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Handbook

HB

Handbook of Pediatric Neurology

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Handbook of Pediatric Neurology

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PREFACE

It is with great humility and talent that each of our authors has combined the historical medical experience and literature of their own and those of their own personal mentors, to write these chapters. No text can duplicate the richness of personal experience, but it is our hope that these can guide in overview and detail the evaluation and care of pediatric-age patients who present with a wide range of neurodevelopmental difficulties. The summary and succinct outline format is aimed to give the reader quick and easy access to a brief overview of each category of disorder, to include a focused differential diagnosis, and to offer clear initial management guidelines. In addition to selected references, the authors have highlighted several online resources, which should aid the reader in identifying the most up-to-date information. Neuromedical assessment by history and physical examination is a relatively stable task for the neurologist, but diagnostic tools, medications, and interventions are often rapidly changing. We urge the reader to use this handbook as a guide but to always seek local expertise as available and to use their best medical judgment, observation, and re-evaluation as appropriate to each clinical case.

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Katherine B. Sims
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LIST OF ABBREVIATIONS

a/w	Associated with
aa	Amino acid
AAC	Augmentative and alternative communication
AAN	American Academy of Neurology
ABC	Autism Behavior Checklist
ACA	Anterior cerebral artery
ACC	Anterior cingulate cortex
ACT	Actigraphy
AD	Autosomal dominant
ADDM	Autism and developmental disabilities monitoring
ADEM	Acute demyelinating encephalomyelopathy
ADHD	Attention deficit hyperactivity disorder
ADNFLE	Autosomal dominant nocturnal frontal lobe epilepsy
adPEO	Autosomal dominant progressive external ophthalmoplegia
ADS	Acute demyelinating syndrome
AED	Antiepileptic drugs
AGS	Acetylglutamate synthetase deficiency
AHS	Alpers–Huttenlocher syndrome
AICA	Anterior inferior cerebellar artery
AIDP	Acute inflammatory demyelinating polyneuropathy
ALD	Adrenoleukodystrophy
AMAN	Acute motor axonal neuropathy
AMN	Adrenomyeloneuropathy
AMS	Altered mental status
AMSAN	Acute motor-sensory axonal neuropathy
ANE	Acute necrotizing encephalopathy
ANS	Ataxia neuropathy spectrum disorders
Ant	Anterior
AOM	Acute otitis media
aPTT	Activated partial thromboplastin time
AR	Autosomal recessive
ARAS	Ascending reticular activating system
arPEO	Autosomal recessive progressive external ophthalmoplegia
AS	Argininosuccinate deficiency
ASD	Autism spectrum disorder

ASD	Autism spectrum disorders
ASDS	Asperger Syndrome Diagnostic Scale
ASPD	Advanced sleep phase disorder
ASS	Argininosuccinate synthase deficiency
AVED	Ataxia with isolated vitamin- E deficiency
AVM	Arteriovenous malformation
AVMs	Arteriovenous malformations
b/l	Bilateral
BA	Brodmann area
BDZ	Benzodiazepines
BECTS	Benign epilepsy of childhood w/centrotemporal spikes
BFIS	Benign familial infantile seizures
BFIS2	Benign familial infantile seizures 2
BFNS	Benign familial neonatal seizures
BG	Basal ganglia
BHC	Benign hereditary chorea
BL	Bilateral
BMD	Becker muscular dystrophy
BMI	Body mass index
BOHB	Beta-hydroxy butyrate
BS	Brain stem
c/w	Consistent with
CAM	Complementary and alternative medicine
CblC	Cobalamin C deficiency
CBT	Cognitive behavioral therapy
CBZ	Carbamazepine
CC	Corpus callosum
CCHS	Congenital central hypoventilation syndrome
CD	Conduct disorder
CDD	Childhood disintegrative disorder
CDG	Congenital defects of glycosylation
CHO	Carbohydrate
CIDP	Chronic inflammatory demyelinating polyneuropathy
CIS	Clinical isolated syndrome
CK	Creatinine kinase
CLB	Clobazam
CMT	Charcot Marie tooth disease
CMV	Cytomegalovirus
CN	Cranial nerve
CNS	Central nervous system
CNS	Child Neurology Society
CNV	Copy number variant
CP	Cerebral palsy
CPAP	Continuous positive air pressure
CPS	Carbamoyl phosphate synthase deficiency
CRP	C-reactive protein

CSF	Cerebrospinal fluid
CSVT	Cerebral sinus venous thrombosis
CSWS	Continuous spike and wave during slow sleep
CTX	Cerebrotendinous xanthomatosis
CV	Cardiovascular
CVS	Cyclic vomiting syndrome
CVST	Cerebral venous sinus thrombosis
Cx	Cortex
CZP	Clonazepam
d/o	Disorder
DA	Dopamine
DBS	Deep brain stimulation
DD	Developmental delay
DDx	Differential diagnosis
DHPR	Dihydropteridine reductase deficiency
DM	Diabetes mellitus
DM	Dorsomedial nucleus of the thalamus
DMD	Duchennes muscular dystrophy
DMT	Disease-modifying therapies
DNA	Deoxyribonucleic acid
DRPLA	Dentato-rubro-pallidoluysian atrophy
DSPD	Delayed sleep phase disorder
DTR	Deep tendon reflex
Dx	Diagnosis
EBV	Epstein—Barr virus
ECMO	Extra-corporeal membrane oxygenation
ECSWS	Epilepsy with continuous spike and wave during slow wave sleep
ED	Emergency Department
EDS	Excessive daytime sleepiness
EDSS	Expanded Disability Status Scale
EEG	Electroencephalogram
EEG	Electroencephalogram
EKG	Electrocardiogram
EM	Essential myoclonus
EMG	Electromyography
ENT	Ear nose throat
EOG	Electro-oculogram
ERT	Enzyme replacement therapy
ESES	Electrical status epilepticus of sleep
ESR	Erythrosedimentation rate
ET	Essential tremor
EW	Edinger-Westphal
FAO	Fatty acid oxidation disorder
FDP	Fructose 6-diphosphate deficiency
FEF	Frontal eye field
FHM	Familial hemeiplegic migraine
FHx	Family history

FSHD	Febrile seizures
Fxn	Function
GA I	Glutaric acidemia type I
GBS	Guillain—Barré syndrome
GERD	Gastro-esophageal reflux disease
GM1	Gangliosidosis, type 1
GM2	Gangliosidosis, type 2
GS	Gram stain
GSD	Glycogen storage disease
hr(s)	hour(s)
H/I	Hyperactive/Impulsive
HA	Headache
HC	Head circumference
HC	Head circumference
HCO_3	Bicarbonate
HD	Hemodialysis
HD	Huntington disease
HERNS	Hereditary endotheliopathy, retinopathy, nephropathy and strokes
HHT	Hereditary hemorrhagic telangiectasia
HIE	Hypoxic-ischemic encephalopathy
HMG-CoA	3-OH-3-methylglutaryl-coenzyme A synthase deficiency
HMSN	Hereditary motor-sensory neuropathy
HSAN	Hereditary sensory axonal neuropathy
HSV	Herpes simplex virus
Hx	History
IBD	Inflammatory bowel disease
ICH	Intracerebral hemorrhage
ICP	Intracranial pressure
IEM	Inborn errors of metabolism
IH	Idiopathic hypersomnia
IIH	Idiopathic intracranial hypertension
IL	Intralaminar nucleus of thalamus
IPE	Intraparenchymal echodensity
IPH	Intraparenchymal hemorrhage
IS	Infantile spasms
IVA	Isovaleric aciduria
IVH	Intraventricular hemorrhage
IVIG	Intravenous gammaglobulin
JME	Juvenile myoclonic epilepsy
KGD	Ketogenic diet
L	Left
LAS	Lance—Adams syndrome
LCHAD	Long-chain hydroxyacyl dehydrogenase deficiency
LDX	Lisdexamfetamine
LE	Lower extremity
LETM	Longitudinal extensive transverse myelitis

LGA	Lateral geniculate artery
LGN	Lateral geniculate nucleus of thalamus
LKS	Landau—Kleffner syndrome
LMN	Lower motor neuron
LMWH	Low molecular weight heparin
LP	Lateral posterior nucleus of thalamus
LPI	Lysinuric protein intolerance
MCA	Middle cerebral artery
MCHS	Myocerebrohepatopathy spectrum disorder
MDD	Multiple decarboxylase deficiencies
Meds	Medications
MEG	Magneto encephalography
MELAS	Mitochondrial encephalopathy w/lactic acidosis and stroke-like episodes
MENSA	Myoclonic epilepsy myopathy sensory ataxia
MERRF	Myoclonic epilepsy w/ragged red fibers
MGN	Medial geniculate nucleus of thalamus
min	Minute(s)
MLD	Metachromatic leukodystrophy
MLF	Medial longitudinal fasciculus
MMA	Methylmalonic acidemia
MNGIE	MyoNeuroGastroIntestinal encephalopathy
mo(s)	Month(s)
MPS	Mucopolysaccharide disorders
MR	Magnetic resonance
MR	Mental retardation
MR SPECT	Magnetic resonance spectrometry
MRI	Magnetic resonance imaging
MS	Multiple sclerosis
MSE	Myoclonic status epilepticus
MSG	Monosodium glutamate
MSLT	Multiple sleep latency test
MSUD	Maple syrup urine disease
MTHFR	5,10-Methylenetetrahydrofolate reductase
NARP	Neurogeneic weakness w/ataxia and retinitis pigmentosa
NBIA	Neurodegeneration with brain iron accumulation
NBIA	Neurodegeneration with brain iron accumulation
NBS	Newborn screening
NCHCT	Noncontrast head CT
NCL	Neuronal ceroid lipofuscinosis
NCS	Nerve conduction studies
NCSE	Nonconvulsive status epilepticus
NCV	Nerve conduction velocity
NE	Norepinephrine
NKH	Nonketotic hyperglycinemia
NMO	Neuromyelitis optica
NREM	Nonrapid eye movements

OCB	Oligoclonal bands
OCD	Obsessive compulsive disorder
OCP	Oral contraceptive pill
OCT	Optical coherence tomography
ODD	Oppositional defiant disorder
OMS	Opsoclonus—myoclonus—ataxia syndrome
ON	Optic neuritis
OSA	Obstructive sleep apnea
OTC	Ornithine transcarbamylase deficiency
OXA	Oxazepam
p/w	Presenting with
PA	Propionic acidemia
PAH	Phenylalanine hydroxylase
PAN	Polyarteritis nodosum
PAS	Perinatal arterial ischemic stroke
PB	Periodic breathing
PBD	Peroxisome biogenesis disorder
PCA	Posterior cerebral artery
PCD	Pyruvate carboxylase deficiency
PD	Parkinson disease
PDC	Pyruvate dehydrogenase complex
PDD	Pervasive developmental disorders
PDH	Pyruvate dehydrogenase deficiency
PECS	Picture exchange communication system
PET	Positron emission tomography
PFC	Prefrontal cortex
PFO	Patent foramen ovale
PGB	Phenobarbital
PGK	Phosphoglycerate kinase deficiency
PHT	Phenytoin
PICA	Posterior inferior cerebellar artery
PKAN	Pantothenate kinase—associated neurodegeneration
PKU	Phenylketonuria
PLIC	Posterior limb of the internal capsule
PLMD	Periodic limb movement disorder
PLMS	Periodic limb movements of sleep
PME	Progressive myoclonic epilepsy
PMH	Past medical history
POMS	Pediatric onset multiple sclerosis
PPI	Proton pump inhibitor
PPMS	Primary progressive multiple sclerosis
PPRF	Paramedian pontine reticular formation
PSG	Polysomnography
Pt	Patient
PVD	Progressive ventricular dilatation
PVL	Periventricular leukomalacia
R	Right
RA	Rheumatoid arthritis

RAM	Rapid alternating movements
RAPD	Relative afferent pupillary defect
RCD	Respiratory chain defect
RCT	Randomized control trial
RCTs	Randomized clinical trials
REM	Rapid eye movements
RF	Rheumatic fever
RIS	Radiologically isolated syndrome
RLS	Restless leg syndrome
RN	Reticular nucleus of thalamus
RRMS	Relapsing-remitting multiple sclerosis
RSV	Respiratory syncytial virus
s	Second(s)
SAH	Subarachnoid hemorrhage
SAH	Subarachnoid hemorrhage
SANDO	Sensory ataxia neuropathy dysarthria ophthalmoplegia
SCA	Spinocerebellar artery
SCD	Sickle cell disease
SDB	Sleep disordered breathing
SDH	Subdural hematoma
SE	Status epilepticus
SGH	Subgaleal hematoma
SLE	Systemic lupus erythematosis
SLM	Sternocleidomastoid
SMA	Spinal muscular atrophy
SN	Spasmus nutans
SNRI	Serotonin norepinephrine uptake inhibitor
SPMS	Secondary progressive multiple sclerosis
SVT	Sinovenous thrombosis
SWS	Slow wave sleep
SWS	Sturge Weber syndrome
Sx	Symptoms
sz(s)	Seizure(s)
TBI	Traumatic brain injury
TBI	Traumatic brain injury
TCA	Tricarboxcylic acid cycle
TCA	Tricyclic antidepressant
TF	Trifunctional protein deficiency
TGB	Tigabatrine
TH	Tyrosine hydroxylase
TM	Transverse myelitis
TMJ	Temporomandibular joint
TPH1	Tryptophan hydroxylase
TS	Tourette syndrome
TSC	Tuberous sclerosis complex
TTE	Transthoracic echocardiogram
TTH	Tension-type headache
u/l	Unilateral

UCD	Urea cycle disorder
UE	Upper extremity
UMN	Upper motor neuron
US	Ultrasound
VA	Visual acuity
VA	Ventral anterior nucleus of thalamus
VEP	Visual evoked potential
VGAM	Vein of Galen malformation
VGB	Vigabatrin
VL	Ventral lateral nucleus of thalamus
VPA	Valproic acid
VPL	Ventral posterolateral nucleus of thalamus
VPM	Ventral posteromedial nucleus of thalamus
w/o	Without
WD	Wilson disease
WHO	World Health Organization
WM	White matter
y	Year(s)
yo	Year-old
ZNS	Zonisamide

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1 Neurodevelopment and Neurologic Examination

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INTRODUCTION

Understanding normal childhood development and deviations is essential to the pediatric neurologist, for it allows for identification of developmental disorder etiologies, understanding of clinical features, prognosis, and potential interventions. Developmental milestone assessment allows one to identify a delay, confirm normality, provide a quantitative measure of current functioning, and document longitudinal progress or regression.

