pupillary responses to light are preserved. Dysphagia and facial weakness also are common and, in early infancy, feeding difficulties are frequent as the cardinal sign of myasthenia; in severe cases, aspiration and airway obstruction may occur. Poor head control because of weakness of the neck flexors may be prominent. Involvement initially may appear to be limited to bulbar-innervated muscles, but the disease is systemic and progressive weakness eventually involves limb-girdle muscles and distal muscles of the hands in most cases. Fasciculations of muscle, myalgias, and sensory symptoms do not occur. Tendon stretch reflexes may be diminished but rarely are lost. Ocular myasthenia gravis may prove to be transitory over time, but in some patients weakness never progresses to involve axial or appendicular muscles. This group accounts for approximately 25% of all juvenile myasthenia gravis patients and is most frequent in children of Chinese and southeastern Asian descent, suggesting an ethnic genetic predisposition.

Rapid fatigue of muscles is a characteristic feature of myasthenia gravis that distinguishes it from most other neuromuscular diseases. Ptosis increases progressively as patients are asked to sustain an upward gaze for 30-90 sec. Holding the head up from the surface of the examining table while lying supine is very difficult, and gravity cannot be overcome for more than a few seconds. Repetitive opening and closing of the fists produces rapid fatigue of hand muscles, and patients cannot elevate their arms for more than 1-2 min because of fatigue of the deltoids. Patients are more symptomatic late in the day or when tired. Dysphagia can interfere with eating, and the muscles of the jaw soon tire when an affected child chews. Reviewing activities of daily living helps determine the severity of symptoms (Table 612-3).

Left untreated, myasthenia gravis is usually progressive and can become life-threatening because of respiratory muscle involvement and the risk of aspiration, particularly at times when the child is otherwise unwell, such as with an upper respiratory tract infection. Familial myasthenia gravis usually is not progressive.

Myasthenic crisis is an acute or subacute severe increase in weakness in patients with myasthenia gravis, usually precipitated by an intercurrent infection, surgery, or even emotional stress. It may require intravenous cholinesterase inhibitors, immunoglobulin, plasma exchange, gavage feeding, and even transitory ventilator support. It must be distinguished from **cholinergic crisis** secondary to overdosing with anticholinesterase medications. The muscarinic effects include abdominal cramps, diarrhea, profuse sweating, salivation, bradycardia, increased weakness, and miosis. Cholinergic crisis requires only supportive care and withholding of further doses of cholinergic drugs, and it passes within a few hours; the dose of medication to be restarted should be reconsidered, unless the patient had taken an overdose that was not prescribed.

Approximately 30% of affected adolescents show elevations, but anti-AChR antibodies are only occasionally demonstrated in the plasma of prepubertal children. Some with negative titers of AChE exhibit anti–muscle-specific tyrosine kinase (MuSK) circulating antibodies. MuSK is localized at the neuromuscular junction and appears essential to fetal development of this junction. MuSK myasthenia usually occurs in female infants and toddlers and severe bulbar involvement with dysphagia is frequent, but clinical features alone cannot distinguish between these 2 different antibody forms of the disease.

Infants born to myasthenic mothers can have respiratory insufficiency, inability to suck or swallow, and generalized hypotonia and weakness. They might show little spontaneous motor activity for several days to weeks. Some require ventilatory support and feeding by gavage during this period. After the abnormal antibodies disappear from the blood and muscle tissue, these infants regain normal strength and are not at increased risk of developing myasthenia gravis in later childhood. A small minority develop *fetal akinesia sequence* with multiple joint contractures (*arthrogryposis*) that develop in utero from lack of fetal movement. AChR antibodies can usually be demonstrated in maternal blood, but at times maternal antibodies may not be detected.

CONGENITAL MYASTHENIC SYNDROMES

A heterogeneous group of genetic diseases of neuromuscular transmission is collectively called **congenital myasthenic syndromes.** The etiology and pathogenesis of these syndromes are unrelated to either transitory neonatal myasthenia caused by placental transfer of maternal antibodies or to autoimmune myasthenia gravis, despite overlap of clinical symptoms. Congenital myasthenic syndromes are nearly always permanent static disorders without spontaneous remission (see Tables 612-1 and 612-2). Several distinct genetic forms are recognized, all with onset at birth or in early infancy with hypotonia, external ophthalmoplegia, ptosis, dysphagia, weak cry, facial weakness, easy muscle fatigue generally, and sometimes respiratory insufficiency or failure, the last often precipitated by a minor respiratory infection. Cholinesterase inhibitors have a favorable effect in most, but in some forms the symptoms and signs are actually worsened. Most congenital myasthenic syndromes are transmitted as autosomal recessive traits, but the slow channel syndrome is autosomal dominant.

Mutations responsible for congenital myasthenic syndromes have been identified in 18 different genes. The genetic mutations are known in less than half of children with congenital myasthenic syndromes. Of

Table 612-3 Myasthenia Gravis Activities of Daily Living Scale (MG-ADL)

GRADE	0	1	2	3
Talking	Normal	Intermittent slurring or nasal speech	Constant slurring or nasal, but can be understood	Difficult to understand speech
Chewing	Normal	Fatigue with solid food	Fatigue with soft food	Gastric tube
Swallowing	Normal	Rare episode of choking	Frequent choking, necessitating changes in diet	Gastric tube
Breathing	Normal	Shortness of breath with exertion	Shortness of breath at rest	Ventilator dependence
Impairment of ability to brush teeth or comb hair	None	Extra effort, but no rest periods needed	Rest periods needed	Cannot do 1 of these functions
Impairment of ability to arise from a chair	None	Mild, sometimes uses arms	Moderate, always uses arms	Severe, requires assistance
Double vision	None	Occurs, but not daily	Daily, but not constant	Constant
Eyelid droop	None	Occurs, but not daily	Daily, but not constant	Constant
TOTAL MG-ADL SCORE				

From Wolfe GI, Herbelin L, Nations SP, et al: Myasthenia gravis activities of daily living profile. Neurology *52:1487–1489, 1999.*

known genetic defects, *rapsyn* and *downstream-of-kinase-7* (*DOK7*) are demonstrated in 85% of cases. Acetylcholine receptor deficiencies have more than 60 identified genetic mutations. Basal lamina–associated synaptic defects from mutations of the *COLQ* gene that encodes the collagen tail of AChR account for another 10% of cases. Another 5% of cases are presynaptic, attributed to mutations in *ChAT*, encoding choline acetyltransferase. Anti-AChR and anti-MuSK antibodies are usually, but not always, absent in serum, unlike in autoimmune forms of myasthenia gravis affecting older children and adults.

Three **presynaptic congenital myasthenic syndromes** are recognized, all as autosomal recessive traits; some of these have anti-MuSK antibodies. These children exhibit weakness of extraocular, pharyngeal, and respiratory muscles and later show shoulder girdle weakness as well. **Episodic apnea** is a problem in congenital myasthenia gravis. Another synaptic form is caused by congenital absence or marked deficiency of motor end plate AChE in the synaptic basal lamina; this was the first form recognized as caused by an enzymatic deficiency at the neuromuscular junction. Postsynaptic forms of congenital myasthenia are caused by mutations in ACh receptor subunit genes that alter the synaptic response to ACh. An abnormality of the ACh receptor channels appearing as high conductance and excessively fast closure may be the result of a point mutation in a subunit of the receptor affecting a single amino acid residue. Children with congenital myasthenia gravis do not experience myasthenic crises and rarely exhibit elevations of anti-ACh antibodies in plasma.

RARE OTHER CAUSES OF MYASTHENIA

Myasthenia gravis is occasionally associated with hypothyroidism, usually as caused by **Hashimoto thyroiditis.** Other collagen vascular diseases may also be associated with myasthenia gravis. Thymomas, noted in some adults, rarely coexist with myasthenia gravis in children, nor do carcinomas of the lung occur, which produce a unique form of myasthenia in adults called **Eaton-Lambert syndrome.** The Eaton-Lambert syndrome in children is rare but is reported with lymphoproliferative disorders and with neuroblastoma. Postinfectious myasthenia gravis in children is transitory and usually follows a varicella-zoster infection by 2-5 wk as an immune response.

Laboratory Findings and Diagnosis

Myasthenia gravis is one of the few neuromuscular diseases in which electromyography (EMG) is more specifically diagnostic than a muscle biopsy. A *decremental response* is seen to repetitive nerve stimulation; the muscle potentials diminish rapidly in amplitude until the muscle becomes refractory to further stimulation. Motor nerve conduction velocity remains normal. This unique EMG pattern is the electrophysiologic correlate of the fatigable weakness observed clinically and is reversed after a cholinesterase inhibitor is administered. A myasthenic decrement may be absent or difficult to demonstrate in muscles that are not involved clinically. This feature may be confusing in early cases or in patients showing only weakness of extraocular muscles. Microelectrode studies of end plate potentials and currents reveal whether the transmission defect is presynaptic or postsynaptic. Special electrophysiologic studies are required in the classification of congenital myasthenic syndromes and involve estimating the number of ACh receptors per end plate and in vitro study of end plate function. These special studies and patch-clamp recordings of kinetic properties of channels are performed on special biopsy samples of intercostal muscle strips that include both origin and insertion of the muscle but are only performed in specialized centers. If myasthenia is limited to the extraocular, levator palpebrae, and pharyngeal muscles, evoked-potential EMG of the muscles of the extremities and spine, diagnostic in the generalized disease, usually is normal.

Anti-AChR antibodies should be assayed in the plasma but are inconsistently demonstrated. Antibodies against the MuSK receptor should be sought in children without circulating AChR antibodies, a diagnostic finding when elevated, which further delineates the etiology. Many cases of congenital myasthenia gravis result from failure to synthesize or release ACh at the presynaptic membrane. In some cases, the gene that mediates the enzyme choline acetyltransferase for the synthesis of ACh is mutated. In others, there is a defect in the quantal release of vesicles containing ACh. The treatment of such patients with cholinesterase inhibitors is futile. Assays of anti-rapsyn, anti-*Dok7*, *COLQ,* and *ChAT* antibodies are available in a few specialized laboratories.

Other serologic tests of autoimmune disease, such as antinuclear antibodies and abnormal immune complexes, should also be sought. If these are positive, more extensive autoimmune disease involving vasculitis or tissues other than muscle is likely. A thyroid profile should always be examined. The serum creatine kinase level is normal in myasthenia gravis.

The heart is not involved, and electrocardiographic findings remain normal. Radiographs of the chest often reveal an enlarged thymus, but the hypertrophy is not a thymoma. It may be further defined by tomography or by CT or MRI of the anterior mediastinum if the radiographic findings are uncertain, but these imaging modalities are not recommended routinely because of radiation exposure and anesthetic risk, which is higher in myasthenic patients than in normal children.

The role of conventional muscle biopsy in myasthenia gravis is limited. It is not required in most cases, but approximately 17% of patients show inflammatory changes, sometimes called *lymphorrhages,* that are interpreted by some physicians as a mixed myasthenia-polymyositis immune disorder. Muscle biopsy tissue in myasthenia gravis shows nonspecific type II muscle fiber atrophy, similar to that seen with disuse atrophy, steroid effects on muscle, polymyalgia rheumatica, and many other conditions. The ultrastructure of motor end plates shows simplification of the membrane folds; the ACh receptors are located in these postsynaptic folds, as shown by bungarotoxin (snake venom), which binds specifically to the ACh receptors.

A **clinical test for myasthenia gravis** is administration of a short-acting cholinesterase inhibitor, usually edrophonium chloride. Ptosis and ophthalmoplegia improve within a few seconds, and fatigability of other muscles decreases.

Recommendations on the Use of Cholinesterase Inhibitors as a Diagnostic Test for Myasthenia Gravis in Infants and Children

Children 2 Yr and Older

- The child should have a specific fatigable weakness that can be measured, such as ptosis of the eyelids, dysphagia, or inability of the cervical muscles to support the head. Nonspecific generalized weakness without cranial nerve motor deficits is not a criterion.
- An IV infusion should be started to enable the administration of medications in the event of an adverse reaction.
- Electrocardiographic monitoring is recommended during the test.
- A dose of atropine sulfate (0.01 mg/kg) should be available in a syringe, ready for IV administration at the bedside during the edrophonium test, to block acute muscarinic effects of the cholinesterase inhibitor, mainly abdominal cramps and/or sudden diarrhea from increased peristalsis, profuse bronchotracheal secretions that can obstruct the airway, or, rarely, cardiac arrhythmias. Some physicians pretreat all patients with atropine before administering edrophonium, but this is not recommended unless there is a history of reaction to tests. Atropine can cause the pupils to be dilated and fixed for as long as 14 days after a single dose, and the pupillary effects of homatropine can last 4-7 days.
- Edrophonium chloride (Tensilon) is administered IV. Initially, a test dose of 0.01 mg/kg is given to ensure that the patient does not have an allergic reaction or is otherwise very sensitive to muscarinic side effects. In children weighing <30 kg, 0.1 mg/kg is the maximum total delivered dose; in children weighing >30 kg, the total delivered dose is 0.2 mg/kg. After the test dose, intravenous injection of 0.01-0.02 mg is administered every 30-45 sec, as long as dosing does not exceed the recommended maximum dose. In adults, the average edrophonium dose to show positive responses is approximately 3.3 mg for ptosis and

approximately 2.6 mg for oculomotor symptoms. Side effects include nausea and emesis; light-headedness from bradycardia (atropine is the antidote) and bronchospasm are less common side effects. These doses may be given IM or subcutaneously, but these routes are not recommended because the results are much more variable owing to unpredictable absorption, and the test may be ambiguous or falsely negative.

- Effects should be seen within 10 sec and disappear within 120 sec. Weakness is measured as, for example, distance between upper and lower eyelids before and after administration, degree of external ophthalmoplegia, or ability to swallow a sip of water.
- Long-acting cholinesterase inhibitors, such as pyridostigmine (Mestinon), are generally not as useful for the acute assessment of myasthenic weakness. The Prostigmin test may be used (as outlined later) but might not be as definitively diagnostic as the edrophonium test.

For Children Younger Than 2 Yr

- Infants ideally should have a specific fatigable weakness that can be measured, such as ptosis of the eyelids, dysphagia, and inability of cervical muscles to support the head. Nonspecific generalized weakness without cranial nerve motor deficits makes it less easy to assess results but may be a criterion at times.
- An IV infusion should be started as a rapid route for medications in the event of an adverse effect of the test medication.
- Electrocardiographic monitoring is recommended during the test.
- Pretreatment with atropine sulfate to block the muscarinic effects of the test medication is not recommended, but atropine sulfate should be available at the bedside in a prepared syringe. If needed, it should be administered IV in a dose of 0.01 mg/kg.
- Edrophonium is not recommended for use in infants; its effect is too brief for objective assessment and an increased incidence of acute cardiac arrhythmias is reported in infants, especially neonates, with this drug.
- Prostigmin methylsulfate (neostigmine) is administered IM at a dose of 0.04 mg/kg. If the result is negative or equivocal, another dose of 0.04 mg/kg may be administered 4 hr after the first dose (a typical dose is 0.5-1.5 mg). The peak effect is seen in 20-40 min. IV Prostigmin is contraindicated because of the risk of cardiac arrhythmias, including fatal ventricular fibrillation, especially in young infants.
- Long-acting cholinesterase inhibitors administered orally, such as pyridostigmine (Mestinon), are generally not as useful for the acute assessment of myasthenic weakness because onset and duration are less predictable.

The test should be performed in the emergency department, hospital ward, or intensive care unit; the important issue is preparation for potential complications such as cardiac arrhythmia or cholinergic crisis, as outlined.

Treatment

Some patients with mild myasthenia gravis require no treatment. **Cholinesterase-inhibiting drugs** are the primary therapeutic agents. Neostigmine methylsulfate (0.04 mg/kg) may be given IM every 4-6 hr, but most patients tolerate oral neostigmine bromide, 0.4 mg/kg every 4-6 hr. If dysphagia is a major problem, the drug should be given approximately 30 min before meals to improve swallowing. Pyridostigmine is an alternative; the dose required is approximately 4 times greater than that of neostigmine, but it may be slightly longer acting. Overdoses of cholinesterase inhibitors produce cholinergic crises; atropine blocks the muscarinic effects but does not block the nicotinic effects that produce additional skeletal muscle weakness. In the rare familial myasthenia gravis caused by absence of end plate AChE, cholinesterase inhibitors are not helpful and often cause increased weakness; these patients can be treated with ephedrine or diaminopyridine, both of which increase ACh release from terminal axons.