DEVELOPMENTAL MILESTONES

Milestones

Organized according to separate streams (Table 1.1).

Developmental Quotient

An estimate of a child's current level of functioning is often very accurate and aids in understanding of developmental concerns. Calculating a developmental quotient (DQ) in each functional area provides a quantitative measure of current functioning as it suggests when further evaluation should be performed.

$$\text{Developmental Quotient} = \frac{\text{Developmental Age}}{\text{Chronological Age}} \times 100$$

DQ $>$ 85 = routine developmental screening
DQ 75$-$85 = close developmental follow-up
DQ $<$75 = comprehensive evaluation

Neurobehavior and Adaptive Skills

Concomitant evaluation of neurobehavioral development and adaptive skills should be completed. Neurobehavioral disturbances are common in developmental disabilities. These can range from atypical (i.e., stereotypies), deviant (i.e., attentional aberrations), or maladaptive (i.e., noncompliance) behaviors. Adaptive skills, often referred to as self-help skills, require competence in motor and cognitive abilities at age-specific developmental level. Failure to attain success is not necessarily equivalent to having active deficits. Certain developmental failures, however, are important "*red flags*" (Table 1.2).

TABLE 1.1 Normal Developmental Milestones According to Age of Presentation

Age	Gross Motor	Visual / Fine Motor	Expressive Language	Receptive Language	Social Skills
0–2 wk				Alerts to sound	
1 mo	Lifts head only	Visually fixes Follows to midline	Coos		Smiles socially Regards face
2 mo	Holds head in midline Lifts chest off table	Follows past midline			Recognizes parents
3 mo	Supports on forearms in prone	Follows in circular pattern Hand open at rest		Orients to sound	Reaches for familiar people or objects Smiles at reflection
4 mo	Lifts head prone to wrist Rolls prone to supine	Manipulates fingers Shakes rattle	Ah-goos		Enjoys looking around
5 mo	Rolls supine to prone Sits unsupported		Razzes		
6 mo	Sits alone	Reaches with either hand Transfers Uses raking grasp	Babbles		Recognizes strangers
8 mo	Comes to sit Crawls		"mama"/"dada" indiscriminately		
9 mo	Pivots when sitting Pulls to stand Creeps or cruises	Uses pincher grasp Finger feeds Looks to dropped items Probes with forefinger		Gestures	Starts to explore Plays pat-a-cake or peek-a-boo
11 mo			1st word "mama"/"dada" discriminately	1-step command with gesture	

12 mo	Walks alone	Voluntarily releases Uses mature pincher grasp Drinks from cup	Immature jargon 2nd word		Imitates actions Comes when called Cooperates with dressing
14 mo			3rd word	1-step command without gesture	
15 mo	Creeps up stairs Walks backward	Builds 2-block tower Scribbles	4–6 words		Solitary play
17 mo			Mature jargon 7–20 words	Identifies 5 body parts	
18 mo	Runs Throws ball Pushes or pulls objects	Turns 2–3 pages Spoon-feeds	Says "thank you," "stop it," "let's go"	Names 1 picture on command	Copies parents in tasks Recognizes self in mirror Shares enjoyment Points
19 mo			2-word combos	Identifies 8 body parts	
21 mo	Squats Holds hand up stairs	Builds 5-block tower Drinks well from cup	2-word sentences 50 words		Asks for food Asks to use toilet
24 mo	Jumps in place Kicks ball Climbs stairs without help	Turns 1 page well Removes clothes, shoes Imitates pencil stroke Opens box, doors	Uses pronouns inappropriately	2-step command	Parallel plays Tolerates separation
30 mo	Throws ball overhead Jumps with both feet off floor	Unbuttons clothes Holds pencil in mature fashion	Uses pronouns appropriately Repeats 2 digits	Knows gender Understands the concept of "one"	

(continued)

TABLE 1.1 Normal Developmental Milestones According to Age of Presentation (Continued)

Age	Gross Motor	Visual / Fine Motor	Expressive Language	Receptive Language	Social Skills
3 y	Alternates feet up stairs Pedals tricycle	Dresses & undresses partially Copies circle	Uses 3-word sentences Uses plurals Minimum 250 words Repeats 3 digits	Knows full name Knows age Uses prepositions Identifies 3 colors Knows "what" questions	Group plays
4 y	Alternates feet down stairs Hops	Buttons clothing Catches ball Copies square	Asks questions		Tells "tall tales" Plays cooperatively with group
4.5 y				3-step command	
5 y	Skips Jumps over obstacles	Ties shoe Copies triangle Spreads with knife	Uses adult sentence structure Asks what a word means	Knows home address	Plays competitive games Abides by rules Likes to help in household tasks

TABLE 1.2 Developmental Red Flags According to Age of Concern

Age	Red Flag
1 mo	Failure to alert, constantly irritable
2 mo	Rolling before 3 mo
3 mo	No social smile
4–5 mo	Poor head control, no laughing, no visual threat
6 mo	Not rolling, head lag
9 mo	W-sitting, scissoring, persistent primitive reflexes, absent babbling
12 mo	No protective reflexes, inability to localize sound
15 mo	No single words, persistent toe walking
18 mo	Hand dominance (before this age)
21 mo	Lack of social interaction
24 mo	Persistent poor transition, family does not understand speech
3 y	Extended family does not understand speech, persistent echolalic speech
5 y	Non-family members do not understand speech

PEDIATRIC NEUROLOGIC EXAMINATION

The pediatric neurologic exam mirrors, in many ways, the adult examination, but there are striking differences. The general physical exam is important and may aid in diagnosis; observation (behavior, motoric activity, social interaction) is a large part of exam. Key features, unique to the pediatric neurologic exam, include measurement of head circumference (HC), tone, and primitive reflexes. Below is a general outline of the basic examination. Should abnormalities be found in any area, a more comprehensive evaluation is warranted.

Measurements

Vital signs, weight, height, BMI calculation, and HC.

General

Routine HEENT, including fontanelles, lung, heart, GI, and skin exam.

Mental Status

Infants and young children—observations are primary assessment (environmental and visual attention, visual tracking, smile, social interaction, command comprehension and follow). *Older children*—evaluated with age-appropriate mental status testing (naming colors or objects, use of pronouns or prepositions, shape copy, coloring, writing or reading/comprehension).

Cranial Nerves

Full CN I–XII testing if cooperative. *Infants and younger children*—observation of spontaneous activity, quality and strength of cry, adequacy of suck and swallow, spontaneous eye movements, vestibulo-ocular reflex, response to light, visual threat, approach in visual fields, response to sound or loud noise (? startle).

Gross Motor

Observe baseline activity, resting posture, assess muscle bulk, range of motion, tone (ventral and horizontal suspension, head lag and axial). Often formal strength testing of specific muscles is not achievable and one must rely on observation (i.e., spontaneous movements, antigravity) as well as observation during play. Note dystonia, tremor, choreoathetosis, or other abnormal movements/dyscoordination.

TABLE 1.3 Primitive and Protective Reflexes

Reflex	Onset	Disappearance
Moro (startle)	Birth	2 mo
Walking (stepping)	Birth	6 wk
Rooting	Birth	4 mo
Asymmetric tonic neck (fencing)	1 mo	4 mo
Palmar grasp	Birth	5–6 mo
Plantar (Babinski)	Birth	~12 mo
Galant	Birth	4–6 mo
Parachute	6–7 mo	Becomes voluntary
Anterior protection	4–5 mo	Persists
Lateral protection	7 mo	Persists
Posterior protection	9 mo	Persists

Fine Motor

Assess grasp (rake, pincer), crayon/pencil grasp and use, ability to fasten buttons, manipulation of small objects.

Sensation

Detailed exam often difficult, document symmetry of response to tactile stimulation. Response to subjective testing (i.e., position & vibration) often difficult and inconsistent.

Coordination

Observe during play (i.e., stacking blocks, ball catch/throw, balance one foot, running) and hand use.

Reflexes

In addition to typical stretch reflexes, primitive reflexes should also be assessed. Deviations from typical pattern should raise concerns (Table 1.3).

Gait

Observe for asymmetry, especially arm swing/posturing during walking (stressed gait, hopping, skipping) or running. Wide-based ataxic gaits may be normal during early ambulation.

DISORDERS OF HEAD GROWTH

The measurement of HC is vital. Longitudinal measurements are plotted on standard growth curves; adjust for prematurity until ~24 mo of age. HC increases by 5 cm at these intervals, leading to the "rule of 3s, 5s, & 9s." (See Table 1.4.)

Microcephaly

Defined as <2 SD (standard deviation) from the normal distribution for age. HC <3 SD generally indicates concurrent intellectual disability.[1,2]

Primary Microcephaly

Results from abnormal cerebral genesis.[3] Evaluation requires assessment for known genetic etiologies.[4]

TABLE 1.4 Average Head Circumference by Age

Age	Average HC (cm)
Birth	35
3 mo	40
9 mo	45
3 y	50
9 y	55

Secondary Microcephaly

Results from injury to a previously normal brain. Etiologies include TORCH infections, HIE, metabolic diseases, or destruction from hemorrhage or stroke.

Macrocephaly

Defined as >2 SD from the normal distribution for age and results from a variety of causes,[5] including subdural hematoma, external hydrocephalus,[6] neurogenetic syndromes (leukoencephalopathies,[7] chromosomal syndromes), neurocutaneous-vascular syndromes,[8] or increased intracranial pressure (aqueductal stenosis, infectious causes, hemorrhage) (see Table 1.5).

TABLE 1.5 Representative Causes of Microcephaly and Macrocephaly

	Microcephaly	Macrocephaly
Anatomic	Neural tube defects, holoprosencephaly, lissencephaly, schizencephaly, polymicrogyria, pachygyria	Neurocutaneous disorders (Sturge–Weber, Klippel–Trénaunay–Weber), autism spectrum disorders, achondroplasia, cerebral gigantism, mass (cyst, tumor, abscess), hematologic (hemorrhage, arteriovenous malformation), primary bone disorders, hydrocephalus
Isolated	AR primary microcephaly type I–VI, X-linked microcephaly	Familial megalencephaly, pseudotumorcerebri
Metabolic	Maternal diabetes, phenylketonuria, methylmalonicaciduria, citrullinemia, NCL disorders, PDH, LD, infantile Krabbe	Leukodystrophies (Alexander, Canavan), lysosomal storage disorder (gangliosidoses, MPS)
Environmental	Congenital infection (TORCH, syphilis, HIV, enterovirus), meningitis, *in utero* toxin exposures (alcohol, tobacco, antiepileptic medications, cocaine), perinatal insult (hypothyroidism, hypopituitarism, hypoglycemia), ischemia, hypoxia	Toxins (lead, vitamin A deficiency or excess), meningitis, subdural hematomas
Genetic	Trisomies (13, 18, 21), Smith–Lemli–Opitz, Williams, Miller–Dieker, Wolf–Hirschhorn, Rubinstein–Taybi, Cockayne, Angelman, Cornelia de Lange, Rett	Fragile X, PTEN hamartoma syndromes, NF, TSC

ABNORMAL NEURODEVELOPMENT

Neurodevelopmental disability disorders are characterized by disturbance in developmental progress in one or more developmental domains. Prevalence of neurodevelopmental disabilities is ~12%.[9]

Global Developmental Delay and Intellectual Disability

Terminology

Developmental delay can be limited to a single specific domain (language, motoric, or social) or several developmental domains.