Because of the autoimmune basis of the disease, long-term **steroid treatment** with prednisone may be effective. **Thymectomy** should be considered and might provide a cure. Thymectomy is most effective in patients who have high titers of anti-ACh receptor antibodies in the plasma and who have been symptomatic for <2 yr. Thymectomy is ineffective in congenital and familial forms of myasthenia gravis. Treatment of hypothyroidism usually abolishes an associated myasthenia without the use of cholinesterase inhibitors or steroids.

If the specific genetic mutation can be identified in a patient with one of the congenital myasthenic syndromes, specific therapeutic approaches are available for some that differ from the treatments listed above; these are well outlined by Eyemard et al (2013).

Plasmapheresis is effective treatment in some children, particularly those who do not respond to steroids, but plasma exchange therapy provides only temporary remission. **IV immunoglobulin** is beneficial and should be tried before plasmapheresis because it is less invasive. Plasmapheresis and IV immunoglobulin appear to be most effective in patients with high circulating levels of anti-ACh receptor antibodies. Refractory patients might respond to rituximab, a monoclonal antibody to the B-cell CD20 antigen.

Neonates with transient maternally transmitted myasthenia gravis require cholinesterase inhibitors for only a few days or occasionally for a few weeks, especially to allow feeding. No other treatment is usually necessary. In non–maternally transmitted congenital myasthenia gravis, identification of the specific molecular defect is important for treatment; Table 612-4 summarizes specific therapies for each type.

Complications

Children with myasthenia gravis do not tolerate neuromuscular-blocking drugs, such as succinylcholine and pancuronium, and may be paralyzed for weeks after a single dose. An anesthesiologist should carefully review myasthenic patients who require a surgical anesthetic and such anesthetics should be administered only by an experienced physician/anesthesiologist. Also, certain antibiotics can potentiate myasthenia and should be avoided; these include the aminoglycosides (gentamicin and others).

Prognosis

Some patients with autoimmune myasthenia gravis experience spontaneous remission after a period of months or years; others have a permanent disease extending into adult life. Immunosuppression, thymectomy, and treatment of associated hypothyroidism might provide a cure. Genetically determined congenital myasthenic syndromes may show initial worsening in infancy but then remain static throughout childhood and into adult life.

Other Causes of Neuromuscular Blockade

Organophosphate chemicals, commonly used as insecticides, can cause a myasthenia-like syndrome in children exposed to these toxins (see Chapter 63).

Botulism results from ingestion of food containing the toxin of *Clostridium botulinum,* a Gram-positive, spore-bearing, anaerobic bacillus (see Chapter 210). The mechanism is cleavage by the botulinum toxin of several of the structural glycoproteins of the wall (i.e., membrane) of synaptic vesicles within axonal terminals. These glycoproteins include synaptobrevin and synaptotagmin, but synaptophysin is resistant. Honey is a common source of contamination. The incubation period is short, only a few hours, and symptoms begin with nausea, vomiting, and diarrhea. Cranial nerve involvement soon follows, with diplopia, dysphagia, weak suck, facial weakness, and absent gag reflex. Generalized hypotonia and weakness then develop and can progress to respiratory failure. Neuromuscular blockade is documented by EMG with repetitive nerve stimulation. Respiratory support may be required for days or weeks until the toxin is cleared from the body. No specific antitoxin is available. Guanidine, 35 mg/kg/24 hr, may be effective for extraocular and limb muscle weakness but not for respiratory muscle involvement.

Tick paralysis is a disorder of ACh release from axonal terminals due to a neurotoxin that blocks depolarization. It also affects large

Table 612-4	Potential Therapies in Congenital Myasthenic Syndromes
AChE	Ephedrine 3 mg/kg/day in 3 divided doses; begin with 1 mg/kg; not obtainable in several countries If ephedrine is not obtainable, 3,4-diaminopyridine 1 mg/kg/day in 4 divided doses, up to 60 mg/day in adults Avoid AChE inhibitors
AChR deficiency	AChE inhibitors: pyridostigmine bromide (Mestinon) 4-5 mg/kg/day in 4-6 divided doses If necessary add 3,4-diaminopyridine 1 mg/kg/day in 4 divided doses, up to 60 mg/day in adults
AChR fast channel	AChE inhibitors: pyridostigmine bromide (Mestinon) 4-5 mg/kg/day in 4-6 divided doses If necessary add 3,4-diaminopyridine 1 mg/kg/day in 4 divided doses, up to 60 mg/day in adults
AChR slow channel	Quinidine sulfate • Adults: Begin for 1 wk with 200 mg tid; gradual increase to maintain a serum level of 1-25 μg/mL • Children: 15-60 mg/kg/day in 4-6 divided doses; not available in several countries If quinidine sulfate is not available, fluoxetine 80-100 mg/day in adults Avoid AChE inhibitors
ChAT	AChE inhibitors: pyridostigmine bromide (Mestinon) 4-5 mg/kg/day in 4-6 divided doses If necessary add 3,4-diaminopyridine 1 mg/kg/day in 4 divided doses, up to 60 mg/day in adults
Dok7	Ephedrine 3 mg/kg/day in 3 divided doses; begin with 1 mg/kg; not obtainable in several countries If ephedrine is not obtainable, 3,4-diaminopyridine 1 mg/kg/day in 4 divided doses, up to 60 mg/day in adults Avoid AChE inhibitors
Laminin β_2	Ephedrine 3 mg/kg/day in 3 divided doses; begin with 1 mg/kg; not obtainable in several countries Avoid AChE inhibitors
MuSK	AChE inhibitors: pyridostigmine bromide (Mestinon) 4-5 mg/kg/day in 4-6 divided doses 3,4-Diaminopyridine 1 mg/kg/day in 4 divided doses, up to 60 mg/day in adults
Rapsyn	AChE inhibitors: pyridostigmine bromide (Mestinon) 4-5 mg/kg/day in 4-6 divided doses If necessary add 3,4-diaminopyridine 1 mg/kg/day in 4 divided doses, up to 60 mg/day in adults

Modified from Eyemard B, Hantaï D, Estounet B: Congenital myasthenic syndromes, Handb Clin Neurol *113:1469-1480, 2013.*

myelinated motor and sensory nerve fibers. This toxin is produced by the wood tick or dog tick, insects common in the Appalachian and Rocky Mountains of North America. The tick embeds its head into the skin, usually the scalp, and neurotoxin production is maximal about 5-6 days later. Motor symptoms include weakness, loss of coordination, and sometimes an ascending paralysis resembling Guillain-Barré syndrome. Tendon reflexes are lost. Sensory symptoms of tingling paresthesias can occur in the face and extremities. The diagnosis is confirmed by EMG and nerve conduction studies and by identifying the tick. The tick must be removed completely and the buried head not left beneath the skin. Patients then recover completely within hours or days.

Bibliography is available at Expert Consult.

612.2 Spinal Muscular Atrophies

Harvey B. Sarnat

Spinal muscular atrophies (SMAs) are degenerative diseases of motor neurons that begin in fetal life and continue to be progressive in infancy and childhood. The progressive denervation of muscle is compensated for in part by reinnervation from an adjacent motor unit, but giant motor units are thus created with subsequent atrophy of muscle fibers when the reinnervating motor neuron eventually becomes involved. Motor neurons of cranial nerves III, IV, and VI to extraocular muscles, as well as those of the sacral spinal cord innervating striated muscle of the urethral and anal sphincters, are selectively spared. Upper motor neurons (layer 5 pyramidal neurons in the cerebral cortex) also remain normal.

SMA is classified clinically into a severe infantile form, also known as **Werdnig-Hoffmann disease** or SMA type 1; a late infantile and more slowly progressive form, SMA type 2; and a more chronic or juvenile form, also called **Kugelberg-Welander disease,** or SMA type 3. A severe fetal form that is usually fatal in the perinatal period has been described as SMA type 0, with motor neuron degeneration demonstrated in the spinal cord as early as midgestation. These distinctions of types are based upon age at onset, severity of weakness, and clinical course; muscle biopsy does not distinguish types 1 and 2, though type 3 shows a more adult than perinatal pattern of denervation and reinnervation. Type 0 can show biopsy features more similar to myotubular myopathy because of maturational arrest; scattered myotubes and other immature fetal fibers also are demonstrated in the muscle biopsies of patients with types 1 and 2, but they do not predominate. Approximately 25% of patients have type 1, 50% type 2, and 25% type 3; type 0 is rare and accounts for <1%. Some patients are transitional between types 1 and 2 or between types 2 and 3 in terms of clinical function. A variant of SMA, **Fazio-Londe disease,** is a progressive bulbar palsy resulting from motor neuron degeneration more in the brainstem than the spinal cord, but cranial nerves of extraocular muscles also are spared in this form. Table 612-5 lists other variants.

Autonomic motor neurons of both the sympathetic and parasympathetic systems are not spared, but usually do not show clinical manifestations until late stages. Autonomic deficits may involve the detrusor muscle of the urinary bladder or the smooth muscle urethral and anal sphincters, in all 3 forms of SMA. In some patients with type 1 SMA and respiratory distress there may be severe autonomic dysregulation with dysautonomia and cardiovascular collapse leading to death or to severe ischemic brain damage.

ETIOLOGY

The cause of SMA is genetic as an autosomal recessive mendelian trait. Neuropathologically it appears to be a pathologic continuation of a process of programmed cell death (apoptosis) that is normal in embryonic life. A surplus of motor neuroblasts and other neurons is generated from primitive neuroectoderm, but only about half survive and mature to become neurons; the excess cells have a limited life cycle and degenerate. If the process that arrests physiologic cell death fails to intervene by a certain stage, neuronal death can continue in late fetal life and postnatally. The survivor motor neuron gene *(SMN)* arrests apoptosis of motor neuroblasts. Unlike most genes that are highly conserved in evolution, *SMN* is a uniquely mammalian gene. An additional function of *SMN*, both centrally and peripherally, is to transport RNA-binding proteins to the axonal growth cone to ensure an adequate

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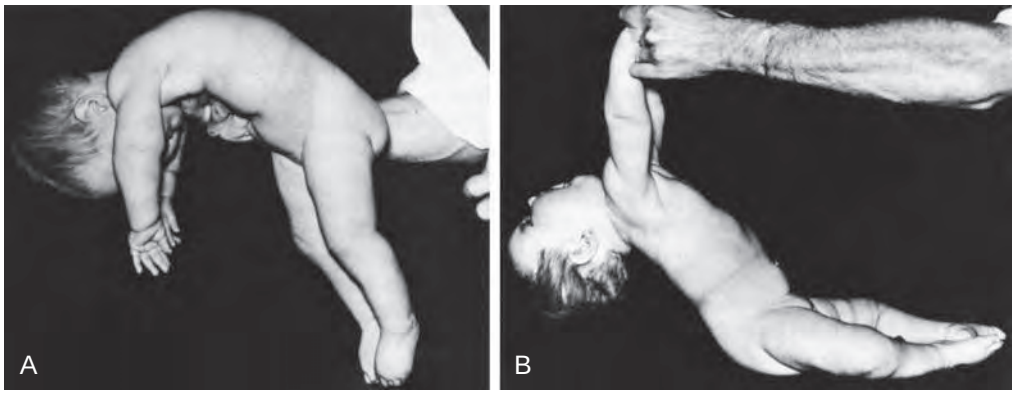


Figure 612-1 Type 1 spinal muscular atrophy (Werdnig-Hoffmann disease). Clinical manifestations of weakness of limb and axial musculature in a 6 wk old infant with severe weakness and hypotonia from birth. Note the marked weakness of the limbs and trunk on ventral suspension **(A)** and of neck on pull to sit **(B).** *(From Volpe JJ:* Neurology of the newborn, *ed 4, Philadelphia, 2001, WB Saunders, p. 644.)*

Table 612-5 Spinal Muscular Atrophy Variants: Progressive or Severe Neonatal Anterior Horn Cell Disease Not Linked to *SMN*

VARIANT	MAJOR FEATURES
SMA with respiratory distress type 1 (SMARD1)	Mild hypotonia, weak cry, distal contractures initially Respiratory distress from diaphragmatic paralysis 1-6 mo, progressive distal weakness Autosomal recessive, locus 11q13.2, gene: immunoglobulin mu-binding protein 2 (IGHMBP2)
Pontocerebellar hypoplasia type 1	Arthrogryposis, hypotonia, weakness, bulbar deficits early; later, microcephaly, extraocular defects, cognitive deficits: pontocerebellar hypoplasia Molecular defect unknown Likely autosomal recessive
X-linked infantile SMA with bone fractures	Arthrogryposis, hypotonia, weakness, congenital bone fractures, respiratory failure Lethal course as in severe type 1 SMA Most cases X-linked (X9/11.3-q11.2), a few cases likely autosomal recessive
Congenital SMA with predominant lower limb involvement	Arthrogryposis, hypotonia, weakness, especially distal lower limbs early Nonprogressive but severe disability Autosomal dominant or sporadic; locus 12q23-24

SMA, spinal muscular atrophy; *SMN*, survivor motor neuron gene.
From Volpe JJ: Neurology of the newborn, *ed 5, Philadelphia, 2008, Saunders Elsevier, Table 18-7, p. 775.*

amount of protein-encoding transcripts essential for growth cone mobility both during fetal development and in postnatal synaptic remodeling.

CLINICAL MANIFESTATIONS

The cardinal features of **SMA type 1** are severe hypotonia (Fig. 612-1); generalized weakness; thin muscle mass; absent tendon stretch reflexes; involvement of the tongue, face, and jaw muscles; and sparing of extraocular muscles and sphincters. Diaphragmatic involvement is late. Infants who are symptomatic at birth can have respiratory distress and are unable to feed. Congenital contractures, ranging from simple clubfoot to generalized arthrogryposis, occur in approximately 10% of severely involved neonates. Infants lie flaccid with little movement, unable to overcome gravity (see Fig. 607-1 in Chapter 607). They lack head control. More than 65% of children die by 2 yr of age, and many die early in infancy.

In **type 2 SMA,** affected infants are usually able to suck and swallow, and respiration is adequate in early infancy. These children show progressive weakness, but many survive into the school years or beyond, although confined to an electric wheelchair and severely handicapped. Nasal speech and problems with deglutition develop later. Scoliosis becomes a major complication in many patients with long survival. Gastroesophageal reflux may lead to malnutrition or to aspiration with acute airway obstruction or pneumonia.

Kugelberg-Welander disease is the mildest **SMA (type 3),** and patients can appear normal in infancy. The progressive weakness is proximal in distribution, particularly involving shoulder girdle muscles. Patients are ambulatory. Symptoms of bulbar muscle weakness are rare. Approximately 25% of patients with this form of SMA have muscular hypertrophy rather than atrophy, and it may easily be confused with a muscular dystrophy. Longevity can extend well into middle adult life. Fasciculations are a specific clinical sign of denervation of muscle. In thin children, they may be seen in the deltoid and biceps brachii muscles and occasionally the quadriceps femoris muscles, but the continuous, involuntary, worm-like movements may be masked by a thick pad of subcutaneous fat. Fasciculations are best observed in the tongue, where almost no subcutaneous connective tissue separates the muscular layer from the epithelium. If the intrinsic lingual muscles are contracted, such as in crying or when the tongue protrudes, fasciculations are more difficult to see than when the tongue is relaxed. Cramps and myalgias of appendicular and axial muscles are common, especially in later stages, and problems of micturition may present, though adolescent patients may be too embarrassed to state them unless the physician directly inquires.

The outstretched fingers of children with SMA often show a characteristic tremor owing to fasciculations and weakness. It should not be confused with a cerebellar tremor.