Global developmental delay (GDD) diagnostically refers to delays in 2 or more developmental domains, should be reserved for children <5 y of age, and arises from a wide variety of causes.[10,11] **Intellectual disability (ID)** is a disability characterized by significant limitation both in intellectual functioning and in adaptive behavior as expressed in conceptual, social, and practical adaptive skills[12]; measured by IQ testing in older children. **Adaptive skills** are those an individual must acquire to function within expectation in context of everyday life. At the core, both GDD and ID reflect disorders in learning. The diagnosis of GDD or ID should be made only after thorough evaluation and use of developmental testing.

Evaluation

Role of Pediatric Neurologist[13]: (1) ***Characterize and classify*** the precise neurodevelopmental disability. (2) Ascertain a possible ***underlying etiology*** (history, physical examination, selective laboratory and diagnostic testing). (3) Identify and arrange for needed ***supports*** and ***rehabilitation services*** and ***interventions*** (Early Intervention, school system, private therapies).[14] (4) Provide ***family counseling*** (recurrence risk, implications, prognosis, predicted outcome). (5) Identify possible ***intercurrent medical or behavioral conditions*** that require specific medical or other interventions (i.e., seizures, attentional issues, behavioral issues, spasticity, sleep).

History: (1) ***Birth and neonatal history:*** Pregnancy complications, infections, toxic exposures, perinatal issues, evidence of perinatal depression. (2) ***Past medical history:*** Hypotonia, poor feeding, seizures, recurrent infections, intolerance of fasting, lethargy with illness/fasting, vision and hearing, social skills. (3) ***Family history:*** Consanguinity, previous infantile/neonatal deaths or maternal pregnancy loss, ethnicity. (4) ***Psychosocial history:*** History of neglect or abuse. (5) ***Developmental history:*** Attainment of developmental milestones, competency in activities of daily living (toileting, dressing, feeding, hygiene). Ask about specific developmental status at a certain milestone age.

- Assess for loss of skills/regression
- Determine whether developmental delay is limited to single domain or more widespread

(6) ***Comorbidities:*** Autism spectrum disorders, paroxysmal behaviors, sleep disturbance, behavioral disorders, feeding difficulty.

Physical Examination: (1) ***General exam:*** General somatic features dysmorphism (may make specific measurements, e.g., ear position, intercanthal distance, philtrum length), abnormal head size, neurocutaneous stigmata, spine defects, hepatosplenomegaly, cardiac murmurs, congenital anomalies and deformities. (2) ***Neurological exam:*** Acuity, visual field defects, pupil abnormalities, ocular position, fundoscopic changes, nystagmus, facial paresis, hearing, excessive drooling, dysphagia, dysarthria, head

tilt, asymmetries or lateralizing features, abnormal limb movements, weakness, dexterity, and coordination.

Neurodevelopmental Assessment[13] (1) ***Observation of child:*** Playing with toys and interacting in the environment. Assess for level of play, spontaneous speech, command comprehension and follow (age-appropriate, simple or complex), cognitive skills (naming, shape copy, drawing, writing, reading, spelling, proverbs). (2) ***Standardized screening tools and developmental assessments***[11]***:***

- *Screening:* Denver Developmental Screening Test, 2nd edition (0–6 y); Bayley Infant Neurodevelopmental Screener (3–24 mo); Battelle Developmental Inventory Screening Test (6 mo–8 y); Early Screening Inventory (4–6 y); First STEP for Preschool Evaluation (33–74 mo)
- *Cognitive Screening:* Slosson Intelligence Test (2 wk–adult); Cognitive Adaptive Test / Clinical Linguistic and Auditory Milestone Scale (1–36 mo)
- *Language Screening:* Early Language Milestone Scale, 2nd edition (birth–36 mo); Peabody Picture Vocabulary Test–Revised (30 mo–adult); Token Test (3–12 y)
- *Neuromotor Screening:* Milani-Comparetti Motor Development Screening Test–R (birth–2 y); Alberta Infant Motor Scales (birth–indep. walking); Toddler and Infant Motor Evaluation (4 mo–3.5 y)
- *Behavioral Screening:* Vineland Adaptive Behavior Scales (preschool–18 y); Pediatric Symptom Checklist (3–18 y); Eyberg Child Behavior Inventory (2–16 y)

Determining Etiology

Diagnostic categories: Chromosomal abnormalities, Fra(X) and other known MR/genetic syndromes (>200 known genes), fetal environmental syndromes, neurometabolic disorders, neurocutaneous disorders, hypoxic-ischemic encephalopathy, other encephalopathies, epileptic syndromes, CNS dysgenesis syndromes.

Reason for Testing

Often considerable family motivation to understand reason for child's developmental disability. Etiologic diagnosis may only occasionally lead to specific therapy, but a diagnosis can provide understanding of etiology, presumed pathophysiology, improve prognostic information, allow recurrence risk assessment (genetic etiologies, toxin exposures), carrier screening, and prenatal testing. Proactive management of medical and behavioral comorbidities is important. Specific diagnosis can relieve caregiver anxiety and uncertainty, allow for involvement in support and research networks, and reduce continued diagnostic testing and limit invasive testing.

Yield of Testing

Wide variation in reported yield of diagnostic testing for GDD (10%–81%).[15–17] Genetic testing, specifically with chromosomal microarray (CMA), has the highest diagnostic yield, and karyotype gives higher yield, especially in patients with syndromic/dysmorphic features or with more severe impairment.[11] Rule of ⅓s[13]:

- ⅓: etiologic diagnoses are made subsequent to history and exam alone.
- ⅓: lab testing used to confirm diagnosis suspected on basis of history and exam.
- ⅓: etiologic diagnosis made on basis of lab testing alone, usually on a screening basis.

Major etiologic categories (75% of causes)[13]:

- Genetic syndromes, chromosomal anomalies[18]
- Intrapartum asphyxia[19,20]
- Cerebral dysgenesis[21,22]
- Early severe psychosocial deprivation
- Antenatal toxin exposure

Diagnostic Studies

Guidelines from expert opinion and consensus statements are available from the American Academy of Neurology/Child Neurology Society[23] and specifically on the genetic and metabolic testing in children with GDD.[11] The American College of Medical Genetics (see URL) has a number of resources, including guidelines for evaluation of GDD or ID.[24] When obtaining diagnostic tests, consider diagnostic yield given data from proband and family history, clinical features, and availability, invasiveness, and cost of testing.[11] (1) **Standard history, physical examination.** (2) **Ancillary testing:** EEG, EMG/NCV, neuroimaging, metabolic screening. (3) **Karyotype:** Overall yield of 4% to 18.6%, and should be reserved for patients with signs of a specific chromosomal syndrome or parental history of multiple miscarriages.[11] (4) **Subtelomeric FISH testing:** 2nd line, yield of 0.5% to 7.4%.[11] (5) **Chromosomal microarray:** 7.8% to 10.6% yield of diagnosis of copy number variation (CNV); yield is highest if syndromic features. Recommended as first-line whole genome testing over FISH and karyotyping for children with unexplained GDD/ID.[11] (6) **X-linked genetic testing:** Accounts for 10% of all cases of ID. There are >70 genes for X-linked ID (XLID), 42% positive yield in definite X-linked families, and 17% in possible X-linked families. XLID genetic screening by panel should be considered in males with strong history suggestive of X-linked inheritance.[11] (7) ***FMR1*: >200 repeats; associated with dysmorphism, ID, and social impairment. The diagnostic yield is at least 2% in males and females with mild GDD/ID.[11] (8) ***MECP2* gene studies:** 1.5% in girls with moderate/severe GDD/ID, <0.5% of males with GDD/ID.[11] *MECP2* genetic testing is recommended for girls with severe impairment, regardless of whether the specific clinical features of Rett syndrome are present. (9) **Metabolic Screening:** Overall yield of 0.2% to 4.6%; depends on presence of clinical indicators and characteristics of population tested. Yield <1% if appropriate population not selected, but can increase to 14% with stepwise approach.[11]

Factors that increase risk of metabolic disorder:

- FH of similarly affected child
- Parental consanguinity
- Developmental regression
- Episodic decompensation with metabolic stress (fever, illness, fasting)
- Suggestive dysmorphology
- Failure of appropriate head or somatic growth
- Ophthalmologic/retinal abnormalities
- Failure to perform successful newborn screening (list of metabolites screened varies between states)
- Neuroimaging: basal ganglia involvement in absence of intrapartum asphyxia, unexplained white matter changes

Initial metabolic testing includes:

- Capillary blood gas, serum lactate, ammonia, LFTs, serum amino acids, and urine organic acids
- Additional metabolic testing may include serum carnitines and acylcarnitines (FAOD), creatine synthesis and transport disorders, and congenital disorders of glycosylation (CDG), or specialized testing (see Chapter 7)

(10) **Lead screening:** Target to those with known identifiable risk factors.[23] (11) **Thyroid screening:** Not indicated if newborn screening successful, unless there are specific features of thyroid dysfunction or increased risk (e.g., Down syndrome). (12) **Neuroimaging:** Brain MRI is recommended by the AAN as part of the diagnostic evaluation of the child with GDD,[23] particularly if associated physical features including abnormal head size, focal or motor findings. Diagnostic yield is 48.6% to 65.5%,[23] but lower for treatable etiology.

Motor Delay

Evaluation

Motor delay can be due to impairments of tone, strength, motor control, and/or motor planning. Neuromuscular and neurodegenerative disorders can also present with motor delay. See examples of "Neuromotor Screening" tests above.

- Suspect **neuromuscular** when there is significant feeding or swallowing difficulties, hypotonia (axial or appendicular), failure or regression of motor milestones, depressed or absent DTRs. Take family history. (See Chapter 6.)
- Progressive and increased developmental gap in any domain—consider **metabolic or genetic** degenerative disorders (See Chapter 7). More urgent and/or more definite diagnosis needed.
- Assess for deficits in **proprioception**, **sensory integration**, **visual processing**.

Cerebral Palsy (CP)

Definition

Nonprogressive, static impairment in neuromotor control (movement and posture) due to deficit/lesion in developing brain that can occur pre-, peri-, or postnatally but diagnosed by age 2 y. Injury occurs before brain has matured. Primary abnormality must be motor impairment, but 70% have additional impairments (typically mental retardation). There is no regression/loss of skills, only delay. Not always permanent; 20% to 30% with mild impairments at 1 y show no motor deficit by 7 y.[25,26]

Epidemiology

Worldwide incidence is 2 to 2.5 per 1,000 live births. In United States 10,000 infants per year develop CP. More common in very premature or term: 36% born <28 wk, 37% at term.[25] Prevalence has increased among premature as more have survived.[27]

Classification[28]

Helpful for descriptive purposes, but not necessarily correlate with prognosis or treatments. ***Based on 4 components:*** Type and severity of motor dysfunction, anatomical distribution, associated impairments, timing of causal event (pre-, peri-, postnatal). ***Tone:*** hypo- or hypertonic. ***Motor impairment:*** Spastic, ataxic, dyskinetic (dystonia or choreoathetosis), or mixed. ***Anatomical distribution:*** Diplegia, hemiplegia, quadriplegia, etc.

Comorbidities

ID, 30% to 65%; epilepsy, 30% to 50%; speech and language impairments, 40%; visual deficits, 40%; hearing impairments, 5% to 15%; psychosocial and behavioral problems, 20%; autism spectrum disorders, 9%.[28] Speech and language impairments can include mild articulation problems, severe dysarthria, verbal dyspraxia, or complete inability to communicate intelligibly.[26]

Etiologies[28]

Heterogeneous list of causes/risk factors, including brain malformations, infections, genetic disease, early anoxic injury. Most commonly reported risk factors include prematurity, low birth weight, birth asphyxia, infection, maternal fever during delivery, ischemic stroke, coagulation disorders, multiple gestations, maternal thyroid disease, placental abnormality. Despite frequent mention, most are not *caused* by birth asphyxia and are rarely preventable by obstetricians. Although finding an abnormality on testing or neuroimaging often leads to correlation with CP, cannot always assume causation. Alternative hypotheses for etiologies have been proposed, including possibility that CP may be due to numerous diverse genomic abnormalities, which have not been thoroughly explored.

Clinical Presentation

See Table 1.6.