The heart is not involved in SMA. Intelligence is normal, and children often appear brighter than their normal peers because the effort they cannot put into physical activities is redirected to intellectual development, and they are often exposed to adult speech more than to juvenile language because of the social repercussions of the disease. Progressive deterioration of ambulation and the high risk of falling and fracturing long bones or the pelvis eventually require use of a

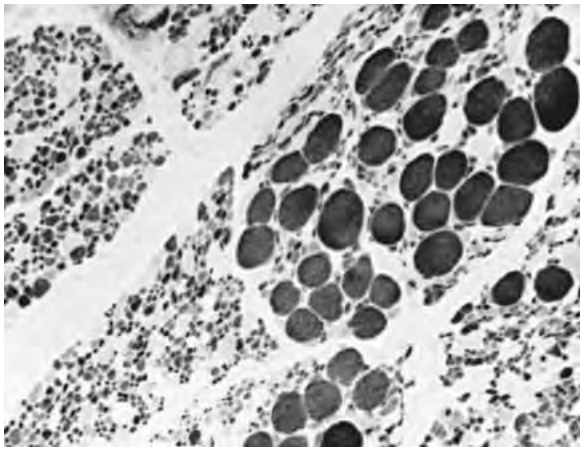


Figure 612-2 Muscle biopsy of neonate with infantile spinal muscular atrophy. Groups of giant type I (darkly stained) fibers are seen within muscle fascicles of severely atrophic fibers of both histochemical types. This is the characteristic pattern of perinatal denervation of muscle. Myofibrillar adenosine triphosphatase, preincubated at pH 4.6 (×400).

wheelchair; an electric wheelchair often is needed because weakness of the upper extremities does not allow the patient to manually push the wheels. Progressive scoliosis is another serious complication and may have a further adverse effect on respiration.

LABORATORY FINDINGS

The serum creatine kinase level may be normal but more commonly is mildly elevated in the hundreds. A creatine kinase level of several thousand is rare. The chest x-ray in early-onset disease demonstrates thin ribs. Results of motor nerve conduction studies are normal, except for mild slowing in terminal stages of the disease, an important feature distinguishing SMA from peripheral neuropathy. EMG shows fibrillation potentials and other signs of denervation of muscle. A secondary mitochondrial DNA depletion is sometimes demonstrated in the muscle biopsy of infants with SMA. The molecular genetic test of the *SMN* gene provides definite confirmation of the diagnosis.

DIAGNOSIS

The simplest, most definitive diagnostic test is a molecular genetic marker in blood for the *SMN* gene. Muscle biopsy used to be the diagnostic test before the genetic marker from blood samples became available, and muscle biopsy now is used more selectively in patients showing equivocal or negative genetic findings. The muscle biopsy in infancy reveals a characteristic pattern of perinatal denervation that is unlike that of mature muscle. Groups of giant type I fibers are mixed with fascicles of severely atrophic fibers of both histochemical types (Fig. 612-2). Scattered immature myofibers resembling myotubes also are demonstrated. In juvenile SMA, the pattern may be more similar to adult muscle that has undergone many cycles of denervation and reinnervation. Neurogenic changes in muscle also may be demonstrated by EMG, but the results are less definitive than by muscle biopsy in infancy. Sural nerve biopsy is now performed only occasionally, but shows mild sensory neuropathic changes, and sensory nerve conduction velocity may be slowed; hypertrophy of unmyelinated axons also is seen. At autopsy, mild degenerative changes are seen in sensory neurons of dorsal root ganglia and in somatosensory nuclei of the thalamus, but these alterations are not perceived clinically as sensory loss or paresthesias. The most pronounced neuropathologic lesions are the extensive neuronal degeneration and gliosis in the ventral horns of the spinal cord and brainstem motor nuclei, especially the hypoglossal nucleus.

GENETICS

Molecular genetic diagnosis by DNA probes in blood samples or in muscle biopsy or chorionic villi tissues is available for diagnosis of suspected cases and for prenatal diagnosis. Most cases are inherited as an autosomal recessive trait. The incidence of SMA is 10-15 in 100,000 live births, affecting all ethnic groups; it is the second most common neuromuscular disease, following Duchenne muscular dystrophy. The incidence of heterozygosity for autosomal recessive SMA is 1 in 50.

The genetic locus for all 3 of the common forms of SMA is on chromosome 5, a deletion at the 5q11-q13 locus, indicating that they are variants of the same disease rather than different diseases. The affected *SMN1* gene has a molecular weight of 38 kDa and contains 8 exons that span 20 kb and telomeric and centromeric exons that differ only by 5bp and produce a transcript encoding 294 amino acids. *SMN1* is duplicated in a highly homologous gene called *SMN2* and both genes are transcribed. *SMN2* remains present in all patients with SMA, but cannot fully compensate the *SMN1* defect. However, a molecular basis for correlation between the SMN2 copy number and clinical severity of the SMA is the capability of *SMN2* to encode a small amount of an identical *SMN* protein. The critical difference between *SMN1* and *SMN2* genes is a cytosine (C) to thymine (T) transition in exon 7 of *SMN2*. Another gene, the *neuronal apoptosis inhibitory gene (NAIP),* is located next to the *SMN* gene and in many cases there is an inverted duplication with 2 copies, telomeric and centromeric, of both genes; isolated mutations or deletions of *NAIP* do not produce clinical SMA and generate a mostly nonfunctional isoform lacking the carboxy-terminus amino acids encoded by exon 7. Milder forms of SMA have more than 2 copies of *SMN2*, and in late-onset patients with homozygous deletion of the *SMN1* gene, there are 4 copies of *SMN2.* An additional gene mapped to 11q13-q21 in SMA may help explain early respiratory failure in some patients. Nucleotide expansions account for only 5-10% of cases of SMA, and deletions or splicing out of exons 7 and 8 are the genetic mechanism in the great majority of cases. Another pair of genes adjacent to the *SMN1* and *SMN2* genes, *SERF1* and *SERF2*, also may play a secondary role. The *SMN* gene product modulates axonal growth and localization of β-actin messenger RNA in growth cones of motor neurons.

Infrequent families with autosomal dominant inheritance are described, and a rare X-linked recessive form also occurs. Carrier testing by dose analysis is available.

TREATMENT

No medical treatment is able to delay the progression. Supportive therapy includes orthopedic care with particular attention to scoliosis and joint contractures, mild physiotherapy, and mechanical aids for assisting the child to eat and to be as functionally independent as possible. Most children learn to use a computer keyboard with great skill but cannot use a pencil easily. Valproic acid is sometimes administered because it increases SMN2 protein, and gabapentin and oral phenylbutyrate also may slow the progression, but these treatments do not alter the course in all patients. A benefit of antioxidants is unproved. Gene replacement and protein replacement therapies remain theoretical and experimental. Potential therapeutic genetic strategies in SMA include upregulation of *SMN2* gene expression, preventing exon 7 skipping of SMN2 transcripts and improving the stability of the protein lacking the amino acid sequence encoded by exon 7.

Bibliography is available at Expert Consult.

612.3 Other Motor Neuron Diseases

Harvey B. Sarnat

Motor neuron diseases other than SMA are rare in children. *Poliomyelitis* used to be a major cause of chronic disability, but with the routine use of polio vaccine, this viral infection is now rare (see Chapter 249). Other enteroviruses, such as coxsackievirus and echovirus, or the live polio vaccine virus can also cause an acute infection of motor neurons with symptoms and signs similar to poliomyelitis, although usually

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milder. Specific polymerase chain reaction tests and viral cultures of cerebrospinal fluid are diagnostic. Motor neuron infection with the West Nile virus also occurs.

A **juvenile form of amyotrophic lateral sclerosis** is rare. Upper and lower motor neuron loss is evident clinically, unlike in SMA. The course is progressive and ultimately fatal.

Pena-Shokeir and **Marden-Walker syndromes** are progressive motor neuron degenerations associated with severe arthrogryposis and congenital anomalies of many organ systems. **Pontocerebellar hypoplasias** are progressive degenerative diseases of the central nervous system that begin in fetal life; type 1 also involves motor neuron degeneration resembling an SMA, but the *SMN* gene on chromosome 5 is normal.

Motor neurons become involved in several metabolic diseases of the nervous system, such as gangliosidosis (Tay-Sachs disease), ceroid lipofuscinosis (Batten disease), and glycogenosis II (Pompe disease), but the signs of denervation may be minor or obscured by the more prominent involvement of other parts of the central nervous system or of muscle.

Chapter 613

Hereditary Motor-Sensory Neuropathies

Harvey B. Sarnat

The hereditary motor-sensory neuropathies (HMSNs) are a group of progressive diseases of peripheral nerves (Table 613-1). Motor components generally dominate the clinical picture, but sensory and autonomic involvement is expressed later. Sural nerve biopsy used to be the most definitive means of diagnosis, but with the expanded knowledge

Text continued on p. 3003

Table 613-1 Hereditary Peripheral Neuropathies

DISORDER (OMIM NO.)	CLINICAL FEATURES	NERVE CONDUCTION STUDIES	GENE OR LOCUS
CMT1 (DEMYELINATING)			
CMT1 A-F (HMSN type I)	Autosomal dominant. Onset 1st-4th decade. Predominant distal weakness, decreased DTRs, mild distal sensory loss, hypertrophy of nerves common	Delayed motor and sensory conduction studies. Motor studies typically <38 m/s	
1A (118220)	Commonest form recognized, seen in all ages (but more adults)		*PMP22* duplication or point mutation
1B (118200)	Approximately 5% of CMT1 group		*MPZ*
1C (601098)	Childhood onset, starts with abnormal gait, then distal weakness and wasting, occasional nerve hypertrophy. Rarely, early-onset hearing loss		*LITAF*
1D (607678)	Possible cranial nerve involvement. Late onset in childhood or early adulthood		*EGR2*
1E (118300)	Associated with deafness (29-45%)		*PMP22*
1F (607734)			*NEFL*
Hereditary neuropathy with liability to pressure palsies (tomaculous neuropathy) (162500)	Autosomal dominant. Recurrent mononeuropathy simplex or multiplex frequently related to trauma	Significant slowing of motor and sensory conduction velocities in clinically affected nerves but also in unaffected nerves	*PMP 22* deletion
Slowed NCVs Asymptomatic	Often a miscellaneous group. Incidentally detected with no clinical symptoms. Autosomal dominant	Moderately slowed conduction velocities	*ARHGEF10*
CMT2 (AXONAL)			
CMT2 A-L (HMSN type II)	Autosomal dominant (A, B, D, E, F, G, I) Autosomal recessive (BI, B2, H, K) Clinically similar to CMT type 1, except for later onset, absence of peripheral nerve enlargement, and less marked weakness	Nerve conduction velocities greater than HMSN type I (>38 m/s) but below normal range occasionally	
2A1 (118210) 2A2 (609260)	CMT2A: prominent distal weakness, proximal weakness also present in 60%. Optic atrophy and central involvement reported. Main form related to *MFN2* mutations		2A1: *KIF1B* (one family) 2A2: *MFN2*
2B (600882) 2B1 (605588)	CMT2B: severe sensory loss: often complications with infections, arthropathy, amputations, foot ulcers, distal weakness		2B: *RAB7* 2B1: *LMNA*
2B2 (605589)	Average onset 34 yr (Costa Rican family)		*?MED25*
2C (606071)	Vocal cord, diaphragm, and respiratory involvement, decreased longevity. Allelic with congenital dSMA (600175) and scapuloperoneal muscular atrophy (181405)		*TRP4* 12q23–q24 *TRP4*
2D (601472) (allelic to dSMA)	Upper limb predominance		*GARS*
2E (607684) (1F dominant is allelic to CMT2E)	30% associated with deafness, early childhood onset with gait abnormalities, occasional hyperkeratosis, increased sensory involvement	Intermediate/slow nerve conduction studies	*NEFL*

Continued

Table 613-1 Hereditary Peripheral Neuropathies—cont'd

DISORDER (OMIM NO.)	CLINICAL FEATURES	NERVE CONDUCTION STUDIES	GENE OR LOCUS
2F (606595)	Trophic changes feet and knees		*HSPB1* (*HSP27*)
2G (608591)	Onset age 9-76 yr, average age 20 yr, large Spanish family. Also severe form with early onset		12q12–q13
2H (607731) 2H (allelic to CMT4A–CMT4C2 in original publication)	Pyramidal involvement, vocal cord involvement	Intermediate/slow nerve conduction studies	*GDAP1*
2I (607677)	CMT I and J: possible late onset, pupillary anomalies, pain, hearing loss, dysphagia		*MPZ*
2J (607736)	Vocal cord paralysis, more severe early-onset form		*MPZ*
2K (607831)	Occasional proximal leg weakness (like dHMN II), large Chinese family, with onset at age 15-33 yr. Scoliosis		*GDAP1*
2L (608673)			*HSPB8* 12q24
HMSN II with onset in early childhood (EOHMSN) Severe early-onset axonal neuropathy (SEOAN)	Autosomal dominant or recessive. Weakness within 1st 5 yr, rapid progression of weakness, usually complete paralysis below elbows and knees by teens, absent DTRs, moderate sensory changes in most cases. Normal CSF protein. Occasional optic atrophy or spasticity	Axonal pattern with axonal-degenerative polyneuropathy. Absent SNAPs, no response to stimulation in cerebral palsy nerve, upper limb nerves normal or mildly slowed. EMG: denervation	*MFN2*; *GDAP1* Heterogeneous
Spinal muscular atrophy with respiratory distress type 1 (SMARD1)/severe infantile axonal neuropathy with respiratory failure (SIANR) Allelic to dHMN6 dSMA1 (604320)	Autosomal recessive. Onset in infancy (3-6 mo), respiratory failure, progressive distal weakness, eventual plateau. No recovery	Absent conduction in most cases	*IGHMBP2*
Hereditary motor and sensory neuropathy (HMSN-P) (Okinawa type)	Adult onset (after 30 yr). Autosomal dominant. Slowly progressive proximal dominant area of weakness. Fasciculations of extremities and trunk. Raised creatine kinase, hyperlipidemia, diabetes mellitus, eventual loss of ambulation, absent DTRs, sensory disturbances. Most patients described from Japan	Motor and sensory axonal neuropathy. SNAPs, CMAPs, MNCVs, and SNCVs reduced or absent EMG: fasciculations, fibrillations, and neuromyotonic picture early on	3q13
CMT3* AND 4			
CMT3 (Dejerine-Sottas syndrome) (145900)	Onset 1st 2 yr, overall disability ?less severe than CMT4. Hypotonia, motor delay by 1st yr, poor coordination, ataxia, distal weakness (max. lower limbs), short stature. By 2nd decade, proximal weakness, hand and foot deformities. Nerve hypertrophy. Moderate to severe sensory loss. Scoliosis. Common cranial nerve involvement, nystagmus, deafness, and mild bifacial weakness. Raised CSF protein	Motor conduction velocities usually <10 m/s. SAPs absent. EMG: chronic denervation	*PMP22, MPZ, PRX, EGR2, FIG4*
CMT4 (A-J) Autosomal recessive	Clinical picture similar to or slightly more severe than in CMT1 form, increased ataxia, areflexia, scoliosis. Nerve hypertrophy rare	Moderate slowing of nerve conduction studies	
4A (214400)	Onset <2 yr, Tunisian and Moroccan families. Severe progressive. Less-severe European phenotypes	25-35 m/s	*GDAP1*
4B1 (601382)	Ophthalmoplegia, vocal cord paralysis, facial, bulbar weakness (all infrequent). Weakness below 5 yr, proximal and distal weakness, absent DTRs	9-20 m/s	*MTMR2, (MPZ)*
4B2 (604563)	Early onset: 1st decade; glaucoma and deafness sometimes. Recorded in Tunisia, Japan, and Turkey	15-30 m/s	*SBF2, MTMR13*
4C (601596)	Early-onset scoliosis, commoner in Algerians, glaucoma and neutropenia. 1st and 2nd decades	4-37 m/s	*SH3TC2* (*KIAA1985*)
4D (601455) (HMSN-Lom)	Closed gypsy pedigree; onset <10 yr. Deafness (by 2nd-3rd decade). Tongue atrophy	10-20 m/s	*NDRG1*
4E (605253)	Congenital hypomyelinating neuropathy	5-20 m/s	*ERG2/KROX 20, MPZ*

Table 613-1 Hereditary Peripheral Neuropathies—cont'd

DISORDER (OMIM NO.)	CLINICAL FEATURES	NERVE CONDUCTION STUDIES	GENE OR LOCUS
4F (145900)	Severely affected at birth or by 7 yr; arthrogryposis multiplex congenita common; respiratory and feeding difficulties; often die young	<5 m/s	*PRX*
4G (605285)	Type Russe. Onset 8-16 yr. Origin Bulgaria	30-35 m/s	10q22
4H (609311)	Increased in Lebanese/Turkish. Onset infancy to childhood (1-2 yr). Delayed motor milestones. Occasional scoliosis, increased distal weakness, usually absent DTRs	<10 m/s or absent	*FDG4*
4J (611228)	Onset by 5 yr. Severe disorder. Similarities to motor neuron disease	2-7 m/s; some cases higher	*FIG4*
CCFDN (604168)	Congenital cataract, microcornea, facial dysmorphism, mental retardation, distal motor peripheral neuropathy	19-33 m/s	*CTDP1*
MIXED PATHOLOGY (AXONAL AND DEMYELINATING)			
CMT X X-linked CMT X1 (302800)	X-linked dominant. Onset 1st-2nd decade. Progressive wasting and weakness of distal limb musculature, especially hands, more marked in affected males than carrier females	Median nerve motor conduction studies <40 m/s (but faster than CMT1A). Intermediate slowing less uniform along nerves with dispersion more pronounced	*GJB1*
X2 (302801)	X-linked recessive. Rare infantile onset, intellectual disability, females very mildly affected	Mixed demyelinating/axonal	Xp22.2
X3 (302802)	X-linked recessive. ± Spasticity. Females unaffected	Mixed demyelinating/axonal	Xq26
X4 (310490)	X-linked (Cowchock syndrome). Severe neuropathy, females very mildly affected. Isolated case reports. Onset birth to early childhood. Slowly progressive. Many develop deafness by 5 yr. Mental retardation commonly seen. Occasional optic atrophy	Axonal neuropathy. Motor conduction velocities: mild delay (33-56 m/s). Sensory very abnormal. EMG: denervation, large motor unit potential, and fasciculation	Xq24–26.1
X5 (311070)	X-linked. Mild to moderate neuropathy, deafness, optic atrophy. Allelic with Rosenberg-Chutorian (opticoacoustic neuropathy) and Arts syndromes	Axonal neuropathy–mild demyelinating changes	Xq21.32–q24 *PRPS1*
Intermediate forms of CMT	Patients have neurophysiologic results that fall between axonal and demyelinating ranges	"Intermediate values" 30-40 m/s–most accurate from median motor nerves. Some forms have normal nerve conduction studies (DI-CMTB)	
DI-CMTA	Italian family		10q24.1–q25.1
DI-CMTB (606482)	American family		*DNM2*
DI-CMTC (608323)			*YARS*
DI-CMTD (607791)	Myelin protein zero		*MPZ*
A–autosomal recessive form (608340)	Overlap conditions: Recessive CMT with *GADP1* mutations: (CMT2K and 4A) Spanish and Tunisian family–severe childhood forms reported. Also called DI-CMTA autosomal recessive form CMT with NF-L: (CMT1F and 2E)		Overlap: *GJB1* *NF-L* *GDAP1*
OTHER HMSN AND HMN SYNDROMES			
HMSN V/spastic paraplegia with HMSN type V/CMT5 (CMT with pyramidal signs) (600631)	Variable inheritance. Spasticity in lower limbs causing difficulty walking and toe walking. Autosomal recessive form associated with mental retardation. Lower limb marked spasticity with little weakness, increased DTRs, extensor plantars, pes cavus, often distal amyotrophy. Expanding field with multiple subforms, n = 37. Not all associated with peripheral neuropathy CMT with pyramidal signs: part of HMSN V but described without spasticity	Small/absent SNAPs. Motor studies axonal in type	*SPG3A, SPAST, NIPA1, BSCL2, SPG4, SPG7, SPG20, SPG21, SPG30, PLP1* CMT with pyramidal signs: *MFN2*
HMSN VI (allelic CMT2A)	Visual impairment due to optic atrophy. Dominant and recessive forms. Onset in 1st decade. Distal weakness, often proximal involvement too. Less sensory involvement. Scoliosis	No response or motor conduction around 45 m/s. Sensory nerves often cannot be stimulated	*MFN2*
HMSN VII	HMSN with retinitis pigmentosa. CSF protein raised. Usually adult onset. Rare entity described in a few families, mainly of adult onset		

Continued

Table 613-1 Hereditary Peripheral Neuropathies—cont'd

DISORDER (OMIM NO.)	CLINICAL FEATURES	NERVE CONDUCTION STUDIES	GENE OR LOCUS
DISTAL HEREDITARY MOTOR NEURONOPATHIES (DHMN)			
dHMNI (182960)	Autosomal dominant. Juvenile onset. Distal weakness and wasting	Normal nerve conduction studies, occasional mild slowing. EMG neurogenic	*HSPB1* 7q34–q36
dHMNII (608634)	Autosomal dominant. Adult onset, distal weakness and wasting		*HSPB8, HSPB3*
dHMNIIjuv (158590)	(Allelic CMT2F, CMT2L)		*HSPB1*
dHMNIII	Autosomal recessive. Infantile to adult onset. Slow, progressive muscle wasting and weakness, variable diaphragmatic paralysis		11q13.3
dHMNIV (607088) Distal SMA type 3	Autosomal recessive. Juvenile onset. Severe muscle wasting and weakness and diaphragmatic paralysis		11q13
dHMNV (600794)	(Allelic CMT2D) Autosomal dominant. Upper limb predominance, occasional pyramidal features		*GARS*
dHMN type V (Silver syndrome) (270685)	Autosomal dominant. Prominent hand muscle weakness and wasting, mild to severe spasticity of lower limbs		*BSCL2*
dHMNVI (604320)	(Allelic SMARD1) Autosomal recessive. Severe infantile form with respiratory distress		*IGHMBP2*
dHMNVIIA (158580)	Autosomal dominant. Onset with vocal cord paralysis		*DCTN1*
dHMNVIIB (607641)	Autosomal dominant. Onset with vocal cord paralysis and facial weakness		2q14 Xq13–q21
X-linked dHMN dHMN/ALS4 (602433)	X-linked recessive. Juvenile onset with distal wasting and weakness		*SETX*
dHMN-J (Jerash)	Autosomal dominant. Early onset symptomatic in 2nd decade with pyramidal tract signs		9p21.1–p12
Congenital distal SMA (600175)	Autosomal recessive. Onset from 6-10 yr with pyramidal features in 1 Jordanian family Autosomal dominant congenital nonprogressive distal HMN with contractures		12q23–q24
Peripheral neuropathy with agenesis of corpus callosum (Charlevoix disease or Andermann syndrome) (218000)	Autosomal recessive. Increased in French Canadian populations. Progressive axonal neuropathy. CNS malformations—absence/hypoplasia of corpus callosum in most, early onset, developmental delay, areflexia, dysmorphology. Later, increased motor disability, hallucinatory psychosis. Death by 3rd decade	EMG: denervation. Axonal neuropathy	*SLC12A6 (KCC3)*
Hereditary neuralgic amyotrophy (brachial plexus neuropathy) (162100)	Autosomal dominant. Episodes of paralysis and muscle weakness initiated by severe pain. Onset can be from birth or later childhood but usually adult onset. Outcome usually good but some left with residual dysfunction. Episodes often triggered by infections, immunizations, and stress. Some pedigrees dysmorphic with hypotelorism	Normal or mildly prolonged MNCVs distal to affected brachial plexus	*SEPT9*
HEREDITARY SENSORY AND AUTONOMIC NEUROPATHIES			
HSN (HSAN) 1 (162400)	Type 1: Autosomal dominant. Onset 2nd–5th decade. Predominant loss of pain and temperature sensation, preservation of vibration sense, lancinating pain, variable distal motor involvement	Normal to low-normal MNCVs, disturbance of sensory conduction of variable severity Type 1B: Autosomal dominant. Predominantly sensory neuropathy with cough and gastroesophageal reflux, rarely foot ulcers. More often adult onset. Hearing often abnormal	*SPTLC1* *RAB7* 3p24–p22
HSN (HSAN) 2(A) (201300)	Autosomal recessive. Onset in infancy/early childhood–1st 2 decades. Mutilating acropathy. Often unrecognized fractures. Marked sensory loss affecting all cutaneous modalities, most marked distally in all limbs. Autonomic dysfunction less marked. Absent or decreased DTRs	Normal MNCVs; SNAPs are absent	*WNK1*
HSN (HSAN) 2B (223900)	Autosomal recessive. Impaired sensation, ulcers, and arthropathy develop in childhood		*FAM134B*

Table 613-1 Hereditary Peripheral Neuropathies—cont'd

DISORDER (OMIM NO.)	CLINICAL FEATURES	NERVE CONDUCTION STUDIES	GENE OR LOCUS
HSN (HSAN) 3 (Riley-Day syndrome, familial dysautonomia) (223900)	Autosomal recessive. History of neurologic abnormality and of difficult feeding from birth. Failure to produce tears regularly. Absent or reduced DTRs. Absent corneal reflexes, postural hypotension, emotional lability. Relative indifference to pain, absence of fungiform papillae on tongue, absence of flare with intradermal histamine. Normal intelligence	Motor conduction velocities usually slightly below control values. Sensory conduction normal or decreased	*IKBAP*
HSN (HSAN) 4 (congenital insensitivity to pain with anhidrosis, CIPA) (256800)	Autosomal recessive. Onset from infancy, often high fevers due to truncal anhidrosis during hot weather. Painless injuries of extremities and oral structures, often self-mutilation. Lack of pain sensation, both peripheral and visceral, inability to distinguish hot and cold. Preservation of DTRs. Mild mental retardation. Hyperactivity and emotional lability common	Nerve conduction studies normal. Sympathetic skin responses are absent (histamine test)	*NTRK1*
HSN (HSAN) 5 (608654)	Autosomal recessive. Onset in early life. Rare disorder. Painless injuries of the extremities. Lack of pain and thermal sensitivity in the limbs but preservation of response to tactile and mechanical stimuli. Preservation of muscle strength and DTRs. Distal anhidrosis. Bone and joint fractures; arthropathy. Normal intelligence	Normal motor and sensory nerve conduction studies	*NGFβ*

*The term CMT3 should be reserved for hereditary neuropathies in which hypomyelination is the dominant feature. This would include congenital hypomyelinating neuropathy, Dejerine-Sottas disease, and congenital amyelinating neuropathy.

CCFDN, congenital cataract, microcornea, facial dysmorphism, mental retardation, distal motor peripheral neuropathy; CIPA, congenital insensitivity to pain with anhidrosis; CMAP, compound motor unit action potential; CMT, Charcot-Marie-Tooth disease; CP, common peroneal; CSF, cerebrospinal fluid; dHMN, distal hereditary motor neuronopathy; DI, dominant intermediate; dSMA, distal spinal muscular atrophy; DTR, deep tendon reflex; EMG, electromyography; EOHMSN, early-onset HMSN; HMN, hereditary motor neuropathy; HMSN, hereditary motor and sensory neuropathy; HSAN, hereditary sensory and autonomic neuropathy; HSN, hereditary sensory neuropathy; MNCV, motor nerve conduction velocity; OMIM, Online Mendelian Inheritance in Man; SAP, sensory action potential; SEOAN, severe early-onset axonal neuropathy; SMA, spinal muscular atrophy; SNAP, sensory nerve action potential.

From Wilmshurst JM, Ouvrier R: Hereditary peripheral neuropathies of childhood: an overview for clinicians, Neuromuscul Disord *21(11):763–775, 2011.*

of the molecular genetics of this group of diseases, the diagnosis of most can be confirmed by less invasive genetic testing. Electromyography (EMG) remains a useful adjunct to clinical diagnosis and helps distinguish between **demyelinating** or **hypomyelinating** and **axonal** forms.

Classification of HMSNs is difficult because no simple unifying scheme is capable of incorporating all the clinical presentations and overlapping genetics (see Table 613-1). In some neuropathies, a diverse genotype of mutations of different genes at different chromosomal loci may produce a similar phenotype. One classification identifies: I. Hereditary neuropathies secondary to general diseases; II. Primary neuropathies as: IIa. Hereditary motor sensory neuropathies; IIb. Distal hereditary motor neuropathies; IIc. Hereditary sensory ± autonomic neuropathies; III. Syndromic neuropathies including congenital hypomyelinating neuropathies; and IV. Hereditary sensory neuropathy (Refsum disease).

613.1 Peroneal Muscular Atrophy (Charcot-Marie-Tooth Disease, Hereditary Motor-Sensory Neuropathy Type IIa)

Harvey B. Sarnat

Charcot-Marie-Tooth disease is the most common genetically determined neuropathy and has an overall prevalence of 3.8/100,000 population. It is transmitted as an autosomal dominant trait with 83% expressivity; the 17p11.2 locus is the site of the abnormal gene. Autosomal recessive transmission also is described but is rarer. The gene product is peripheral myelin protein 22 (PMP22). A much rarer X-linked HMSN type I results from a defect at the Xq13.l locus, causing mutations in the gap junction protein connexin-32. Other forms have been reported (see Table 613-1).

CLINICAL MANIFESTATIONS

Most patients are asymptomatic until late childhood or early adolescence, but young children sometimes manifest gait disturbance as early as the 2nd yr of life. The peroneal and tibial nerves are the earliest and most severely affected. Children with the disorder are often described as being clumsy, falling easily, or tripping over their own feet. Application of the Cumberland Ankle Instability Tool for Youth is a means of objectively documenting and following this manifestation. The onset of symptoms may be delayed until after the 5th decade.

Muscles of the anterior compartment of the lower legs become wasted, and the legs have a characteristic stork-like contour. The muscular atrophy is accompanied by progressive weakness of dorsiflexion of the ankle and eventual footdrop. The process is bilateral but may be slightly asymmetric. Pes cavus deformities invariably develop as a result of denervation of intrinsic foot muscles, further destabilizing the gait. Atrophy of muscles of the forearms and hands is usually not as severe as that of the lower extremities, but in advanced cases contractures of the wrists and fingers produce a claw hand. Proximal muscle weakness is a late manifestation and is usually mild. Axial muscles are not involved.

The disease is slowly progressive throughout life, but patients occasionally show accelerated deterioration of function over a few years. Most patients remain ambulatory and have normal longevity, although orthotic appliances are required to stabilize the ankles.

Sensory involvement mainly affects large myelinated nerve fibers that convey proprioceptive information and vibratory sense, but the threshold for pain and temperature can also increase. Some children complain of tingling or burning sensations of the feet, but pain is rare. Because the muscle mass is reduced, the nerves are more vulnerable to trauma or compression. Autonomic manifestations may be expressed as poor vasomotor control with blotching or pallor of the skin of the feet and inappropriately cold feet.

Nerves often become palpably enlarged. Tendon stretch reflexes are lost distally. Cranial nerves are not affected. Sphincter control remains well preserved. Autonomic neuropathy does not affect the heart, gastrointestinal tract, or bladder. Intelligence is normal. A unique point mutation in *PMP22* causes progressive auditory nerve deafness in addition, but this is usually later in onset than the peripheral neuropathy.

Davidenkow syndrome is a variant of HMSN type I with a scapuloperoneal distribution.

LABORATORY FINDINGS AND DIAGNOSIS

Motor and sensory nerve conduction velocities are greatly reduced, sometimes as slow as 20% of normal conduction time. In new cases without a family history, both parents should be examined, and nerve conduction studies should be performed.

EMG and muscle biopsy are not usually required for diagnosis, but they show evidence of many cycles of denervation and reinnervation. Serum creatine kinase level is normal. Cerebrospinal fluid (CSF) protein may be elevated, but no cells appear in the CSF.

Sural nerve biopsy is diagnostic. Large- and medium-size myelinated fibers are reduced in number, collagen is increased, and characteristic **onion bulb formations** of proliferated Schwann cell cytoplasm surround axons. This pathologic finding is called **interstitial hypertrophic neuropathy.** Extensive segmental demyelination and remyelination also occur.

The definitive molecular genetic diagnosis may be made in blood.

TREATMENT

Stabilization of the ankles is a primary concern. In early stages, stiff boots that extend to the midcalf often suffice, particularly when patients walk on uneven surfaces such as ice and snow or stones. As the dorsiflexors of the ankles weaken further, lightweight plastic splints may be custom made to extend beneath the foot and around the back of the ankle. They are worn inside the socks and are not visible, reducing self-consciousness. External short-leg braces may be required when footdrop becomes complete. Surgical fusion of the ankle may be considered in some cases.

The leg should be protected from traumatic injury. In advanced cases, compression neuropathy during sleep may be prevented by placing soft pillows beneath or between the lower legs. Burning paresthesias of the feet are not common but are often abolished by phenytoin, carbamazepine, or gabapentin. No medical treatment is available to arrest or slow the progression.

613.2 Peroneal Muscular Atrophy (Axonal Type)

Harvey B. Sarnat

Peroneal muscular atrophy is clinically similar to HMSN type I, but the rate of progression is slower and the disability is less. EMG shows denervation of muscle. Sural nerve biopsy reveals axonal degeneration rather than the demyelination and whorls of Schwann cell processes typical in type I. The locus is on chromosome 1 at 1p35-p36; this is a different disease than HMSN type I, although both diseases are transmitted as autosomal dominant traits. An autosomal recessive infantile motor axonal neuropathy can closely mimic infantile spinal muscular atrophy.