Diagnostic Assessment

Per AAN Practice Parameter 2004.[25]

(1) ***Confirm diagnosis & classification:*** History and exam. Confirm no findings of progressive or degenerative condition. Classify as described above. (2) ***Screen for associated conditions:*** Developmental delay/MR, ophtho/hearing impairments, speech/language delay, feeding/swallowing impairment. (3) ***EEG:*** If history suggestive of seizures. (4) ***Neuroimaging:*** Recommended if etiology not yet established by perinatal imaging or other early/neonatal studies. MRI preferred to CT. (5) ***Metabolic and genetic studies:*** Not routinely recommended except as follows:

- If brain malformation found on imaging.
- If brain malformation not found on imaging and one of following:
  - Clinical history/medical evaluation reveals no specific etiology
  - Child displays evidence/episodes of metabolic decompensation
  - Family history of childhood disorder associated with "CP"

(6) ***Coagulation studies:*** Perform if unexplained stroke on imaging.

Treatment[26,27]

Should be multidisciplinary.

(1) ***Supportive:*** Early Intervention, PT, OT, speech therapy, bracing, assistive devices, psychosocial & educational supports, augmentative/nonverbal communication training when needed, participation in adaptive sports (e.g., swimming). (2) ***Antispasticity medications:*** Oral meds can be sedating but used for generalized spasticity. Include diazepam (central muscle relaxant), dantrolene (decreases contractility of skeletal muscles), baclofen (GABA agonist), tizanidine (central α-2-agonist). Also consider intrathecal baclofen pump. (3) ***Botulinum toxin A:*** Injections provide relief for 4 to 6 mo for localized spasticity. (4) ***Surgical:*** Tenotomy to enhance gait and prevent progressive skeletal deformities. Osteotomy for secondary bone deformities. Selective posterior rhizotomy for spastic hypertonicity. (5) ***Other:*** Anticholinergic medications or surgery (e.g., transposition of parotid and/or submandibular ducts) for severe drooling, AEDs for seizures, ophthalmology referral (patching and/or surgery) for strabismus, treatment of comorbid neurobehavioral disorders.

Prognosis: Ambulation: Independent sitting by 1.5 to 2 y is a good prognostic indicator of eventual ambulation out of the home. Independent sitting by 2 to 4 y indicates eventual household ambulation and possibly outdoors with assistance for short distance. If unable to sit by 4 y, unlikely to walk.

TABLE 1.6 Classification and Presentation of Cerebral Palsy

CP Type (Tone)	Clinical Presentation	Commonly Cited Etiologies
Diplegia/ paraplegia (spastic)	Most common type of CP Weakness/spasticity of all 4 extremities, but leg > arm; termed *paraplegic* if arm impairment limited to ↑ DTRs Often hemiplegia superimposed on diplegia due to asymmetric white matter cystic lesions Normal/hypotonic in first 4 months Slowly progressive leg spasticity, evident after 1 year, but ↑ DTRs and abnormal postural reactions Unable to crawl on 4 extremities (use "army" crawl) Sit independently late/never Stand on toes, knees flexed, lumbar lordosis Hyperreflexic in all limbs (clonus, + Babinski, crossed adductor response) Scissoring in ventral suspension Hip subluxation/dislocation common from constant adduction	Periventricular leukomalacia in preterm
Hemiplegia (spastic)	Second most common CP Limb weakness on one side of body Asymmetry rarely evident in 1st few months (upper extremity Moro is symmetric) Fisting of 1 hand noticed 4 mo Tone & reflex changes in UEs usually not until 6 mo (so do not rule out CP if see early handedness but no other "hard" evidence prior to 6 mo) Asymmetric tightness of elbow flexors & wrist pronators is 1st sign Hand dominance established during 1st year (which is never normal) Tone & reflex changes in LEs usually not until 10 mo; more often 12–15 mo Ankle hypertonia usually 1st sign in LEs Delayed asymmetric crawl using normal arm/ leg & dragging contralateral arm/leg Delayed walk Final determination of motor disability may not be evident until 2–3 y Never associated with unilateral face weakness Seizures in 50% May have verbal (if dominant lesion) or nonverbal (if nondominant lesion) deficits	Periventricular hemorrhagic infarction in premature Cerebral malformations (usually migrational defects), infarction & hemorrhage in term

TABLE 1.6 Classification and Presentation of Cerebral Palsy (Continued)

CP Type (Tone)	Clinical Presentation	Commonly Cited Etiologies
Quadriplegia (spastic)	Weakness of all 4 limbs, legs usually more severe (*double hemiplegia* = arms more severe than legs) Early stage of hypotonia before spasticity and hypertonia (as above) but identification as neurologically abnormal occurs early Severe developmental delay Characteristic supine posture: retraction head/neck, flexion at elbows, clenched hands, legs extended Seizures in 50% Moro & tonic-neck reflexes persist & obligatory beyond 6 mo Often supranuclear bulbar palsy (dysphagia, dysarthria) Microcephaly common Vision & ocular motility dysfunction common	Intrauterine malformations HIE in term infant in minority
Ataxic (hypotonic)	Uncommon type of CP Hypotonia trunk/extremities & normal DTRs (pure ataxic form) Some may have mixed ataxic-spastic: will appear hypotonic but have ↑ DTRs Infants rarely display overt ataxic signs (intention tremor, head titubation) Wide-based gait eventually develops Frequent mental retardation	Genetic factors implicated in pure ataxic CP
Athetoid/dyskinetic (hypotonic)	In hyperbilirubinemia, see signs of kernicterus at 3–5 d (high-pitched cry, opisthotonos, ↑ DTRs, ↑ extensor tone) Extensor tone gradually decreases to normal at 2 wk Tone variable/normal at 6 wk Tone "floppy" at 3 mo with return of normal DTRs Obligatory asymmetric tonic neck reflex persists Delayed motor milestones Athetoid/dystonic posturing appears at 12–18 mo during voluntary movement Hypotonia progresses to rigid/cogwheel hypertonia but DTRs still normal Hypertonia & involuntary movements may gradually ↑ over next year (can mistake for progressive CNS disorder)	Hypoxic-ischemic injury of basal ganglia Previously kernicterus was more common

Adapted from Taft LT. Cerebral palsy. *Pediatr Rev.* 1995; 16:411–418. Fenichel GM. *Clinical Pediatric Neurology: A Signs and Symptoms Approach*, 6th ed. Philadelphia, PA: Saunders Elsevier; 2009.[26,27]

In terms of CP type: babies with spastic hemiplegia typically walk by 1.5 to 3 y. Some type of ambulation usually obtained in 80% to 90% of diplegia, 50% of quadriparesis, and 70% of dyskinetic type.[26]

Speech and Language Delay

Language Development

Predictors: Development of language and vocabulary depends heavily on family and early school experiences.[29] Socioeconomic background affects known variability in acquisition of milestones. A well-known study showed that economically advantaged children were exposed to an average of 215,000 words per week vs. 62,000 words in economically disadvantaged families, and by age 3 y, children had a vocabulary of 1,100 words vs. 525 words.[30] Similarly, the amount of time spent reading to children affects later reading proficiency.[31]

Bilingualism: Learning two languages can occur simultaneously or sequentially. If simultaneous, first words may be slightly delayed but still within a normal range. Children may mix the languages (words or grammar) early on, but are usually proficient in both languages by 3 to 5 y of age. If a child has normal language-learning potential, *bilingualism itself does NOT cause language delay!*[31,32]

Normal developmental milestones: (See Table 1.1.) Additional helpful mnemonics:

Rule of 4s for understandable speech: Amount of understandable speech is child's age in years divided by 4. At 1 y, 25% of speech is understandable; at 2 y, 50% understandable; at 3 y, 75% understandable; at 4 y, 100% understandable.[29]

Clues by age: (Note that there is variability in normal range and these are generalizations.)[29,31]

- **½ y** ("part of a year"): can speak "parts" of words (i.e., babbling)
- **1 y:** speaks **1** word, follows **1**-step command, points with **1** finger (i.e., index pointing)
- **1½ y:** "between words and sentences"
- **2 y:** speaks **2**-word sentences, follows **2**-step commands, points to **2** pictures
- **3 y:** speaks **3**-word sentences, follows **3**-step commands, points to **3** colors (not yet naming, however), knows **3** basic facts (first name, age, gender)
- **4 y:** names **4** colors, competent in the **4** *P*s (plurals, pronouns, prepositions, past tense)
- **5 y:** knows **5** facts/categories (full name, address, shapes, some numbers, some letters)

Definition and Classifications

Many classification systems: Based on etiology/pathophysiology (e.g., primary vs. secondary language disorders, developmental vs. acquired types), impairments (e.g., expressive, receptive, mixed, and/or pragmatic), and functional limitations. Language delays can be classified separately from problems with speech production (see below).

American Speech–Language–Hearing Association (ASHA): Defines a speech disorder as impairment in speech articulation, fluency, or voice. Language disorder defined as impairment in comprehension, spoken, written, and/or other symbol systems, including language form (syntax, phonology, morphology), content (semantics), and/or function (pragmatics).[33]

DSM-IV: Describes four disorders under category of "Communication Disorders," including 2 disorders of language (expressive language disorder and mixed receptive–expressive language disorder) and 2 disorders of speech production (phonological disorder and stuttering).[34] Exclusion of distinct receptive language disorder due to observation that in children, receptive disorders seldom, if ever, occur without concomitant deficits in expression (as opposed to Wernicke aphasia in adults). DSM-IV language disorders allow for existence of comorbid conditions (e.g., mental retardation) as long as language deficits are in excess of what would be expected with the comorbid disorder alone.

Specific language impairment (SLI): Core feature is impairment in language skills disproportionate when compared with achievement in nonlanguage developmental domains.[35] Clinically delayed expressive and/or receptive language, or impaired scores on standardized language skill tests. Discrepancy between language and nonverbal skills with normal nonverbal performance IQ and language measure 1.25 SD below the mean or below the 10th percentile.[31,35] This term/definition often used in research settings and sometimes interchanged with mixed receptive–expressive language disorder; however, unlike DSM-IV, SLI does not allow for contributory comorbid disorders (low IQ, genetic disorders, environmental deprivation, hearing loss, autism spectrum, emotional disturbances).[36]

Primary Speech/Language Delay[29,31,36]

Language impairment in the absence of a causative underlying disorder.

(1) **Developmental speech and language delay ("maturational delay" or "late talker"):** Delayed speech with normal comprehension, articulation, intelligence, and emotional relationships. Considered a normal variant, but is diagnosis of exclusion because ~50% still have language impairments at 5 y of age. More common in boys; family history is risk factor. Excellent prognosis, with normal speech by school age. Once child starts talking, little long-term risk of speech, language, or learning disorder. Speech–language therapy can be effective.

(2) **Expressive language disorder:** Similar presentation as above, so difficult to distinguish at young age. Not self-correcting, so requires active intervention. Speech–language therapy can be effective.

(3) **Receptive language disorder:** Delayed speech but also sparse, agrammatic, and articulation deficits. May not point or look toward objects/people in environment named by others due to poor comprehension. Normal response to nonverbal auditory stimuli. Speech–language therapy less effective than for expressive types, and prognosis not as good; rarely develop normal oral language (so actually presents as mixed expressive–receptive).

Secondary Speech/Language Delay[29,31,36]

Deficit/delay attributable to another condition.

Includes: autism spectrum disorder (See Chapter 15), CP w/ oromotor spasticity/coordination difficulty, dysarthria (problem with motor control of muscles), ID, hearing impairments, selective mutism, traumatic brain injury, genetic syndromes (e.g., Williams, Turner, and velocardiofacial syndrome—all have pragmatic deficits).

Childhood apraxia of speech: Difficulty imitating and spontaneously producing speech sounds due to impairment in planning, sequencing, and coordination of oral–motor movements. Hallmark is inconsistency of

sound production. May say a word clearly once but then cannot repeat it if requested. Speech can appear labored, and children often appear frustrated.

Evaluation

See "standardized screening tools" earlier in the chapter. All children with a language delay should have formal audiological evaluation. Always elicit a family history of language milestones. Screen for an autism spectrum diagnosis.[37] (See Chapter 15.) Evaluate for otitis media with effusions. Refer to speech and language pathologist. If clinical signs/symptoms of underlying disorder leading to secondary language delay, evaluate according to suspected disorder.

Treatment

Speech and language therapy effective for expressive disorders, less so for receptive disorders, and works best if longer than 8 wk. Parents can provide the therapy if 1st trained by a speech–language pathologist.[29] If <3 y, refer to local Early Intervention program. If >3 y, refer to public school early childhood program. Children will need IEP (Individualized Education plan) in preschool and school.

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ONLINE RESOURCES

www.childneurologysociety.org/resources/practice-parameters – Child Neurology Society; see practice parameters

www.acmg.net – American College of Medical Genetics; see publications, practice parameters

www.summaries.cochrane.org – See Neurology subset for evidence-based reviews

2 Neuroanatomy and Lesion Localization

Aaron D. Boes and Verne S. Caviness

SKULL ANATOMY

Description

The brain is protected by bony encasement of the skull. See Figure 2.1 for anatomy of bones, sutures, and fontanelles. Sphenoid bone is major component of middle cranial fossa (not visible in figure) and surrounds anterior temporal lobes and houses pituitary gland.