613.3 Congenital Hypomyelinating Neuropathy and Dejerine-Sottas Disease (Hereditary Motor-Sensory Neuropathy Type III)

Harvey B. Sarnat

Congenital hypomyelinating neuropathy is an interstitial hypertrophic neuropathy of autosomal dominant transmission, clinically similar to HMSN type I but more severe. Symptoms develop in early infancy and are rapidly progressive, with hypotonia and breathing and feeding difficulties. Pupillary abnormalities, such as lack of reaction to light and *Argyll Robertson pupil,* are common. Kyphoscoliosis and pes cavus deformities complicate approximately 35% of cases. Nerves become palpably enlarged at an early age. Dejerine-Sottas disease is a more slowly progressive variant with onset usually before age 5 yr.

An autosomal recessive form of congenital hypomyelinating neuropathy also is known and may be caused by various genetic mutations, including *MTMR2*, *PMP22*, *EGR2*, and *MPZ*. Neonatal hypotonia and developmental delay in infancy are hallmark clinical features. Many patients exhibit congenital insensitivity to pain. Cranial nerves are inconsistently involved, and respiratory distress and dysphagia are rare complications. Tendon reflexes are absent. **Arthrogryposis** is present at birth in at least half the cases.

The onion bulb formations seen in the sural nerve biopsy specimen are pronounced. Hypomyelination also occurs. In the recessive form, hypomyelination may not be accompanied by interstitial hypertrophy in all cases.

The genetic locus of 17p11.2 is identical to that of HMSN type I or Charcot-Marie-Tooth disease. Monoallelic mutations in *MPZ* (myelin protein zero), *PMP22,* or *EGR2* (early grow response 2) are the most frequent genetic causes. The clinical and pathologic differences may be phenotypical variants of the same disease, analogous to the situation in Duchenne and Becker muscular dystrophies. An autosomal recessive form of Dejerine-Sottas disease is incompletely documented.

613.4 Roussy-Lévy Syndrome

Harvey B. Sarnat

Roussy-Lévy syndrome is defined as a combination of HMSN type II and cerebellar deficit resembling Friedreich ataxia, but it does not have cardiomyopathy.

613.5 Refsum Disease (Hereditary Sensory Neuropathy Type IV) and Infantile Refsum Disease

Harvey B. Sarnat

See Chapter 86.2.

Refsum disease is a rare autosomal recessive disease caused by an enzymatic block in β-oxidation of phytanic acid to pristanic acid. Phytanic acid is a branched-chain fatty acid that is derived mainly from dietary sources: spinach, nuts, and coffee. Levels of phytanic acid are greatly elevated in plasma, CSF, and brain tissue. The CSF shows an albuminocytologic dissociation, with a protein concentration of 100-600 mg/dL. Genetic linkage studies identify 2 distinct loci at 10p13 and 6q22-q24 with *PHYH* and *PEX7* genetic mutations, respectively. The infantile form also can be caused by *PEX1*, *PEX2,* or *PEX26* genes, which produce both clinical and biochemical differences from the classical form, and include minor facial dysmorphism, retinitis pigmentosa, sensorineural hearing loss, hypercholesterolemia, hepatomegaly, and failure to thrive. Phytanic acid accumulation in infantile Refsum disease is secondary to a primary peroxisomal disorder; hence autosomal recessive Refsum disease is really a different disease.

Clinical onset of classical Refsum disease is usually between 4 and 7 yr of age, with intermittent motor and sensory neuropathy. Ataxia, progressive neurosensory hearing loss, retinitis pigmentosa with loss of night vision, ichthyosis, and liver dysfunction also develop in various degrees. Skeletal malformations from birth and cardiac findings of conduction disturbances and cardiomyopathy appear in the majority. Motor and sensory nerve conduction velocities are delayed. Sural nerve biopsy shows loss of myelinated axons. Treatment is by dietary management and periodic plasma exchange. With careful management, life expectancy can be normal.

613.6 Fabry Disease

Harvey B. Sarnat

See Chapter 86.4.

Fabry disease, a rare X-linked recessive trait, results in storage of ceramide trihexose because of deficiency of the enzyme ceramide trihexosidase, which cleaves the terminal galactose from ceramide trihexose (ceramide-glucose-galactose-galactose), resulting in tissue accumulation of this trihexose lipid in central nervous system neurons, Schwann cells and perineurial cells, ganglion cells of the myenteric plexus, skin, kidneys, blood vessel endothelial and smooth muscle cells, heart, sweat glands, cornea, and bone marrow. It results from a missense mutation disrupting the crystallographic structure of α-galactosidase A.

CLINICAL MANIFESTATIONS

The presentation is in late childhood or adolescence, with recurrent episodes of burning pain and paresthesias of the feet and lower legs so severe that patients are unable to walk. These episodes are often precipitated by fever or by physical activity. Objective sensory and motor deficits are not demonstrated on neurologic examination, and reflexes are preserved. Characteristic skin lesions are seen in the perineal region, scrotum, buttocks, and periumbilical zone as flat or raised red-black telangiectases known as **angiokeratoma corporis diffusum.** Hypohidrosis may be present. Corneal opacities, cataracts, and necrosis of the femoral heads are inconstant features. Tortuosity of retinal vessels and of the vertebral and basilar arteries can occur. The disease is progressive. Hypertension and renal failure are usually delayed until early adult life. Recurrent strokes result from vascular wall involvement. Death often occurs in the 5th decade owing to cerebral infarction or renal insufficiency, but a significant morbidity already occurs in childhood despite the absence of major organ failure. Heterozygous female carriers may be asymptomatic or, rarely, are as affected as males; corneal opacities involve 70-80%, though cataracts are rare.

LABORATORY FINDINGS

Motor and sensory nerve conduction velocities are normal to only mildly slow, showing preservation of large myelinated nerve fibers. CSF protein is normal. Proteinuria is present early in the course.

Calcifications often are seen in pulvinar of the thalamus, as demonstrated by CT or MRI and are specific imaging findings, believed caused by cerebral hyperperfusion. Positron tomography, by contrast, shows reduced cerebral blood flow velocity and impaired autoregulation because of the glycosphingolipid storage in vascular endothelial cells.

Pathologic features are usually first detected in skin or sural nerve biopsy specimens. Electron microscopy demonstrates crystalline glycosphingolipids, appearing as *zebra bodies*, in lysosomes of endothelial cells, in smooth myocytes of arterioles, and in Schwann cells. Nerves show a selective loss of small myelinated fibers and relative preservation of large and medium-sized axons, contrasting to most axonal neuropathies in which large myelinated fibers are most involved.

Assay for the deficient enzyme, α-galactosidase-A, may be performed from skin fibroblasts, leukocytes, and other tissues. This test permits detection of the female carrier state and provides a reliable means of prenatal diagnosis.

TREATMENT

See Chapter 86.4 for specific therapy of Fabry disease, including enzyme replacement.

Medical therapy of painful neuropathies includes management of the initiating disease and therapy directed to the neuropathic pain independent of etiology. Pain may be burning or associated with paresthesia, hyperalgesia (abnormal response to noxious stimuli), or allodynia (induced by non–noxious stimuli; see Chapter 62). Neuropathic pain is often successfully managed by tricyclic antidepressants; selective serotonin reuptake inhibitors are less effective. Anticonvulsants (carbamazepine, phenytoin, gabapentin, lamotrigine) are effective, as are narcotic and nonnarcotic analgesics. Enzyme replacement therapy has improved the short- and long-term prognosis of the clinical neuropathy and also reverses the increased blood flow velocity in the brain.

613.7 Giant Axonal Neuropathy

Harvey B. Sarnat

Giant axonal neuropathy is a rare autosomal recessive disease with onset in early childhood. It is a progressive mixed peripheral neuropathy and degeneration of central white matter, similar to the leukodystrophies. Ataxia and nystagmus are accompanied by signs of progressive peripheral neuropathy. A large majority of affected children have frizzy hair, which microscopically shows variation in diameter of the shaft and twisting, similar to that in Menkes disease; hence, microscopic examination of a few scalp hairs provides a simple screening tool in suspected cases. Focal axonal enlargements are seen in both the peripheral nervous system and the central nervous system, but the myelin sheath is intact. The disease is a general proliferation of intermediate filaments, including neurofilaments in axons, glial filaments (i.e., Rosenthal fibers) in brain, cytokeratin in hair, and vimentin in Schwann cells and fibroblasts.

Nonsense and missense mutations or deletions occur in the *GAN* gene, with allelic heterogeneity, at 16q24. These mutations are responsible for defective synthesis of the protein gigaxonin, a member of the cytoskeletal BTB/kelch superfamily, crucial to linkage between intermediate proteins and the cell membrane. MRI shows white matter lesions of the brain similar to leukodystrophies, and MR spectroscopy demonstrates increased ratios of choline : creatine and myoinositol : creatine, with a normally preserved ratio of *N*-acetyl aspartate : creatine, indicating demyelination and glial proliferation without axonal loss. Gigaxonin is expressed in a wide variety of neuronal cell types and is localized to the Golgi apparatus and endoplasmic reticulum.

The diagnosis is established by microscopy of scalp hair and by MRI and MR spectroscopy of the brain; it is confirmed by sural nerve biopsy and/or by genetic studies, if available, of the *GAN* gene. A mutation of *BAG3*, one of several genes associated with myofibrillar myopathy (see Chapter 608.5), also can cause giant axonal neuropathy as another genetic etiology not associated with the more frequent *GAN* gene.

613.8 Tomaculous (Hypermyelinating) Neuropathy; Hereditary Neuropathy with Liability to Pressure Palsies

Harvey B. Sarnat

This hereditary neuropathy is characterized by redundant overproduction of myelin around each axon in an irregular segmental fashion so that tomaculous (sausage-shaped) bulges occur in the individual myelinated nerve fibers. Other sections of the same nerve can show loss of myelin. Such nerves are particularly prone to pressure palsies, and patients, usually beginning in adolescence, present with recurrent or intermittent mononeuropathies secondary to minor trauma or entrapment neuropathies, such as carpal tunnel syndrome, peroneal palsies, and even "writer's cramp." It is transmitted as an autosomal dominant trait, with loci identified at 17p11.2 and 17p12, deletion of exons in the *PMP22* gene, in some patients only microdeletions. Duplication of the same 17p12 locus leads to Charcot-Marie-Tooth disease type 1A, myelin protein zero *(MPZ)* gene mutation. Sural nerve biopsy is diagnostic, but special teased fiber preparations should be made to demonstrate the myelin abnormalities most clearly. Skin or conjunctival biopsies also may be diagnostic. Electrophysiologic nerve conduction studies are abnormal but nonspecific. Genetic studies are definitive.

Treatment is supportive and includes avoiding trauma and prolonged nerve compression, including postures when sitting or lying.

Surgical release of entrapped nerves is indicated at times, particularly of the ulnar nerve.

613.9 Leukodystrophies

Harvey B. Sarnat

Several hereditary degenerative diseases of white matter of the central nervous system also cause peripheral neuropathy. The most important are Krabbe disease (globoid cell leukodystrophy), metachromatic leukodystrophy, and adrenoleukodystrophy (see Chapters 86 and 599).

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Chapter 614

Toxic Neuropathies

Harvey B. Sarnat

Many chemicals (organophosphates), toxins, and drugs can cause peripheral neuropathy (Table 614-1). Heavy metals are well-known neurotoxins. Lead poisoning, especially if chronic, causes mainly a motor neuropathy selectively involving large nerves, such as the common peroneal, radial, and median nerves, a condition known as **mononeuritis multiplex** (see Chapter 721). Arsenic produces painful burning paresthesias and motor polyneuropathy. Exposure to industrial and agricultural chemicals is a less-common cause of toxic neuropathy in children than in adults, but insecticides are neurotoxins for both insects and humans, and if they are used as sprays in closed spaces, they may be inhaled and induce lethargy, vomiting, seizures, and neuropathy, particularly with recurrent or long-term exposure. Working adolescents and children in developing countries are also at risk. Puffer fish poisoning, which can be acquired even when fish contaminated with the venom has been cooked, produces a Guillain-Barré–like syndrome. Ethanol abuse can be neurotoxic and particularly affects the optic nerves, but optic neuritis is not a true peripheral neuropathy.

The most frequent cause of toxic neuropathies in children is prescribed medications, though street drugs also can be neurotoxic. Antimetabolic and immunosuppressive drugs, such as vincristine, cisplatin, and paclitaxel, produce polyneuropathies as complications of chemotherapy for neoplasms and immunologic disorders, such as juvenile idiopathic arthritis. This "iatrogenic" cause is usually an axonal degeneration rather than primary demyelination, unlike primary autoimmune neuropathies. Excessive vitamin intake ("megavitamins") can be neurotoxic.

Chronic uremia is associated with toxic neuropathy and myopathy. The neuropathy is caused by excessive levels of circulating parathyroid hormone. Reduction in serum parathyroid hormone levels is accompanied by clinical improvement and a return to normal of nerve conduction velocity. Peripheral nerve axonal damage, particularly of small fibers, can be secondary to mitochondrial loss or dysfunction in toxic neuropathies. Abnormal toxic complex lipids, generated in Schwann cells by deficient mitochondrial respiration, are capable of damaging or destroying neighboring axons, a secondary mitochondrial toxic neuropathy. Small heat-shock proteins can be provoked that also may contribute to toxic neuropathy.

Biologic neurotoxins associated with diphtheria, Lyme disease, West Nile virus disease, leprosy, herpesviruses (Bell palsy), and rabies also produce peripheral nerve– or ventral horn cell–induced weakness or paralysis. HIV infections also produce neuropathy and this infection is particularly prevalent in children in several African countries, including those who immigrate to western countries as refugees. Tick paralysis, botulism, and paralytic shellfish poisoning cause neuromuscular junction blockade rather than true neuropathy. Various inborn errors of metabolism are also associated with peripheral neuropathy from metabolite toxicity or deficiencies (see Part XI and Table 614-1).

Table 614-1 Toxic and Metabolic Neuropathies

METALS	Nitrofurantoin
Arsenic (insecticide, herbicide)	Nitrous oxide
Lead (paint, batteries, pottery)	Nucleosides (antiretroviral agents dideoxycytidine [ddC], didanosine [ddI], d4T, others)
Mercury (metallic, vapor)	Penicillamine
Thallium (rodenticides)	Pentamidine
Gold	Phenytoin
OCCUPATIONAL OR INDUSTRIAL CHEMICALS	Pyridoxine (excessive)
Acrylamide (grouting, flocculation)	Statins
Carbon disulfide (solvent)	Stilbamidine
Cyanide	Suramin
Dichlorophenoxyacetate	Tacrolimus
Dimethylaminopropionitrite	Taxanes (paclitaxel, docetaxel)
Ethylene oxide (gas sterilization)	Thalidomide
Hexacarbons (glue, solvents)	Tryptophan (eosinophilia-myalgia syndrome)
Organophosphates (insecticides, petroleum additive)	Vincristine
Polychlorinated biphenyls	**METABOLIC DISORDERS**
Tetrachlorbiphenyl	Fabry disease
Trichloroethylene	Krabbe disease
DRUGS	Leukodystrophies
Amiodarone	Porphyria
Chloramphenicol	Tangier disease
Chloroquine	Tyrosinemia
Cisplatin	Uremia
Colchicine	**BIOLOGIC AND INFECTIOUS NEUROPATHIES**
Dapsone	Diphtheria
Ethambutol	Herpesviruses
Ethanol	HIV
Fluoroquinolones	Leprosy
Gold	Lyme disease
Hydralazine	Rabies
Isoniazid	West Nile virus
Metronidazole	

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Chapter 615

Autonomic Neuropathies

Harvey B. Sarnat

Involvement of small, lightly or unmyelinated autonomic nerve fibers may be seen in many peripheral neuropathies; the autonomic manifestations are usually mild or subclinical. Certain autonomic neuropathies are more symptomatic and demonstrate varying degrees of involvement of the autonomic nervous system regulation of the cardiovascular, gastrointestinal, genitourinary, thermoregulatory, sudomotor, and pupillomotor systems. Figure 615-1 shows the classification of autonomic disorders (dysautonomias).