Craniosynostosis

Premature closure of a suture: sagittal → **scaphocephaly**, unilateral coronal → **anterior plagiocephaly**, unilateral lambdoid → **posterior plagiocephaly**, metopic → **trigonocephaly**, bilateral coronal → **brachycephaly**.

MENINGES, VENTRICLES, AND CEREBROSPINAL FLUID (CSF)

Meninges

The brain is protected by 3 layers of meninges (Fig. 2.2): (1) **Dura mater** ("tough mother"): outermost layer, tough connective tissue adherent to skull. Separates into outer periosteal and inner meningeal layers around dural venous sinuses. Inner projections form falx cerebri and tentorium cerebelli. (2) **Arachnoid:** middle layer, surrounds CSF-filled subarachnoid space. (3) **Pia mater:** innermost layer, closely adherent to the brain.

Pachymeninges (thick meninges) = dura. Leptomeninges (thin meninges) = arachnoid + pia.

Meningeal Spaces

EPIDURAL SPACE: Potential space between skull periosteum and dura. Contains middle meningeal artery; laceration → epidural hematoma (arterial, convex, not cross suture lines, often overlying skull fracture). **SUBDURAL SPACE:** Potential space between dura and arachnoid. Traversed by bridging veins from subarachnoid space to dural venous sinuses; rupture → SDH (venous, concave, can cross suture lines). **SUBARACHNOID SPACE:** actual space between arachnoid and pia. Contains CSF and vessels. SAH often from spontaneous aneurysm rupture or trauma; classic symptom is "thunderclap" headache.

Ventricular System and CSF Flow (Fig. 2.3)

CSF PRODUCTION: Produced by choroid plexus: a modified capillary network lying mostly within the lateral ventricles.

CSF FLOW: From 2 lateral ventricles → interventricular foramina of Monro → 3rd ventricle → cerebral aqueduct of Sylvius (within midbrain) → 4th ventricle (at pontomedullary junction on posterior surface of

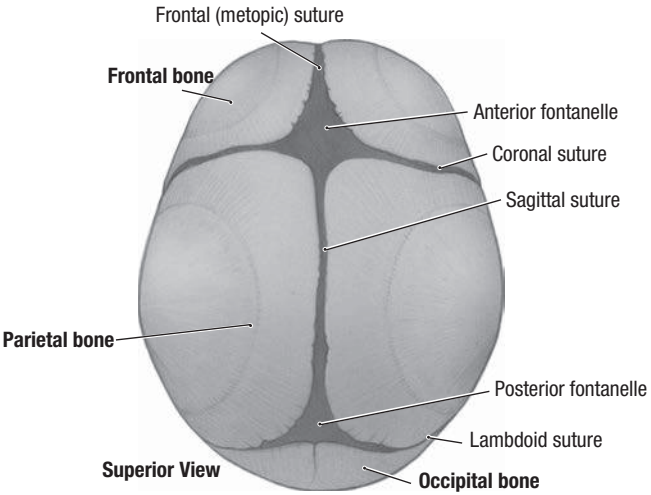


FIGURE 2.1 Skull Anatomy. (From Agur AM, Dalley AF. Grant's Atlas of Anatomy, 13th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2012.)

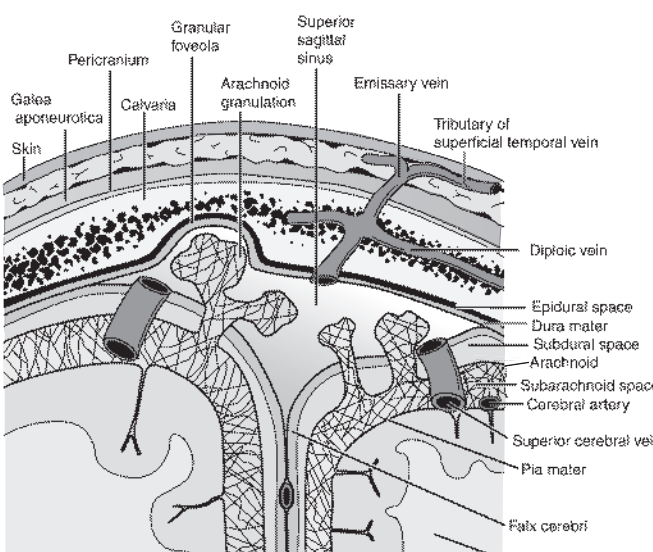


FIGURE 2.2 Scalp, Meninges, and Associated Structures. (From Chung KW, Chung HM. *Gross Anatomy*, 4th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2011.)

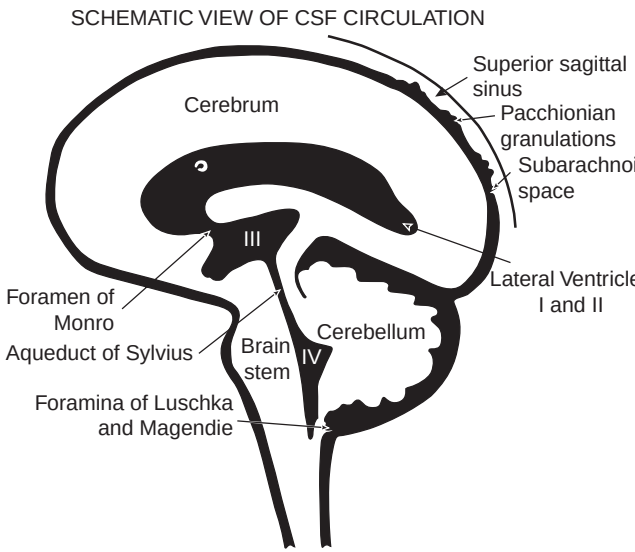


FIGURE 2.3 Ventricles and CSF Flow. (From Cohen ME, Duffner PK. *Weiner & Levitt's Pediatric Neurology*, 4th ed. Philadelphia: Lippincott Williams & Wilkins; 2003.)

brainstem) → exits ventricular system via foramen of Magendie (midline) and 2 foramina of Luschka (lateral) → subarachnoid space.

CSF REABSORPTION: Reabsorbed into venous system at arachnoid granulations penetrating into dural sinuses.

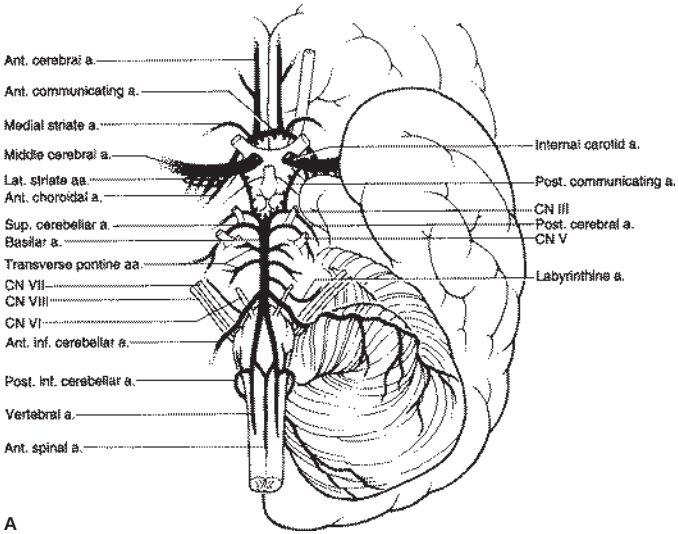
HYDROCEPHALUS: Noncommunicating/obstructive: Blockage within ventricular system preventing outflow (commonly at cerebral aqueduct). **Communicating:** Blockage of CSF after it exits ventricles; disruption of reabsorption in subarachnoid space. **Symptoms:** HA, irritability/lethargy, N/V, bulging fontanelle (in infants), papilledema, ophthalmoplegia (commonly CN VI palsy, vertical gaze palsy/"sunsetting" from pressure on dorsal midbrain).

VASCULAR ANATOMY

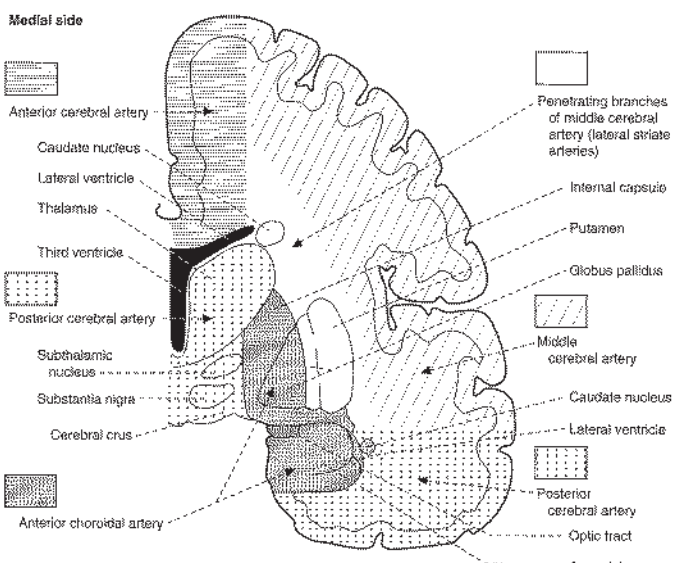
See Figure 2.4 for overview of vascular anatomy. Stroke syndromes are described in subsequent sections.

OVERVIEW OF CNS TOPOGRAPHY

Major divisions of the CNS (Fig. 2.5) include the spinal cord, brainstem, diencephalon (thalamus and hypothalamus), cerebellum, basal ganglia (BG), and cerebral cortex. The cerebral cortex, forming the surface of the forebrain, is characterized by a species-typical pattern of gyral elevations (protrusions) and sulci (valleys) between the gyri. The **interhemispheric fissure** divides the right and left hemispheres, which are connected by the **corpus callosum**, a massive white matter commisural tract seen in the midline brain. The **central sulcus** ("Rolandic fissure") separates the frontal and parietal lobes. The **lateral sulcus** ("Sylvian fissure") forms superior boundary of the temporal lobe.

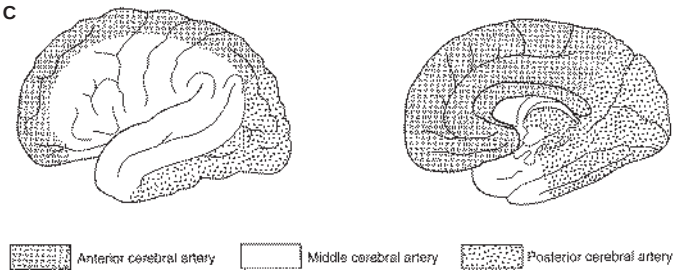


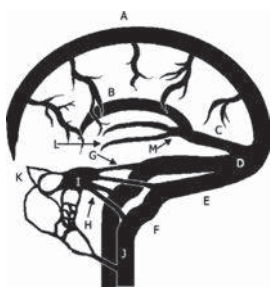
A



B

FIGURE 2.4 A: Arteries of the base of the brain and brainstem, including the arterial circle of Willis. **B:** Coronal section through the cerebral hemisphere at the level of the internal capsule and thalamus showing the major vascular territories. **C:** Cortical territories of the 3 major cerebral arteries. (**A–C** from Fix JD . *High-Yield Neuroanatomy*, 4th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2009.) **D:** Venous anatomy. (From Greer DM, et al. *Pocket Neurology*. Philadelphia, PA: Lippincott Williams & Wilkins; 2010.)





A. Superior sagittal sinus
B. Inferior sagittal sinus
C. Straight sinus
D. Confluence of sinuses
E. Transverse sinus
F. Sigmoid sinus
G. Superior petrosal sinus
H. Inferior petrosal sinus
I. Cavernous sinus
J. Internal jugular vein
K. Ophthalmic veins
L. Basal vein of Rosenthal
M. Great cerebral vein of Galen

FIGURE 2.4 *(Continued)*

Cerebral Cortex

Frontal Lobe (Fig. 2.6A)

PRIMARY MOTOR CX (BA 4): Lesion causes contralateral UMN deficits most prominent in distal muscles/fine motor skills. Legs represented on medial surface. Moving inferiorly along lateral surface: trunk/UE/face. **PREMOTOR CX (BA 6):** Involved in motor planning. Lesion causes apraxia ± contralateral weakness. **INFERIOR FRONTAL GYRUS:** Dominant side

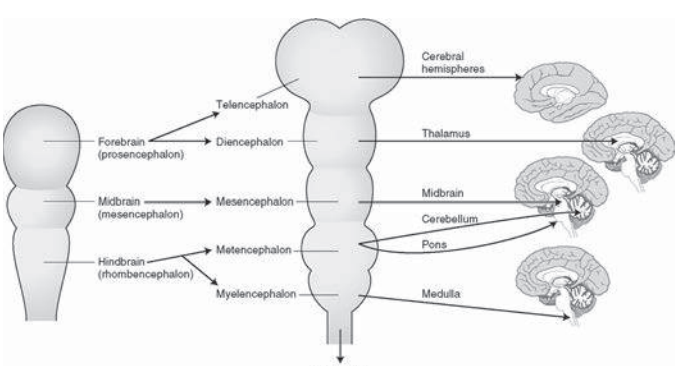


FIGURE 2.5 CNS Development. (From Mehta S, et al. *Step-Up to USMLE Step 1*, 4th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2010.)

lesion causes Broca's aphasia (BA 44, 45), nondominant side involved in prosody, nonverbal communication. **MIDDLE FRONTAL GYRUS:** Includes frontal eye fields (FEF, BA 8). FEF directs gaze toward contralateral side (e.g., left FEF directs gaze to right). Lesion = gaze directed toward lesion. Stimulation = gaze directed away (e.g., look away from seizure focus). **SUPERIOR FRONTAL GYRUS:** Involved in working memory, attention. **ORBITOFRONTAL AND MEDIAL PREFRONTAL/ANTERIOR CINGULATE:** Localization often difficult; may cause disinhibition, emotional dysregulation, lack of empathy, lack of planning/myopia for the future. Posterior lesions may cause akinetic mutism, abulia.