The differential diagnosis is noted in Tables 613-1 (in Chapter 613) and 615-1; Table 615-2 compares the neonatal-infantile onset

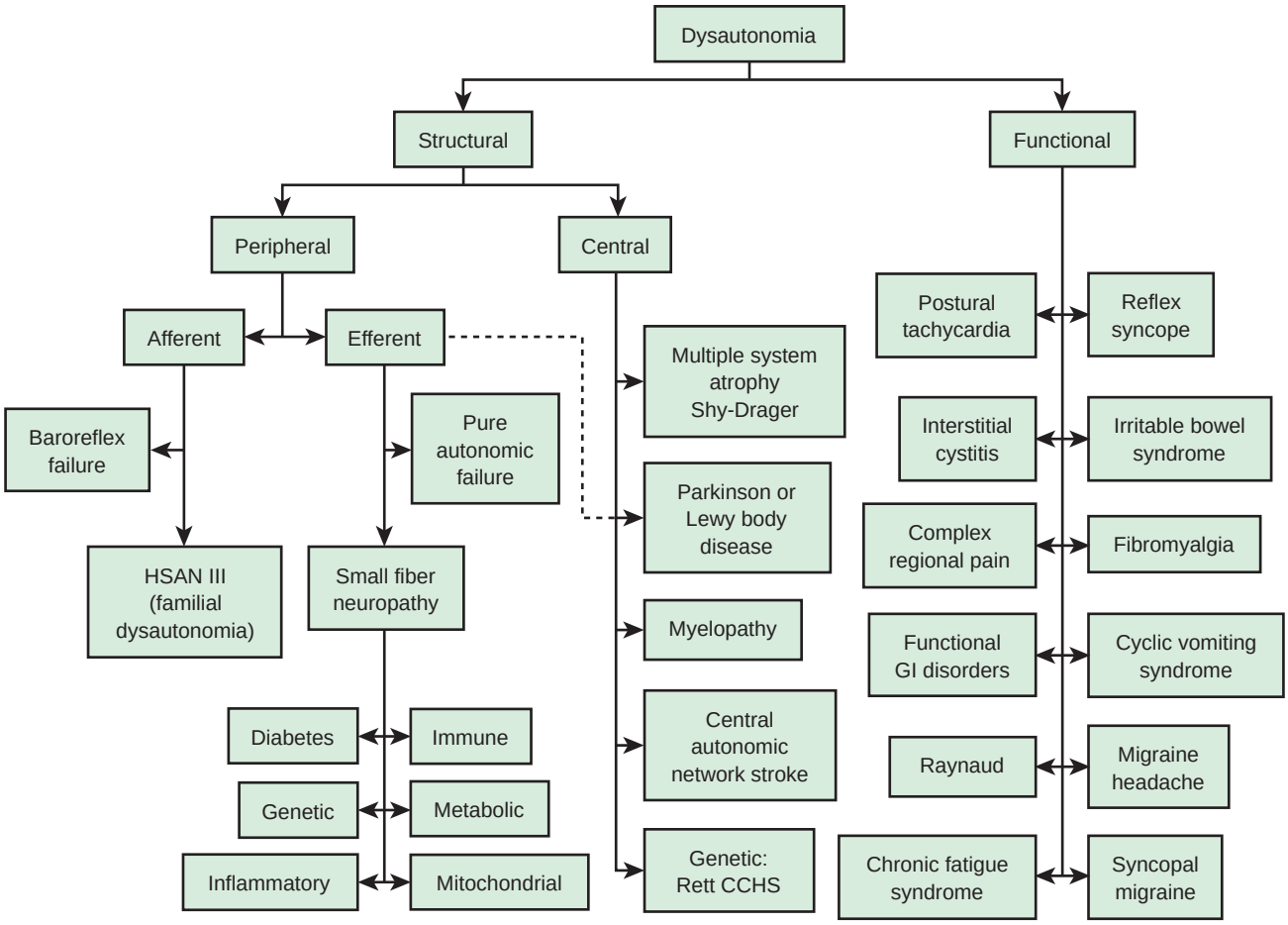


Figure 615-1 **Classification of autonomic disorders or dysautonomias.** The first conceptual division is between a structural and functional disorder. The word "functional" is being used in its true meaning of a disturbance in autonomic function, without clear evidence of structural damage to the autonomic nervous system, akin to the use of the word "functional" in functional gastrointestinal disorders, and without implication of a psychiatric etiology. In the absence of any evidence of consistent structural abnormalities functional disorders clearly cannot be localized in the nervous system. In contrast, structural disorders can be further divided into those localized in the central and peripheral nervous systems, with the division point usually taken at the sympathetic ganglion. Finally, peripheral nervous system disorders can be further classified based on whether they primarily involve afferent or efferent nerves. It should be emphasized that there is overlap between these groups, for example, diabetes will often involve afferent nerve fibers, but this classification emphasizes the predominant fiber involvement. A *dotted line* links Parkinson disease to a peripheral efferent group as Lewy bodies are present in the both parasympathetic and sympathetic ganglia, impairing peripheral autonomic function. See below for discussion of specific disorders. *CCHS*, Congenital central hypoventilation syndrome; *HSAN*, hereditary sensory autonomic neuropathy. *(From Chelimsky T, Robertson D, Chelimsky G: Disorders of the autonomic nervous system. In Daroff RB, Fenichel GM, Jankovic J, Mazziotta JC, editors*: Bradley's neurology in clinical practice*, ed 6, Philadelphia, 2012, WB Saunders, Fig. 77-1, p. 2018.)*

Table 615-1 Autonomic Neuropathies

Guillain-Barré syndrome (see Chapter 608)
Non–Guillain-Barré syndrome autoimmunity
- Paraneoplastic (type I antineuronal nuclear antibody)
- Lambert-Eaton syndrome
- Antibodies to neuronal nicotinic acetylcholine receptors
- Antibodies to P/Q-type calcium channels
- Other autoantibodies
- Systemic lupus erythematosus

Hereditary sensory and autonomic neuropathies
- Type I autosomal dominant
- Type II autosomal recessive (Morvan disease)
- Type III autosomal recessive (Riley-Day)
- Type IV autosomal recessive (congenital insensitivity to pain with anhidrosis)
- Type V absence of pain

Metabolic
- Fabry disease
- Diabetes mellitus
- Tangier disease
- Porphyria

Infectious
- HIV
- Chagas disease
- Botulism
- Leprosy
- Diphtheria

Other
- Triple A (Allgrove) syndrome
- Navajo Indian neuropathy
- Multiple endocrine neoplasia type 2b

Toxins (see Table 614-1 in Chapter 614)

Table 615-2 Major Clinical Features of Hereditary Sensory-Autonomic Neuropathy Types II, III, and IV

CLINICAL FEATURES	HSAN TYPE II	HSAN TYPE III	HSAN TYPE IV
Onset	Birth	Birth	Birth
Initial symptoms (from birth to age 3 yr)	Swallowing problems Self-mutilation (65%) Delayed development	Swallowing problems Aspiration pneumonia Breech presentation (37%) Hypothermia Delayed development	Fevers Self-mutilation (88%)
Unique features	No axon flare Lack of fungiform papilla Hearing loss (30%)	No axon flare Lack of fungiform papilla Alacrima	No axon flare Anhidrosis Consanguinity 50%
Sensory dysfunction			
Depressed deep tendon reflexes	Frequent (71%)	Almost consistent (99%)	Infrequent (9%)
Pain perception	Absent	Mild to moderate decrease	Absent
Temperature perception	Severe decrease	Mild to moderate decrease	Absent
Vibration sense	Normal	Normal	Normal to moderate decrease
Autonomic			
Gastroesophageal reflux	Frequent (71%)	Frequent (67%)	Uncommon (24%)
Postural hypotension	Uncommon (25%)	Almost consistent (99%)	Uncommon (29%)
Episodic hypertension	Rare	Frequent	Rare
Ectodermal features			
Dry skin	No	No	Consistent
Fractures	29%	40%	71%
Scoliosis	59%	85%	23%
Intelligence			
IQ <65	Common (38%)	Uncommon (10%)	Common (33%)
Hyperactivity	Common (41%)	Uncommon	Common (54%)

Frequency definitions: rare = <1%; infrequent = <10%; uncommon = <30%; common = 30-65%; frequent = >65%.
From Axelrod FB, Gold-von Simson G: Hereditary sensory and autonomic neuropathies: types II, III, and IV, Orphanet J Rare Dis *2:39, 2007, Table 2.*

Table 615-3 Autonomic Function Testing

Sympathetic and parasympathetic divisions of the autonomic nervous system are involved in all tests of autonomic function
CARDIAC PARASYMPATHETIC NERVOUS SYSTEM FUNCTION
Heart rate variability with deep respiration (respiratory sinus arrhythmia); time-domain and frequency-domain assessments
Heart rate response to Valsalva maneuver
Heart rate response to standing
SYMPATHETIC ADRENERGIC FUNCTION
Blood pressure response to upright posture (standing or tilt table)
Blood pressure response to Valsalva maneuver
Microneurography
SYMPATHETIC CHOLINERGIC FUNCTION
Thermoregulatory sweat testing
Quantitative sudomotor-axon reflex test
Sweat imprint methods
Sympathetic skin response

From Freeman R: Autonomic peripheral neuropathy, Lancet *365:1259–1270, 2005.*

Table 615-4 Management of Autonomic Neuropathies

PROBLEM	TREATMENT
Orthostatic hypotension	Volume and salt supplements Fluorohydrocortisone (mineralocorticoid) Midodrine (α agonist)
Gastroparesis	Prokinetic agents (metoclopramide, domperidone, erythromycin)
Hypomotility	Fiber, laxatives
Urinary dysfunction	Timed voiding; bladder catheterization
Hyperhidrosis	Anticholinergic agents (glycopyrrolate, propantheline) Intracutaneous botulism toxin

hereditary sensory-autonomic neuropathies (HSANs). Table 615-3 lists autonomic nervous system functional tests. The general treatment of acquired autonomic dysfunction includes treating the primary disorder (systemic lupus erythematosus, diabetes) and long-term management of specific organ system manifestations (Table 615-4). Acute fluctuations of autonomic symptoms may be seen in Guillain-Barré syndrome. Rapid fluctuations of hypertension or tachycardia changing to hypotension or bradycardia should be managed carefully and with very short-acting medications.

615.1 Familial Dysautonomia

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Familial dysautonomia (Riley-Day syndrome) is an autosomal recessive disorder that is common in Eastern European Jews, among whom the incidence is 1 in 10,000-20,000, and the carrier state is estimated to be 1%. It is rare in other ethnic groups but is the most common HSAN. The defective gene is at the 9q31-q33 locus. The familial dysautonomia gene is identified as *IKBKAP* (IκB kinase–associated protein), with aberrant splicing and a truncated protein (see Table 615-2). This and other autonomic neuropathies are often regarded as **neurocristopathies** because the abnormal target tissues are largely derived from neural crest.



Figure 615-2 **A,** Normal tongue with fungiform papillae present on the tip. **B,** Dysautonomic tongue. Note the absence of the highly vascularized fungiform papillae from the tongue tip, which gives the appearance of a smooth tongue. *(From Axelrod FB, Gold-von Simson G: Hereditary sensory and autonomic neuropathies: types II, III, and IV,* Orphanet J Rare Dis *2:39, 2007, Fig. 4.)*

PATHOLOGY

This disease of the peripheral nervous system is characterized pathologically by a reduced number of small unmyelinated nerve fibers that carry pain, temperature, and taste sensations and that mediate autonomic functions including baroreceptors. Large myelinated afferent nerve fibers that relay impulses from muscle spindles and Golgi tendon organs also are deficient. The degree of demonstrable anatomic change in peripheral and especially autonomic nerves is variable. Optic neuropathy with predominant loss of papillomacular nerve fibers may impair visual acuity. Fungiform papillae of the tongue (taste buds) are absent or reduced in number (Fig. 615-2). The number of parasympathetic ganglion cells in the myenteric plexuses is reduced. There is terminal vessel hyperperfusion in tissues, despite an overall hypoperfusion of organs and extremities.

CLINICAL MANIFESTATIONS

Clinical manifestations are highly variable between individuals. The disease is expressed in infancy by poor sucking and swallowing. Aspiration pneumonia can occur. Feeding difficulties with oral incoordination is a major symptom throughout childhood. Vomiting crises can occur, and indeed nausea, retching, and hyperemesis (dysautonomic crisis) are the most disabling symptoms in some children. Apart from dysphagia, esophageal dysmotility can contribute to these symptoms. Episodic somnolence can occur in infants, as does hypotonia. Excessive sweating and blotchy erythema of the skin are common, especially at mealtime or when the child is excited. Infants are vulnerable to heatstroke. Episodic hyperhidrosis is caused by chemical hypersensitivity of the remaining sudomotor axons rather than of the sweat gland secretory cells. Breathholding spells followed by syncope are common in the 1st 5 yr of life. Episodic arterial hypertension and hypotension may be related to loss of baroreceptor modulation of muscle vasoconstrictor drive, and an acute fall in blood pressure manifests as orthostatic hypotension. Chronic and progressive renal disease may result from renal hypoperfusion. Responses to hypoxia are reduced.

As affected children become older, insensitivity to pain becomes evident and traumatic injuries are frequent. Pain and temperature sensation is reduced but is not as severe as in other HSANs (see Table 615-2). Corneal ulcerations are common partly as a result of decreased corneal reflexes and perhaps because of alacrima (absence of tears with emotional crying), which is a universal finding. Newly erupting teeth cause tongue ulcerations and, in older children, dental trauma and oral soft tissue mutilation may be prominent. Walking is delayed or clumsy or appears ataxic because of poor sensory feedback from muscle spindles. The ataxia is probably related more to deficient muscle spindle feedback and to vestibular nerve dysfunction than to cerebellar involvement, but defective ocular saccades also may indicate cerebellar dysfunction and cerebellar atrophy. Tendon stretch reflexes are absent. Scoliosis or kyphosis is a serious complication in the majority of patients and usually is progressive. Overflow tearing with crying does not normally develop until 2-3 mo of age but fails to develop after that time or is severely reduced or absent in children with familial dysautonomia. There is an increased incidence of urinary incontinence. Bradycardia and other cardiac arrhythmias can occur, and some patients require a cardiac pacemaker.

Approximately 40% of patients have generalized major motor seizures; some of these are associated with acute hypoxia during breathholding and some with extreme fevers, but most do not have an apparent precipitating event. Body temperature is poorly controlled; both hypothermia and extreme fevers occur. Impaired intellectual function is not secondary to epilepsy. Emotional lability and learning disabilities are common in school-age children with the disorder. Puberty is often delayed, especially in girls. Short stature can occur, but growth velocity can be accelerated by treatment with growth hormone. Speech is often slurred or nasal.

After 3 yr of age, autonomic crises begin, usually with attacks of cyclic vomiting lasting 24-72 hr or even several days. Retching and vomiting occur every 15-20 min and are associated with hypertension, profuse sweating, blotching of the skin, apprehension, and irritability. Prominent gastric distention can occur, causing abdominal pain and even respiratory distress. Hematemesis can complicate pernicious vomiting. Activation of dopamine receptors may explain the cyclic vomiting and retching.

Allgrove syndrome (triple A syndrome) is a clinical variant, involving early-onset alacrima, feeding difficulties and achalasia, autonomic dysfunction with orthostatic hypotension, altered heart rate variability, hyperreflexia, ataxia, muscle weakness, sensorimotor polyneuropathy, and adrenocorticotropic hormone–resistant adrenal insufficiency (develops in 1st decade). The gene *AAAS* (alacrima-achalasia-adrenal insufficiency neurologic disorder) is located on chromosome 12q13.

LABORATORY FINDINGS

Electrocardiography discloses prolonged corrected QT intervals with lack of appropriate shortening with exercise, a reflection of the aberration in autonomic regulation of cardiac conduction. Chest radiographs show atelectasis and pulmonary changes resembling cystic fibrosis. Urinary vanillylmandelic acid level is decreased, and the homovanillic acid level is increased. Plasma level of dopamine β-hydroxylase (the enzyme that converts dopamine to epinephrine) is diminished. Sural nerve biopsy shows a decreased number of unmyelinated fibers. Electroencephalography is useful for evaluating seizures.

DIAGNOSIS

Slow IV infusion of norepinephrine produces an exaggerated pressor response. The hypotensive response to infusion of methacholine is increased. Intradermal injection of 1 : 1,000 histamine phosphate fails to produce a normal axon flare, and local pain is absent or diminished.