Temporal Lobe

ANTEROMEDIAL: Includes hippocampus (lesion = anterograde memory deficit), amygdala (lesion = fearlessness). **SUPERIOR TEMPORAL/WERNICKE'S AREA (BA 22):** Lesion = verbal comprehension impairment on dominant side (Wernicke aphasia), sensory dysprosody on nondominant side. White matter lesion deep to temporal lobe may cause contralateral

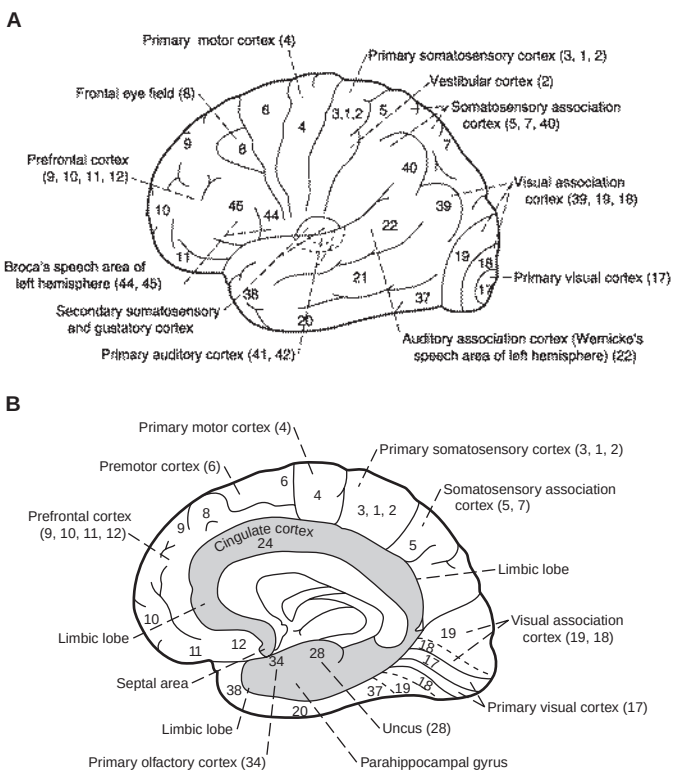


FIGURE 2.6 Cerebral Cortex Anatomy and Syndromes of Cortical Lesions.
A, B: Surface of the cerebral cortex: Lateral and medial surface of the cerebral cortex with Brodmann's areas. **C, D, E:** Focal destructive hemispheric lesions and the resulting syndromes. (From Fix JD. *High-Yield Neuroanatomy*, 4th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2009.)

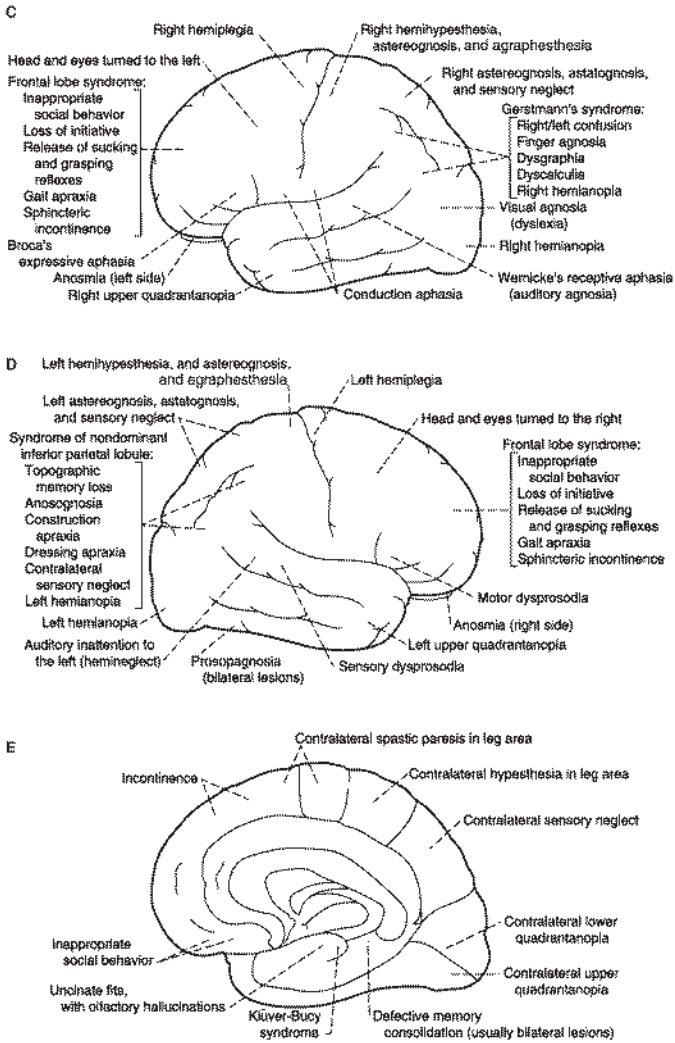


FIGURE 2.6 *(Continued)*

superior quadrantanopia. **INFERIOR TEMPORAL LOBE:** "What" visual pathway involved in visual recognition. Occipitotemporal junction lesion may cause prosopagnosia (inability to identify faces).

Parietal Lobe

PRIMARY SOMATOSENSORY CX (BA 3, 1, 2): Lesion = hemihypesthesia and astereognosis of contralateral face/body. Homunculus parallels motor cortex: Legs on medial surface; trunk/UE/face moving inferiorly along lateral surface. **SUPERIOR PARIETAL (BA 5, 7):** Lesion = contralateral neglect (particularly nondominant side), contralateral astereognosis, astatognosis

(inability to recognize body position in space). **INFERIOR PARIETAL:** ***Angular gyrus (BA 39)*** caps the superior temporal sulcus. ***Supramarginal gyrus (BA 40)*** caps Sylvian fissure. Inferior parietal lesion on dominant side may cause **Gerstmann syndrome:** L–R confusion, acalculia, alexia, finger agnosia, agraphia. Nondominant lesion: anosognosia, construction apraxia, neglect, apraxia for dressing, topographic memory problems. BL parieto-occipital infarcts cause **Balint syndrome:** simultagnosia (inability to perceive visual world in coherent fashion, often as single objects without Gestalt view), optic ataxia, ocular apraxia. CL lower quadrantanopsia: may result from underlying optic radiations en route to cuneate gyrus. **POSTEROMEDIAL CX:** Includes medial parietal cortex and posterior cingulate. Bilateral injury severely impairs consciousness. Region is active in self-referential tasks.

Occipital Lobe

Primarily visual. **CUNEUS** (above calcarine sulcus) represents lower visual field. **LINGUAL GYRUS** (below calcarine sulcus) represents superior visual field. Fovea represented on **OCCIPITAL POLE**. **Anton syndrome:** cortical blindness without awareness of deficit, often seen with lesion of association visual cortices; Alexia without agraphia may result from dominant occipital lesion and splenium of CC.

Major Stroke Syndromes Involving Cerebral Cortex

(For complete details, see Chapter 18. Also see Figure 2.6C–E.)

MIDDLE CEREBRAL ARTERY (MCA): (1) **Superior MCA:** Contralateral hemiparesis (face, UE > LE), expressive aphasia (dominant), gaze deviation toward lesion. (2) **Inferior MCA:** Contralateral sensory loss (face, UE > LE), homonymous hemianopia, Wernicke's aphasia (dominant), neglect (nondominant). (3) **Proximal MCA:** Combination of superior and inferior symptoms.

ANTERIOR CEREBRAL ARTERY (ACA): Contralateral leg weakness, apraxia, sensory loss, urinary incontinence. Bilateral lesion more likely to result in abulia/akinetic mutism.

POSTERIOR CEREBRAL ARTERY (PCA): Homonymous hemianopia, visual recognition difficulty, contralateral sensory loss (thalamus).

Visual System

Principles: Eye and optic nerve pathology causes monocular symptoms. More posterior lesions tend to be more congruous, meaning the visual field deficits are equal in each eye. The lower visual field is transmitted along superior optic radiation in parietal lobe, superior visual field along inferior optic radiation in temporal lobe. Occipital pole typically has both PCA and MCA blood supply and tends to be spared in infarct of these vessels. Extraocular muscles are controlled by CN III, IV, and VI (Fig. 2.7).

Basal Ganglia

The BG (Fig. 2.8) are nuclei deep in the brain involved in starting, stopping, and sequencing movements as well as maintaining posture. This is part of the extrapyramidal motor system, which refers to motor accessory structures outside of the corticospinal system.

MAJOR BG STRUCTURES: Caudate, putamen, globus pallidus, subthalamus, substantia nigra. **Striatum** = caudate + putamen. **Lentiform nucleus** =

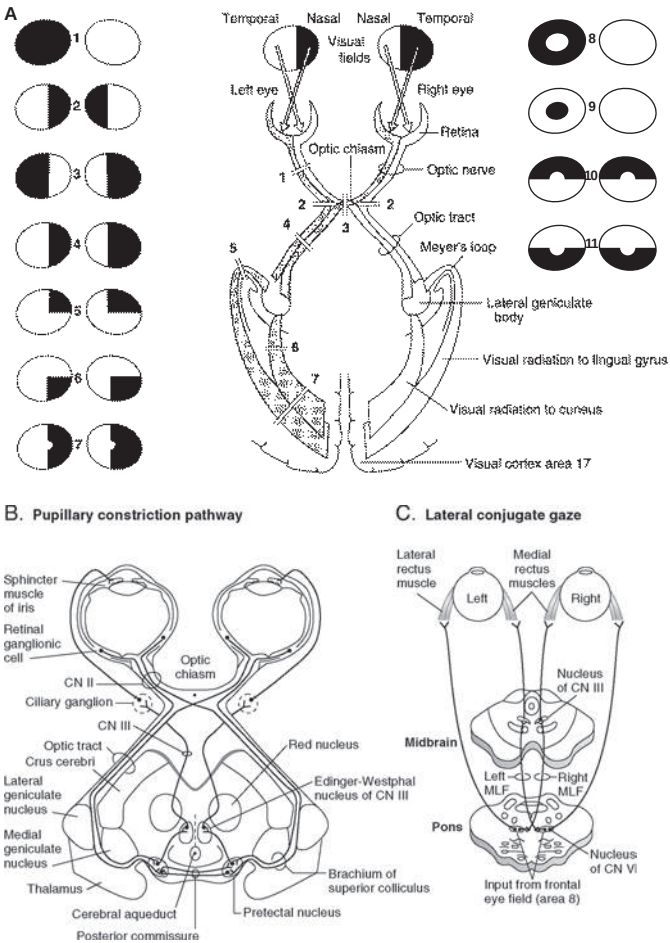
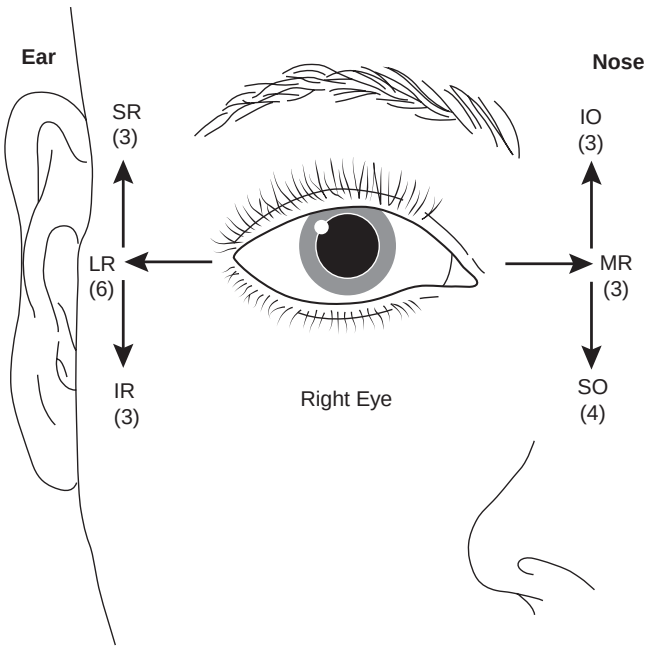


FIGURE 2.7 Visual System Anatomy. A: The visual pathway from the retina to the visual cortex showing visual field defects. (1) Ipsilateral blindness; (2) binasal hemianopia; (3) bitemporal hemianopia; (4) right hemianopia; (5) right upper quadrantanopia from severing optic radiations of the temporal lobe; (6) right lower quadrantanopia from severing optic radiations of the parietal lobe; (7) right hemianopia with macular sparing; (8) left constricted field as a result of end-stage glaucoma; (9) left central scotoma as seen in optic (retrobulbar) neuritis in multiple sclerosis; (10) upper altitudinal hemianopia as a result of bilateral destruction of the lingual gyri, located inferior to the calcarine sulcus; (11) lower altitudinal hemianopia as a result of bilateral destruction of the cuneus gyri, located superior to the calcarine sulcus. (From Fix JD . *High-Yield Neuroanatomy*, 4th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2009.) **B:** Pupillary constriction pathway. **C:** Lateral conjugate gaze. (**B, C** from Mehta S, et al. *Step-Up to USMLE Step 1*, 4th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2010.) **D:** Extraocular muscles. (From Cohen ME, Duffner PK. *Weiner & Levitt's Pediatric Neurology*, 4th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2003.)