Because the skin of a normal infant reacts more intensely to histamine, a 1:10,000 dilution should be used. Instillation of 2.5% methacholine into the conjunctival sac produces miosis in patients with familial dysautonomia and no detectable effect on a normal pupil; this is a nonspecific sign of parasympathetic denervation from any cause. Methacholine is applied to only 1 eye in this test, with the other eye serving as a control; the pupils are compared at 5 min intervals for 20 min. The combination of alacrima, absent fungiform papillae, decreased patellar reflexes, and an abnormal histamine test with Ashkenazi Jewish lineage is diagnostic. Because of variable expression and potential overlap with other HSANs, genetic testing should be used to confirm the diagnosis.

TREATMENT

Symptomatic treatment includes special attention to the respiratory and gastrointestinal systems to prevent aspiration and malnutrition, methylcellulose eyedrops or topical ocular lubricants to replace tears and prevent corneal ulceration, orthopedic management of scoliosis and joint problems, and appropriate anticonvulsants for epilepsy. Chlorpromazine is an effective antiemetic and may be given as rectal suppositories during autonomic crises; however, clonidine may be more effective. It also reduces apprehension and lowers the blood pressure. Diazepam has also been effective in some cases. Dehydration and electrolyte disturbances should be anticipated. A more specific and promising approach is the administration of carbidopa, an inhibitor of dopa-decarboxylase, particularly for the hyperemesis that is so prominent and disabling in many patients. Blockers of dopamine receptors are alternative drugs for cyclic vomiting. It is also useful for enuresis, another common complication, and augments tear production. Protection from injuries is important because of the lack of pain as a protective mechanism. Scoliosis often requires surgical treatment. Antiepileptic drugs may be required. A cardiac pacemaker may be required by some children. Blood pressure monitoring may be important in some cases. A promising genetic approach to treatment, which corrects the splicing defect, is the use of oral kinetin to regulate the expression of *IKBKAP* transcripts. Specific compounds identified from stem cells obtained from dysautonomia patients provide a potential therapy to rescue IKBKAP expression.

PROGNOSIS

Sixty percent of patients die in childhood before the age of 20 yr, usually of chronic pulmonary failure or aspiration. Treatment in a center familiar with the diverse complications greatly extends the life expectancy; some have survived to age 40 yr. Prevention of aspiration with fundoplication, gastrostomy, and tube feeding reduces the risk of aspiration. Newer measures to better control vasomotor stability and vomiting improve the quality of life, but whether they change longevity is not yet known.

Bibliography is available at Expert Consult.

615.2 Other Autonomic Neuropathies

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CONGENITAL INSENSITIVITY TO PAIN AND ANHIDROSIS

Congenital insensitivity to pain and anhidrosis is an autosomal recessive disorder HSAN type IV (see Table 615-2). Onset is in infancy. Patients have episodes of extreme fevers related to warm environmental temperatures because they have absent or reduced sweating. Frequent burns and traumatic injuries result from apparent lack of pain perception. Poor healing of fractures occurs, as does osteomyelitis. Neonatal hypotonia improves with growth but learning problems may develop. Intelligence is normal. Nerve biopsy reveals an almost total absence of unmyelinated nerve fibers that convey impulses of pain, temperature, and autonomic functions. Some cases of hypomyelinating neuropathy manifest clinically as congenital insensitivity to pain (see Chapter 613.3). The sympathetic skin response as an electrophysiologic study is a reliable diagnostic test in cases associated with a mutation in the TrKA receptor for nerve growth factor.

REFLEX SYMPATHETIC DYSTROPHY

Reflex sympathetic dystrophy is a form of local causalgia, usually involving a hand or foot but not corresponding to the anatomic distribution of a peripheral nerve (see Chapter 168.2). A continuous burning pain and hyperesthesia are associated with vasomotor instability in the affected zone, resulting in increased skin temperature, erythema, and edema caused by vasodilation and hyperhidrosis. In the chronic state, atrophy of skin appendages, cool and clammy skin, and disuse atrophy of underlying muscle and bone occur. More than 1 extremity is occasionally involved. The pain is disabling and is exacerbated by the movement of an associated joint, although no objective signs of arthritis are seen; immobilization provides some relief. The most common preceding event is local trauma in the form of a contusion, laceration, sprain, or fracture that occurred days or weeks earlier.

Several theories of pathogenesis have been proposed to explain this phenomenon. The most widely accepted is reflexive overactivity of autonomic nerves in response to injury, and regional sympathetic blockade often affords temporary relief. Physiotherapy also is helpful. Some cases resolve spontaneously after weeks or months, but others continue to be symptomatic and require sympathectomy. A psychogenic component is suspected in some cases but is difficult to prove.

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Chapter 616

Guillain-Barré Syndrome

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Guillain-Barré syndrome is an autoimmune disorder often considered a postinfectious polyneuropathy involving mainly motor but also sensory and sometimes autonomic nerves. This syndrome affects people of all ages and is not hereditary. Most patients in the United States and Europe have a demyelinating neuropathy, but primarily axonal degeneration is documented in some cases, mainly in China, Mexico, Bangladesh, and Japan.

CLINICAL MANIFESTATIONS

The paralysis usually follows a nonspecific gastrointestinal or respiratory infection by approximately 10 days. The original infection might have caused only gastrointestinal *(*especially *Campylobacter jejuni,* but also *Helicobacter pylori*) or respiratory tract (especially *Mycoplasma pneumoniae*) symptoms. Consumption of undercooked poultry, unpasteurized milk, and contaminated water are the main sources of gastrointestinal infections. West Nile virus also can mimic Guillain-Barré–like syndrome, but more often it causes motor neuron disease similar to poliomyelitis. Guillain-Barré syndrome is reported following administration of vaccines against rabies, influenza, and poliomyelitis (oral) and following administration of conjugated meningococcal vaccine, particularly serogroup C. Additional infectious precursors of Guillain-Barré syndrome include mononucleosis, Lyme disease, cytomegalovirus, and *Haemophilus influenzae* (for the Miller-Fisher syndrome).

Initial symptoms include numbness and paresthesia, followed by weakness. There may be associated neck, back, buttock, and leg pain. Weakness usually begins in the lower extremities and progressively involves the trunk, the upper limbs, and, finally, the bulbar muscles, a pattern known as **Landry ascending paralysis.** Proximal and distal muscles are involved relatively symmetrically, but asymmetry is found in 9% of patients. The onset is gradual and progresses over days or weeks; the process plateaus in 1-28 days. Particularly in cases with an abrupt onset, tenderness on palpation and pain in muscles are common in the initial stages. Affected children are irritable. Weakness can progress to inability or refusal to walk and later to flaccid tetraplegia. Maximal severity of weakness is usually reached by 4 wk after onset. The differential diagnosis of acute weakness is noted in Table 607-3 (in Chapter 607) and of Guillain-Barré syndrome in Table 616-1.

Bulbar involvement occurs in about half of cases. Respiratory insufficiency can result. Dysphagia and facial weakness are often impending signs of respiratory failure. They interfere with eating and increase the risk of aspiration. The facial nerves may be involved. Some young patients exhibit symptoms of viral meningitis or meningoencephalitis. Extraocular muscle involvement is rare, but in an uncommon variant, oculomotor and other cranial neuropathies are severe early in the course.

Miller-Fisher syndrome (MFS) consists of acute external and occasionally internal ophthalmoplegia, ataxia, and areflexia. The 6th cranial nerve is most often involved in MFS. Papilledema may precede or follow MFS and suggests a diagnosis of pseudotumor; optic neuritis may also be noted. Although areflexia is seen in MFS, patients do not have significant lower extremity weakness compared with Guillain-Barré syndrome. Distal paresthesias are noted in MFS. Urinary incontinence or retention of urine is a complication in approximately 20% of cases but is usually transient. MFS overlaps with Bickerstaff brainstem encephalitis, which also shares many features with Guillain-Barré syndrome with lower motor neuron involvement.

Tendon reflexes in Guillain-Barré syndrome are lost, usually early in the course, but are sometimes preserved until later; areflexia is common but hyporeflexia may be seen; 10% may have normal reflexes. This variability can cause confusion when attempting early diagnosis. The **autonomic nervous system** is also involved in some cases. Lability of blood pressure and cardiac rate, postural hypotension, episodes of profound bradycardia, or tachycardia and occasional asystole occur. Cardiovascular monitoring is important. A few patients require insertion of a temporary venous cardiac pacemaker.

Subtypes of Guillain-Barré syndrome include an acute inflammatory demyelinating polyneuropathy and an acute motor axonal neuropathy; these are distinguished by nerve conduction studies, geography, and the pattern of antiganglioside antibodies (Table 616-2). Localized forms also occur and include a pattern of facial diplegia with paresthesias and a pattern of pharyngeal-cervical-brachial weakness.

Chronic inflammatory demyelinating polyradiculoneuropathies (CIDPs, sometimes called *chronic inflammatory relapsing polyneuritis* or *chronic unremitting polyradiculoneuropathy*) are chronic varieties of Guillain-Barré syndrome that recur intermittently, or do not improve, or progress slowly and relentlessly for periods of months to years. Approximately 7% of children with Guillain-Barré syndrome suffer an acute relapse. Patients are usually severely weak and can have a flaccid tetraplegia with or without bulbar and respiratory muscle involvement. Hyporeflexia or areflexia is almost universal. Motor deficits occur in 94% of cases, sensory paresthesias in 64%, and cranial nerve involvement in less than a third of patients. Autonomic and micturitional involvement is variable. Cerebrospinal fluid (CSF) shows no pleocytosis and protein is variably normal or mildly elevated. Nerve conduction

Table 616-1 Differential Diagnosis of Childhood Guillain-Barré Syndrome

SPINAL CORD LESIONS
Acute transverse myelitis
Epidural abscess
Tumors
Poliomyelitis (natural or live virus)
Enteroviruses
Hopkins syndrome
Vascular malformations
Cord infarction
Fibrocartilaginous embolism
Cord compression from vertebral subluxation related to congenital abnormalities or trauma
Acute disseminated encephalomyelitis
Bickerstaff brainstem encephalitis for Miller-Fisher syndrome
PERIPHERAL NEUROPATHIES
Toxic
• Vincristine
• Glue sniffing
• Heavy metal: gold, arsenic, lead, thallium
• Organophosphate pesticides
• Fluoroquinolones
Infections
• HIV
• Diphtheria
• Lyme disease
Inborn errors of metabolism
• Leigh disease
• Tangier disease
• Porphyria
Critical illness: polyneuropathy/myopathy
Vasculitis syndromes
Porphyria
Mitochondrial neurogastrointestinal encephalomyopathy
CD59 deficiency
NEUROMUSCULAR JUNCTION DISORDERS
Tick paralysis
Myasthenia gravis
Botulism
Hypercalcemia
Myopathies
Periodic paralyses
Dermatomyositis
Critical illness myopathy/polyneuropathy

From Agrawal S, Peake D, Whitehouse WP: Management of children with Guillain Barré syndrome, Arch Dis Child Educ Pract Ed *92:161–168, 2007.*

Table 616-2 Classification of Guillain-Barré Syndrome and Related Disorders and Typical Antiganglioside Antibodies By Pathology

DISORDER	ANTIBODIES
Acute inflammatory demyelinating polyradiculoneuropathy	Unknown
Acute motor and sensory axonal neuropathy	GM_1, GM_{1b}, GD_{1a}
Acute motor axonal neuropathy	GM_1, GM_{1b}, GD_{1a}, GalNac-GD_{1a}
Acute sensory neuronopathy	GD_{1b}
ACUTE PANDYSAUTONOMIA	
Regional Variants	
Fisher syndrome	GQ_{1b}, GT_{1a}
Oropharyngeal	GT_{1a}
Overlap	
Fisher/Guillain-Barré overlap syndrome	GQ_{1b}, GM_1, GM_{1b}, GD_{1a}, GalNac-GD_{1a}

From Hughes RAC: Treatment of Guillain-Barré syndrome with corticosteroids: lack of benefit? Lancet *363:181–182, 2004.*

velocity studies and sural nerve biopsy are abnormal. Polymorphic nucleotide repeats in the *SH2D2A* gene are associated with a predisposition to CIDP.

Congenital Guillain-Barré syndrome is described rarely, manifesting as generalized hypotonia, weakness, and areflexia in an affected neonate, fulfilling all electrophysiologic and CSF criteria and in the absence of maternal neuromuscular disease. Treatment might not be required, and there is gradual improvement over the 1st few mo and no evidence of residual disease by 1 yr of age. In 1 case, the mother had ulcerative colitis treated with prednisone and mesalamine from the 7th mo of gestation until delivery at term.

LABORATORY FINDINGS AND DIAGNOSIS

CSF studies are essential for diagnosis. The CSF protein is elevated to more than twice the upper limit of normal, the glucose level is normal, and there is no pleocytosis. Fewer than 10 white blood cells/mm^3 may be found. The results of bacterial cultures are negative, and viral cultures rarely isolate specific viruses. The dissociation between high CSF protein and a lack of cellular response in a patient with an acute or subacute polyneuropathy is diagnostic of Guillain-Barré syndrome. MRI of the spinal cord may be indicated to rule out disorders listed in Table 616-1. MRI findings include thickening of the cauda equina and intrathecal nerve roots with gadolinium enhancement. These finds are fairly sensitive and are present in >90% of patients (Fig. 616-1). Imaging in CIDP is similar but demonstrates greater enhancement of spinal nerve roots (Fig. 616-2).

Motor nerve conduction velocities are greatly reduced, and sensory nerve conduction time is often slow. Electromyography shows evidence of acute denervation of muscle. *Serum creatine kinase level may be mildly elevated or normal.* Antiganglioside antibodies, mainly against GM_1 and GD_1, are sometimes elevated in the serum in Guillain-Barré syndrome, particularly in cases with primarily axonal rather than demyelinating neuropathy, and suggest that they might play a role in disease propagation and/or recovery in some cases (see Table 616-1). Muscle biopsy is not usually required for diagnosis; specimens appear normal in early stages and show evidence of denervation atrophy in chronic stages. Sural nerve biopsy tissue shows segmental demyelination, focal inflammation, and wallerian degeneration but also is usually not required for diagnosis.