MR = Medial Rectus	LR = Lateral Rectus
IO = Inferior Oblique	SO = Superior Oblique
SR = Superior Rectus	IR = Inferior Rectus
3 = 3rd Cranial Nerve	
4 = 4th Cranial Nerve	
4 = 6th Cranial Nerve	

D

FIGURE 2.7 *(Continued)*

globus pallidus + putamen. The complex circuits of the BG are less clinically useful than knowing the types of deficits that accompany BG lesions.

Movement Disoders Associated with BG Lesions

PARKINSONISM: Resting tremor, bradykinesia, hypokinesia, rigidity, shuffling gait, mask-like facies, may accompany substantia nigra deficits. **CHOREA:** Sudden, "dance-like" jerky movements without purpose, most notably evident distally in the extremities, but may be generalized. Caudate implicated. Seen with Sydenham chorea, Huntington's, SLE, Wilson's, pre- and perinatal injury. **ATHETOSIS:** Writhing snake-like movements, emphasizing slow alterations between flexion and extension. Caudate implicated, but other BG structures often affected. Similar DDx to chorea but also consider kernicterus, metabolic disorders, medication side effects among others. **BALLISM:** Dramatic flailing movement of a limb, emphasizing proximal joints or one side of body. Contralateral subthalamic nucleus commonly involved. **DYSTONIA:** Sustained abnormal posturing not related to joint fixation. Contralateral globus pallidus commonly involved.

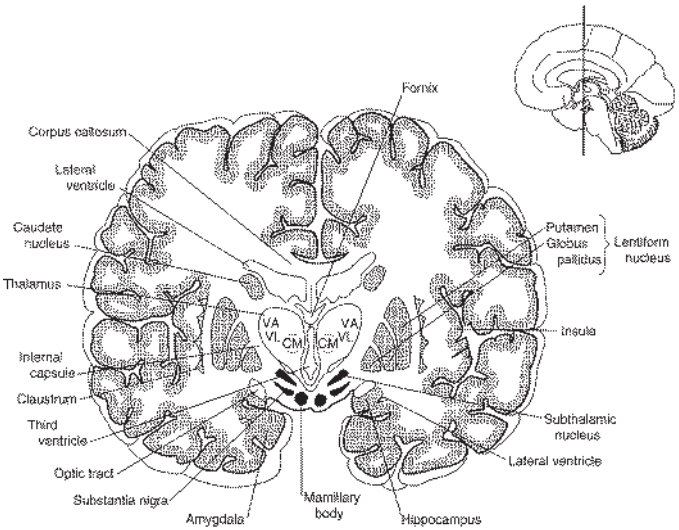


FIGURE 2.8 Basal Ganglia Structures in Coronal Cross Section. CM, centromedian nucleus; VA, ventral anterior nucleus; VL, ventral lateral nucleus. (From Fix JD. High-Yield Neuroanatomy, 4th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2009. Modified from Woolsey TA, et al. *The Brain Atlas: A Visual Guide to the Human Central Nervous System,* 2nd ed. Hoboken, NJ: John Wiley & Sons; 2003.)

Diencephalon: Thalamus and Hypothalamus

Thalamus

A major hub of connectivity between subcortical and cortical structures, including a required synapse for sensory information en route to cortex (olfaction = exception).

THALAMIC BLOOD SUPPLY: The thalamus receives blood from branches of PCA (paramedian [may also come off basilar], posterior choroidal [branch of P2, PCA], thalamogeniculate [inferolateral, branch of P2, PCA], tuberothalamic). Anterior choroidal often supplies LGN.

THALAMIC CLINICAL SYNDROMES: Deficits varied and difficult to distinguish from cortical lesions, including hemiparesis, hemisensory loss, memory loss, changes in mood, pain, aphasia, apathy, coma, visual field deficits, neglect. **Dejerine–Roussy syndrome:** Hemisensory pain syndrome secondary to thalamic lesion. A dystonia of the hand may accompany (thalamic hand syndrome). Lacunar stroke of thalamus may cause pure sensory loss of CL face, arm, leg.

Hypothalamus

Involved in regulation of autonomic and endocrine systems.

BLOOD SUPPLY: Richly supplied by branches of circle of Willis, rarely infarcts.

LESIONS: May cause temperature dysregulation, mood alterations, change in sexual function or pubertal development, hypopituitarism/hormonal changes, diabetes insipidis, bitemporal hemianopia (from pressure on optic chiasm), somnolence, gelastic seizures, changes in appetite, obesity.

Craniopharyngioma and septo-optic dysplasia are common sources of hypothalamic dysfunction in children.

Cerebellum

Structure behind brainstem involved in coordination of movement, balance, cognition, and comparing predicted and anticipated sensory input. It connects to the brainstem via 3 paired peduncles: superior (midbrain), middle (pons), and inferior (medulla). Blood supply in cerebellum from SCA, AICA, PICA. The cerebellum is best thought of in terms of functional subdivisions for the purpose of localization.

Vestibulocerebellum

Includes the flocculonodular node and is connected with vestibular nuclei, influencing eye orientation, smooth pursuit, and truncal corrective movements. Dysfunction involves vertigo, coarse nystagmus, smooth pursuit deficit, truncal ataxia.

Spinocerebellum

Includes the vermis (midline of cerebellum) and paravermis regions of cerebellum. The vermis functions in axial and proximal motor coordination, with the more lateral paravermis having similar effect on more distal musculature. Dysfunction of vermis = truncal ataxia, dysfunction of paravermis = limb ataxia/dysmetria.

Cerebrocerebellum

Includes cerebellar hemispheres and efferents that exit cerebellum via dentate nucleus. Functions during complex movements, with a role in cognition as well. Dysfunction includes limb ataxia/dysmetria, intention tremor, nystagmus, dysarthria, scanning speech, as well as deficits in executive fxn, spatial cognition, language, and personality (**cerebellar cognitive affective syndrome**).

Pancerebellar lesion deficits

Ipsilateral ataxia—awkwardness of posture and gait, fall toward ipsilateral side, hypotonia, dysmetria (overshooting target), difficulty with RAM (dysdiadokinesia), scanning speech, decreased DTRs, and/or pendular reflexes, intention tremor, nystagmus (most pronounced with gaze toward lesion side), vertigo.

Tumors

Medulloblastoma and ependymoma more likely to affect vestibulo and spinocerebellum, while astrocytomas tend to affect the cerebrocerebellum.

Midbrain

Rostral

Red nucleus, superior colliculus, occulomotor nucleus of CN III (innervates extraocular muscles except superior oblique and lateral rectus), Edinger–Westphal (EW; involved in pupil accommodation/constriction).

Caudal

Inferior colliculus (auditory processing), trochlear nucleus (innervates CL superior oblique).

Midbrain Syndromes

Claude syndrome: CN III deficit + CL ataxia and tremor (rubrospinal tract involvement). PCA branches and top of basilar. **Weber syndrome:** CN III deficit + CL hemiplegia (descending corticospinal/corticobulbar tract involvement), PCA branches and top of basilar. **Benedikt syndrome:** CN III deficit + CL ataxia + CL hemiparesis, branches of PCA or basilar. **Parinaud syndrome:** Dorsal midbrain, supranuclear upgaze deficit, pupils do not constrict with accommodation, convergence–retraction nystagmus, eyelid retraction (Collier sign), skew deviation. Often seen with pinealoma and germinoma, supplied by branches of posterior choroidal.

Pons

Overview

Ventral pons occupied by descending corticospinal tracts (aka basis pontis). Tegmentum in dorsal pons contains ascending sensory fibers and ARAS nuclei critical for consciousness. The pons houses nuclei for motor CN V, VI, VII. CN VIII nuclei at pontomedullary junction. 4th ventricle is dorsal to pons.

Pontine Syndromes

Locked-in syndrome: Bilateral involvement of descending corticospinal tracts in ventral pons (basis pontis) results in complete paralysis with exception of some eye movements or blinking, paramedian branches of basilar. **Millard–Gubler syndrome:** Ventral pons (corticospinal tract, CN VI, VII). CL hemiplegia, ipsilateral gaze palsy, ipsilateral upper and lower facial weakness, paramedian branches of basilar. **Foville syndrome:** Involves nuclei of CN VI and VII, MLF, PPRF, contralateral weakness, contralateral hemisensory loss, paramedian branches of basilar. **Lateral inferior pontine syndrome/anterior inferior cerebellar artery (AICA):** Ipsilateral deafness, ipsilateral facial weakness in LMN distribution, ipsilateral hemiataxia (inferior cerebellum, inferior and middle cerebellar peduncles), CL sensory loss, ipsilateral Horner.

Medulla

Overview

Contains nuclei for CN VIII (pontomedullary junction), IX, X, XII. Corticospinal and medial lemniscus pathways decussate in caudal medulla.

Medullary Syndromes

Lateral medullary (Wallenberg) syndrome: N/V/vertigo, ipsilateral Horner, nystagmus, dysphagia, hoarse voice, hiccups, ipsilateral ataxia and gait instability, ipsilateral facial sensory loss, contralateral body sensory loss. Commonly seen in PICA infarct. **Medial medullary (Dejerine) syndrome:** Tongue deviation to side of lesion, contralateral proprioceptive loss, and contralateral hemiparesis. Paramedian branches of basilar and anterior spinal artery.

Cranial Nerves

Organization: (1) Name of nerve, (2) function(s), (3) pathway of nerve fibers, (4) lesion deficits, (5) common types of injury and syndromes.

CN I

Olfactory nerve. Smell. Traverses cribiform plate of ethmoid bone to olfactory bulb. Lesion = anosmia, injured in trauma (shearing), frontal mass,

meningitis, hydrocephalus. Foster Kennedy syndrome: ispilateral anosmia, ipsilateral optic atrophy, contralateral papilledema.

CN II

Optic nerve. Vision. Traverses retina to optic chiasm. Lesion = unilateral blindness, RAPD, optic atrophy. Injured in demyelination, MS, impinging mass.

CN III

Occulomotor nerve. (1) Eye movement, (2) innervates levator palpebrae to raise eyelid, (3) parasympathetic input to eye causing miosis (pupillary sphincter) and accommodation (ciliary muscle). Nuclei-contributing fibers include occulomotor and EW in rostral, dorsomedial midbrain with fibers exiting on ipsilateral ventral midline midbrain into interpeduncular fossa. Threads between SCA and PCA, cavernous sinus, superior orbital fissure. Innervates extraocular muscles (except lateral rectus and superior oblique), levator palpebrae muscle to raise eyelid. EW nucleus contributes parasympathetic fibers for lens accommodation and miosis. Lesion = eye turned down and out, ptosis, fixed and dilated pupil, paralysis of accomodation (cycloplegia). Damaged with uncal herniation, aneurysm, DM (spares outer parasympathetic fibers).

CN IV

Trochlear nerve. Innervates superior oblique muscle that intorts abducted eye and depresses adducted eye. Nucleus in caudal dorsomedial midbrain with fibers crossing posteriorly to exit on contralateral dorsal midbrain surface below inferior colliculus. Passes through cavernous sinus and superior orbital fissure. Lesion = elevation and extorsion of eye at rest, patient tilts head to contralateral side. Vertical diplopia with downgaze, most visible misalignment with downward contralateral gaze. DDx similar to CN III, CN IV as susceptible to pressure against free edge of tentorium cerebelli.