Serologic testing for *Campylobacter* and *Helicobacter* infections helps establish the cause if results are positive but does not alter the course of treatment. Results of stool cultures are rarely positive because

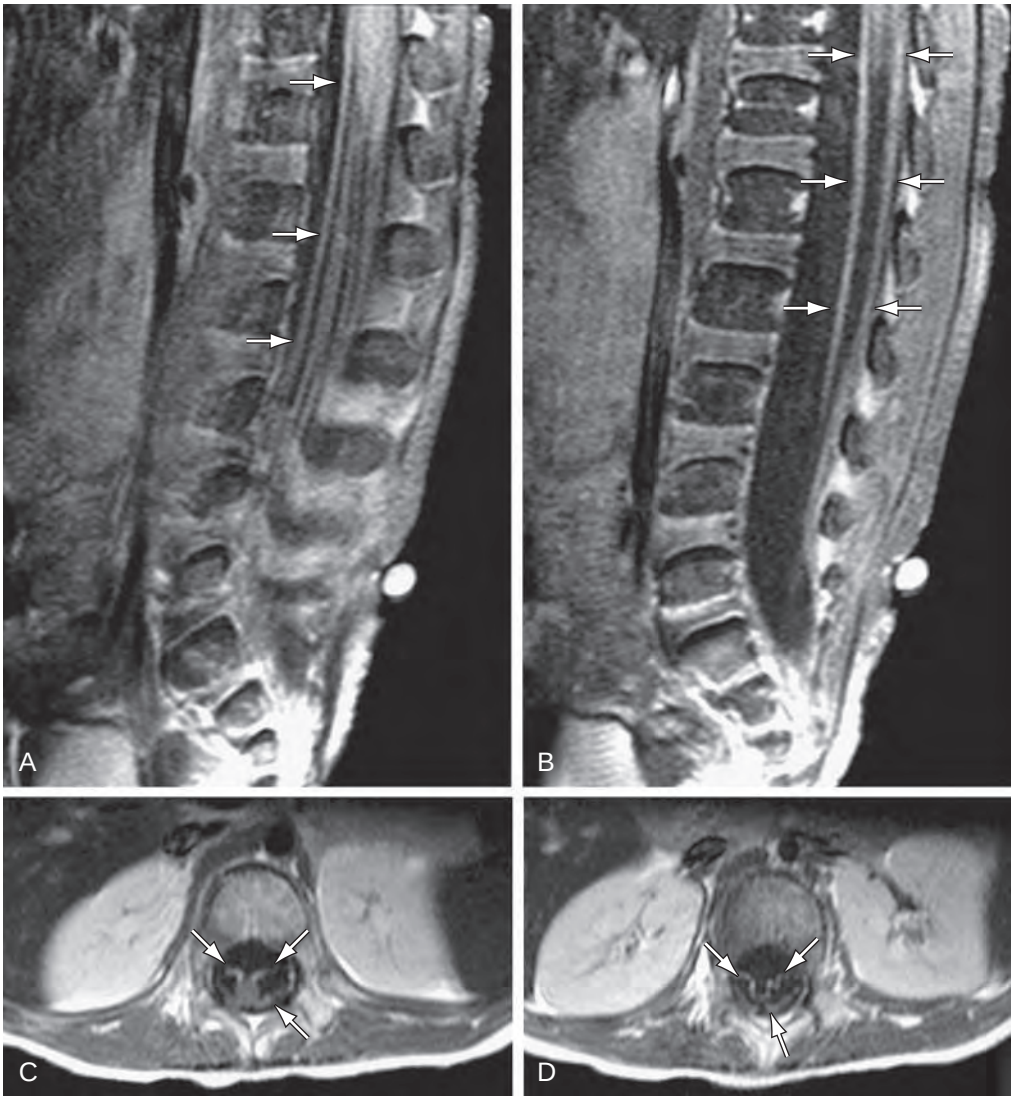


Figure 616-1 Guillain-Barré syndrome. Sagittal off-midline **(A)** and midline **(B)** postgadolinium T1-weighted fat-saturated images through the lumbar spine of a patient who could not ambulate. **C** and **D,** Axial postcontrast T1-weighted images through the conus medullaris and proximal lumbar nerve roots, respectively. The images show extensive contrast enhancement of nerve roots (*arrows* in **A-D**), in keeping with changes of Guillain-Barré. *(From Slovis TL, editor:* Caffey's pediatric diagnostic imaging, *ed 11, Philadelphia, 2008, Mosby, Fig. 65-6.)*

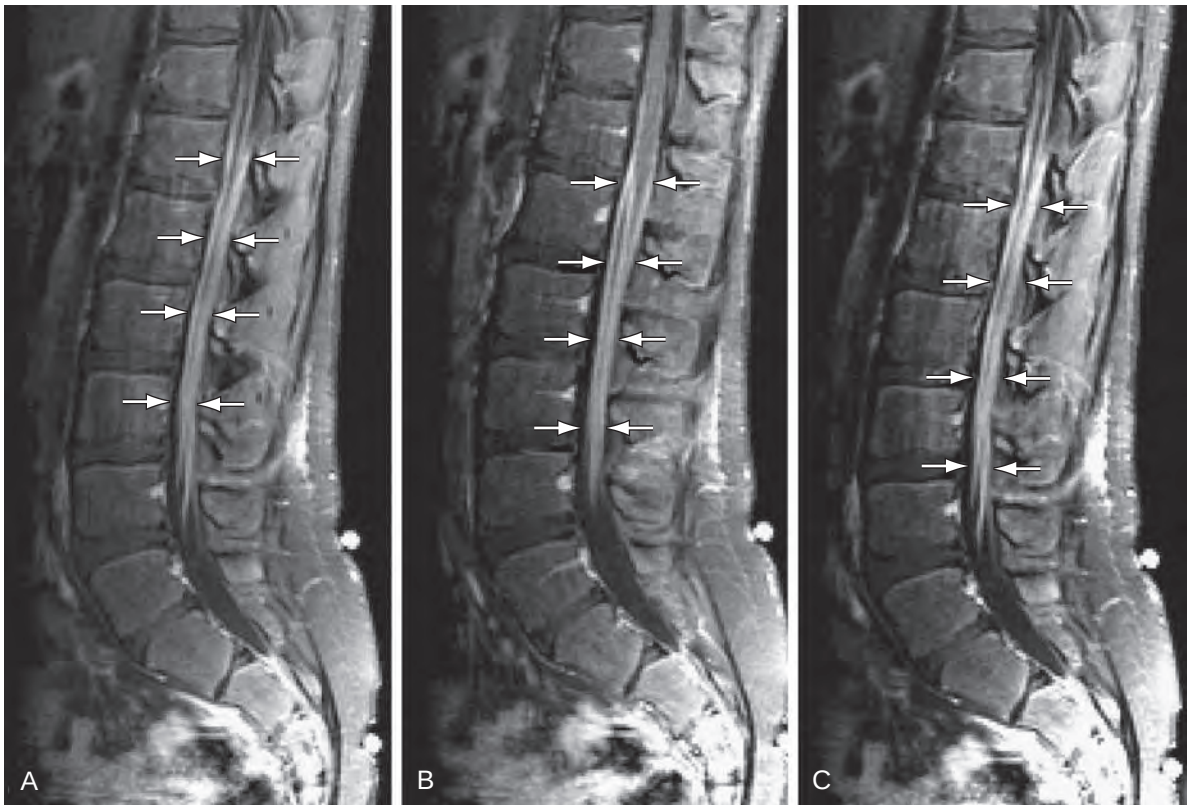


Figure 616-2 Chronic inflammatory demyelinating polyneuropathy (CIDP) in a 13 yr old boy with peripheral neuropathy and gait disturbance. Sagittal fat-saturated T1-weighted images off the midline to the right **(A),** at the midline **(B),** and off the midline to the left **(C).** *(From Slovis TL, editor:* Caffey's pediatric diagnostic imaging, *ed 11, Philadelphia, 2008, Mosby, Fig. 65-7.)*

the infection is self-limited and only occurs for about 3 days, and the neuropathy follows the acute gastroenteritis.

TREATMENT

Patients in early stages of this acute disease should be admitted to the hospital for observation because the ascending paralysis can rapidly involve respiratory muscles during the next 24 hr. Respiratory effort (negative inspiratory force, spirometry) **must** be monitored to prevent respiratory failure and respiratory arrest. Patients with slow progression might simply be observed for stabilization and spontaneous remission without treatment. Rapidly progressive ascending paralysis is treated with intravenous immunoglobulin (IVIG), administered for 2, 3, or 5 days. A commonly recommended protocol is IVIG 0.4 g/kg/day for 5 consecutive days, but some studies suggest that larger doses are more effective (1 g/kg/day for 2 consecutive days) and related to improved outcome. Plasmapheresis and/or immunosuppressive drugs are alternatives if IVIG is ineffective. Steroids are not effective. Supportive care, such as respiratory support, prevention of decubiti in children with flaccid tetraplegia, nutritional support, pain management, prevention of deep vein thrombosis, and treatment of secondary bacterial infections, is important.

CIDPs, whether relapsing-remitting or unremitting, also are treated with oral or pulsed steroids and IVIG. Subcutaneous immunoglobulin infusion may be an alternative to the intravenous route. Plasma exchange, sometimes requiring as many as 10 exchanges daily, is an alternative. Remission in these cases may be sustained, but relapses can occur within days, weeks, or even after many months; relapses usually respond to another course of plasmapheresis. Steroid and immunosuppressive drugs are another alternative, but their effectiveness is less predictable. High-dose pulsed methylprednisolone given intravenously is successful in some cases. The prognosis in chronic forms of the Guillain-Barré syndrome is more guarded than in the acute form, and many patients are left with major residual handicaps.

Even if *C. jejuni* infection is documented by stool culture or serologic tests, treatment of the infection is not necessary because it is self-limited, and the use of antibiotics does not alter the course of the polyneuropathy.

For the treatment of chronic neuropathic pain following Guillain-Barré syndrome, gabapentin is more effective than carbamazepine, and the requirement for fentanyl is reduced. But no pharmacologic treatments for neuropathic pain in this disease are wholly effective.

PROGNOSIS

The clinical course is usually benign, and spontaneous recovery begins within 2-3 wk. Most patients regain full muscular strength, although some are left with residual weakness. The tendon reflexes are usually the last function to recover. Improvement usually follows a gradient opposite the direction of involvement: bulbar function recovering first, and lower extremity weakness resolving last. Bulbar and respiratory muscle involvement can lead to death if the syndrome is not recognized and treated. Although prognosis is generally good and the majority of children recover completely, 3 clinical features are predictive of poor outcome with sequelae: cranial nerve involvement, intubation, and maximum disability at the time of presentation. The electrophysiologic features of conduction block are predictive of good outcome. Long-term follow-up studies of patients who recover from an attack of Guillain-Barré syndrome reveal that many do have some permanent axonal loss, with or without residual clinical signs of chronic neuropathy. Easy fatigue is one of the most common chronic symptoms, but it is not the rapid fatigability of muscles seen in myasthenia gravis. Most patients with the axonal form of Guillain-Barré syndrome had a slow recovery over the 1st 6 mo and could eventually walk, although some required years to recover. Electromyography and nerve conduction velocity electrophysiologic studies do not necessarily predict the long-term outcome.

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Chapter 617

Bell Palsy

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Bell palsy is an acute unilateral peripheral facial nerve palsy that is not associated with other cranial neuropathies or brainstem dysfunction. It is a common disorder at all ages from infancy through adolescence and usually develops abruptly about 2 wk after a systemic viral infection. The preceding infection is caused by the herpes simplex virus, varicella-zoster virus, Epstein-Barr virus, Lyme disease, mumps virus, *Toxocara*, *Rickettsia*, *Mycoplasma,* or HIV infection (Table 617-1). Ramsay Hunt syndrome (herpes zoster oticus) is associated with vesicles in the external auditory canal or auricle and an ipsilateral facial palsy. Active or reactivation of herpes simplex or varicella-zoster virus may be the most common cause of Bell palsy (Fig. 617-1). The disease is occasionally a postinfectious allergic or immune demyelinating facial neuritis. It also may be a focal toxic or inflammatory neuropathy and has been associated with ribavirin and interferon-α therapy for hepatitis C. Hereditary forms are rare, but it may be associated with other genetic polyneuropathies. Rarely, Bell palsy occurs in the context of hypertension or juvenile type 1 diabetes mellitus, most often associated with concomitant viral infections.

Table 617-1 Etiologies of Acute Peripheral Facial Palsy

COMMON	OTHER LESS-COMMON CONDITIONS
Idiopathic	Trauma
Herpes simplex virus type 1*	Schwannoma of facial nerve
Varicella-zoster virus*	Infiltrative tumor
LESS-COMMON INFECTIONS	Aneurysm or vascular malformation
Otitis media ± cholesteatoma	Anomalous narrowing of facial canal
Lyme disease	Hypertension
Epstein-Barr virus	Sjögren syndrome
Cytomegalovirus	Diabetes mellitus, type 1
Mumps	Guillain-Barré syndrome
Human herpesvirus 6	Sarcoidosis
Intranasal influenza vaccine	Melkersson-Rosenthal syndrome†
Mycoplasma	Ribavirin
Toxocara	Interferon
Rickettsia	
AIDS/HIV	

*Implicated in idiopathic Bell palsy.
†Noncaseating granulomas with facial (lips, eyelids) edema, recurrent alternating facial paralysis, family history, migraines, or headaches.

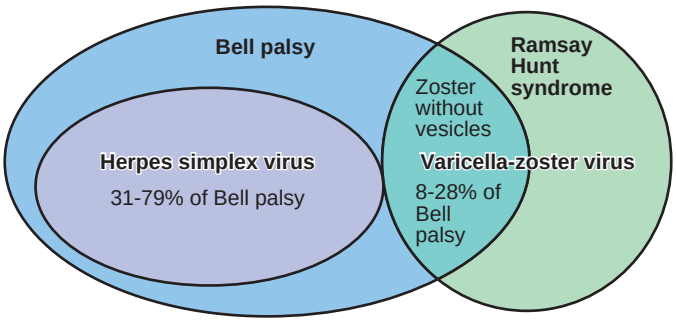


Figure 617-1 Involvement of herpes simplex and varicella-zoster viruses in acute facial palsy. *(Modified from Hato N, Murakami S, Gyo K: Steroid and antiviral treatment for Bell's palsy,* Lancet *371:1818–1820, 2008.)*

CLINICAL MANIFESTATIONS

The upper and lower portions of the face are paretic, and the corner of the mouth droops. Patients are unable to close the eye on the involved side and can develop an exposure keratitis at night. Taste on the anterior two thirds of the tongue is lost on the involved side in approximately 50% of cases; this finding helps to establish the anatomic limits of the lesion as being proximal or distal to the chorda tympani branch of the facial nerve. Numbness and paresthesias do not usually occur, but ipsilateral numbness of the face is reported in a few cases and probably is caused by viral (especially herpes) or postviral immunologic impairment of the trigeminal and the facial nerves. Pain behind the ear may precede weakness. Acute hearing loss may occur in Bell palsy associated with *Rickettsia* infection. Several grading systems have been devised for Bell palsy, including the Sunnybrook, House-Brackmann, and Yanagihara systems.

IMAGING THE FACIAL NERVE AND ITS BONY CANAL

Modern high-resolution MRI, particularly with multiplanar reconstruction, is able to visualize the facial nerve within its canal and determine whether there are bony anomalies, compressive aneurysms, vascular malformations, or nerve sheath or infiltrative tumors that might explain a palsy anatomically. The two sides can be compared and, in particular, the labyrinthine segment within the petrous bone, which is the narrowest site in the facial nerve canal, can be examined. Ultrasound of the facial nerve also has been used, in part as a predictor of functional outcome in Bell palsy. More recently, diffusion tensor tractography enables a tridimensional display of facial nerve axons.

TREATMENT

Oral prednisone (1 mg/kg/day for 1 wk, followed by a 1 wk taper) started within the 1st 3-5 days results in improved outcome and is a traditional treatment, its efficacy confirmed in a recent long-term prospective study in the United Kingdom. Because of the recovery of herpes simplex virus in the neural fluid of the 7th nerve, some also recommend adding oral acyclovir or valacyclovir to the prednisone therapy. Alone, antiviral agents are not effective in reducing adverse sequelae (synkinesis, autonomic dysfunction), but added to prednisone may be associated with an additional small benefit. If a specific infection can be identified as a predisposing cause, specific antiviral or antibacterial treatment is more justified. Surgical decompression of the facial canal, theoretically to provide more space for the swollen facial nerve, is not of value unless imaging provides evidence of nerve compression or an anatomic lesion. Both high- and low-level laser therapy has been used with good results in some cases as a form of physiotherapy. Traditional physiotherapy to the facial muscles is recommended in some chronic cases with poor recovery, but the efficacy of this treatment is uncertain. Protection of the cornea with methylcellulose eyedrops or an ocular lubricant is especially important at night. Botulinum toxin has been applied in adults to the contralateral normal facial muscles for cosmetic purposes to minimize the apparent asymmetry or to treat chronic unilateral ptosis, but this has little application in pediatric patients.

PROGNOSIS

The prognosis for functional recovery is excellent. More than 85% of patients recover spontaneously with no residual facial weakness. Another 10% have mild facial weakness as a sequela, often perceived only as a mild facial asymmetry, and only 5% are left with permanent severe facial weakness. In patients who do not recover within a few weeks (chronic), electrophysiologic examination of the facial nerve helps to determine the degree of neuropathy and regeneration. In chronic cases, other causes of facial neuropathy should be considered, including facial nerve tumors such as schwannomas and neurofibromas, infiltration of the facial nerve by leukemic cells or by a rhabdomyosarcoma of the middle ear, brainstem infarcts or tumors, and traumatic injury of the facial nerve.

Nerve regrowth may be misdirected and result in **synkinesis**, where activation of one muscle group may produce activation of another

inappropriate muscle group; blinking may result in mouth twitching, smiling may cause eye blinking, and lacrimation (crocodile tears) may occur while eating.

FACIAL PALSY AT BIRTH

Facial palsy at birth is usually a compression neuropathy from forceps application during delivery and recovers spontaneously in a few days or weeks in most cases. **Congenital absence of the depressor anguliris oris muscle** causes facial asymmetry, especially when an affected infant cries, and is often associated with other congenital anomalies, especially of the heart. It is not a facial nerve lesion but is a cosmetic defect that does not interfere with feeding. Infants with **Möbius syndrome** can have bilateral or, less commonly, unilateral facial palsy; this syndrome is usually caused by symmetric calcified infarcts in the tegmentum of the pons and medulla oblongata during midgestation or late fetal life, although it rarely is a developmental anomaly of the brainstem.

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