CN V

Trigeminal nerve. (1) Muscles of mastication, (2) facial sensation. Motor nucleus of V located in dorsal pons, sensory nuclei of V extends throughout brainstem. CN V origin in midpons, lateral surface. Divides into V1 ophthalmic (cavernous sinus, superior orbital fissure), V2 maxillary (foramen rotundum), V3 mandibular division (foramen ovale). Lesion = loss of sensation on ipsilateral face V1 above eye, including afferent corneal reflex, V2 sensation of upper lip to eye, V3 lower lip, chin, weak chewing muscles.

CN VI

Abducens nerve. Lateral rectus innervation for lateral eye movement. Nucleus located in caudal dorsomedial pons, fibers exit ventrally in midline at pontomedullary junction. Nerve traverses adjacent to petrous temporal bone, cavernous sinus, superior orbital fissure to innervate lateral rectus. Lesion = ipsilateral gaze palsy, horizontal diplopia. Most common isolated palsy. Congenital palsy seen in Duane syndrome.

CN VII

Facial nerve. (1) Facial expression and stapedius muscle innervation, (2) salivation, (3) taste ant ⅔ tongue, (4) lacrimation, (5) sensation of external ear. Nerve exits ventral pontomedullary junction lateral to CN VI, entering internal auditory meatus and facial canal, exits skull via stylomastoid foramen. Lesion = paralysis of facial expression, loss of efferent wing of corneal reflex, decreased taste, hyperacusis. Unilateral palsy seen in **Bell palsy**. Bilateral

palsy may be seen in **Guillain–Barré syndrome**. Congenital palsy seen in **Mobius syndrome**. **Gradenigo syndrome:** CN VI, VII lesion with retro-orbital pain secondary to petrous lesion often as consequence of untreated acute otitis media.

CN VIII

Vestibulocochlear nerve. (1) Maintenance of equilibrium, (2) hearing. Exits brainstem at pontomedullary junction just lateral to CN VII, enters internal auditory meatus, courses to inner ear. Lesions result in vertigo, nystagmus, disequilibrium, hearing loss, and tinnitus. Acoustic neuroma causes ipsilateral symptoms.

CN IX

Glossopharyngeal nerve. (1) Taste from posterior ⅓ of tongue, (2) innervates stylopharyngeus muscle, (3) stimulates salivation via parotid gland, (4) innervates carotid sinus and body, (5) sensation to external ear/ear canal, (6) sensation of pharynx. Nerve exits postolivary sulcus of medulla and exits jugular foramen. Lesion = lack of afferent gag, syncope secondary to carotid sinus, lack of taste on posterior tongue.

CN X

Vagus nerve. (1) Phonation, (2) swallowing, (3) palate elevation, (4) taste in pharynx, (5) cutaneous sensation of ear canal, (6) innervates viscera to splenic flexure. Nerve exits postolivary sulcus of medulla and exits jugular foramen. Lesion = hoarse voice, dysarthria, dysphagia, loss of efferent gag reflex, heart rate abnormalities.

CN XI

Accessory nerve. Innervation of SCM (turns head) and trapezius (elevates shoulder). Origin at C1–C6, fibers ascend through foramen magnum and exit via jugular foramen. Lesion = difficulty turning head to contralateral side or elevating ipsilateral shoulder. Cranial division of CN XI travels with vagus to innervate larynx (see CN X above).

CN XII

Hypoglossal nerve. Innervation of tongue muscles. Hypoglossal nucleus in caudal medulla exits medulla preolivary sulcus, through hypoglossal canal. Lesion = unilateral tongue weakness, deviation toward weak side, hemiatrophy (LMN only). (See Figure 2.9.)

SPINAL CORD

The spinal cord (Fig. 2.10) extends from the lumbar region of the vertebral column to the foramen magnum (the opening at the base of the skull). Spinal cord anatomy is segmental and consists of 31 pairs of nerves: 8 cervical, 12 thoracic, 5 lumbar, 5 sacral, 1 coccygeal.

Spinal Cord Lesions

UMN lesions: Spastic paresis, hyperreflexia, + Babinski sign. Seen with lesion anywhere from motor cortex, corona radiata, internal capsule, crus cerebri of midbrain, basis pontis of pons, medullary pyramids, lateral corticospinal tract of spinal cord. **LMN lesions:** Flaccid paralysis, areflexia, atrophy, fasciculations, fibrillations, down-going Babinski. Seen with anterior horn lesion, SMA, peripheral nerve injury. **Dorsal column injury:**

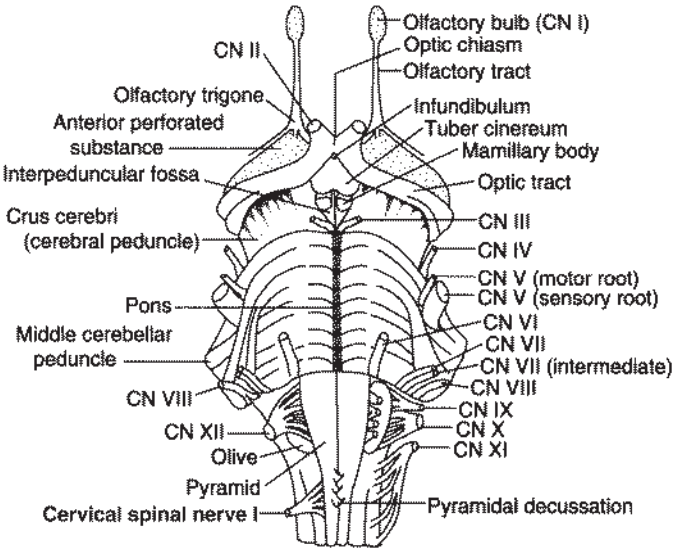


FIGURE 2.9 The Base of the Brain with Attached Cranial Nerves. (From Fix JD. *High-Yield Neuroanatomy*, 4th Ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2009.)

Loss of vibration, tactile discrimination and position sense, + Romberg sign. Seen with tabes dorsalis and B_{12} deficiency, often in combination with lateral column involvement. **Spinal cord hemisection (Brown-Séquard):** Ipsilateral loss of vibration, tactile discrimination and position sense, ipsi spastic paresis, contralateral loss of pain/temp. **Anterior spinal artery occlusion:** bilateral spastic paresis, bilateral loss of pain/temp, bilateral flaccid paralysis at level of infarct. Dorsal columns spared. **Syringomyelia:** LMN and ventral commissure affected, causing flaccid paralysis at

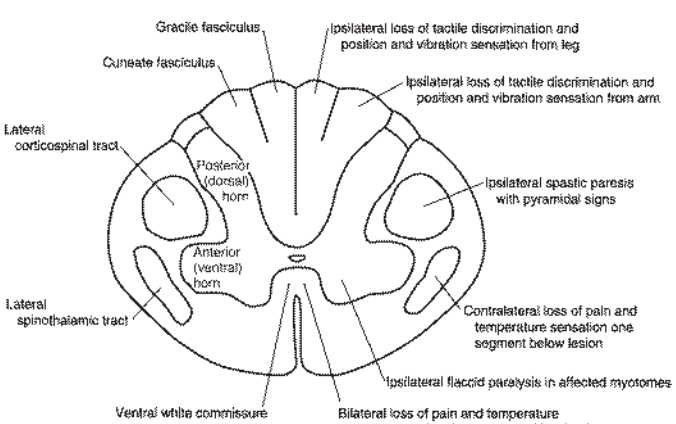


FIGURE 2.10 Transverse Section of the Cervical Spinal Cord. (From Fix JD. *High-Yield Neuroanatomy*, 4th Ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2009.)

TABLE 2.1 Clinically Important Spinal Cord Levels

Level	Commonly Tested Features
C5–C6	Biceps and brachioradialis reflex
C7–C8	Triceps reflex
T4	Dermatome of nipple
T8–T12	Umbilical reflex (deviation toward side of cutaneous stimulation). T10 dermatome–umbilicus
L1–L2	Cremesteric reflex (ipsi elevation of testi with thigh stroke)
L2–L4	Patellar reflex
S1	Ankle reflex
S1–S4	S1–S4: anal wink (perianal cutaneous stimulation elicits) S2–S4: bulbospongiosus (squeeze glans to elicit)

the level of lesion, bilateral loss of temp/pain 1 to 2 levels below lesion. **Cauda equina syndrome:** Gradual-onset severe unilateral radicular pain, muscle atrophy, unilateral saddle-shaped sensory loss. **Conus medullaris syndrome:** Sudden-onset bilateral saddle-shaped anesthesia with incontinence. (See Table 2.1.)

PERIPHERAL NERVOUS SYSTEM (FIGS. 2.11 AND 2.12)

Erb palsy: C5–C6 involved. Arm is limply adducted, internally rotated at shoulder, elbow pronation, wrist flexion. Together this creates the "waiter's tip" position.

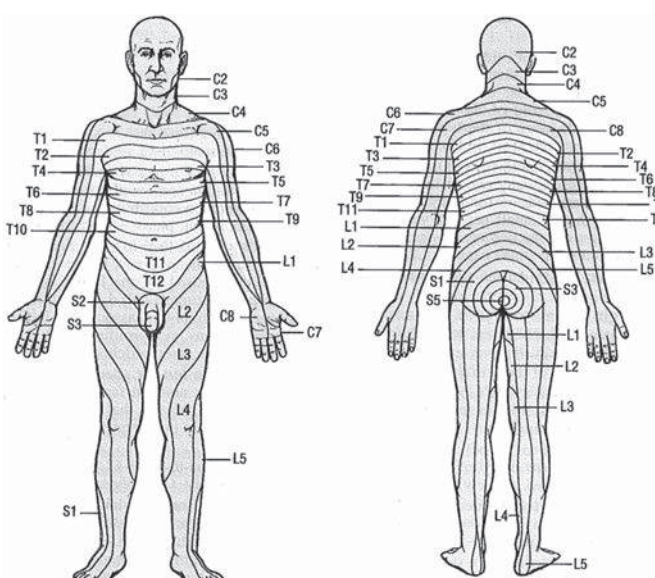
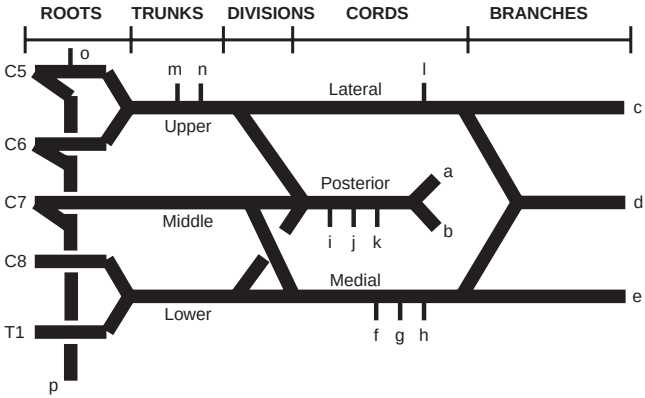


FIGURE 2.11 Dermatome and Peripheral Nerves. (From Flaherty AW, Rost NS. *Massachusetts General Hospital Handbook of Neurology*, 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2007.)



a. Axillary n.
b. Radial n.
c. Musculocutaneous n.
d. Median n.
e. Ulnar n.
f. Medial pectoral n.
g. Medial brachial cutaneous n.
h. Medial antebrachial cutaneous n.
i. Upper subscapular n.
j. Thoracodorsal n.
k. Lower subscapular n.
l. Lateral pectoral n.
m. Suprascapular n.
n. N. to the subclavius
o. Dorsal scapular n.
p. Long thoracic n.

FIGURE 2.12 Brachial Plexus. (From Greer DM, et al. *Pocket Neurology*. Philadelphia, PA: Lippincott Williams & Wilkins; 2010.)

Klumpke paralysis: Rarely occurs in isolation. It involves nerves C7–T1 and results in a claw hand deformity. There may be sensory deficits along the ulnar forearm. Horner syndrome may co-occur (miosis, anhydrosis, ptosis). Phrenic nerve palsy (C3–C5) may also co-occur.

ONLINE RESOURCES

Online Neuroanatomy and Neurovasculature Web-Atlas Resource. http://www.radnet.ucla.edu/sections/DINR/index.htm

University of Washington Interactive Atlases. http://www9.biostr.washington.edu/da.html

University of California–Davis Brain Maps. http://brainmaps.org/index.php

3 Pediatric Neuroimaging

Mark L. Schomer and Sanjay P. Prabhu

BRIEF OVERVIEW OF VARIOUS MODALITIES AND SELECTED TOPICS

Ultrasonography

Advantages include ready access, portability, multiplanar views, and lack of radiation. Disadvantages include limitation to children with open fontanelles and operator dependence for image quality. Primary utility is in the neonates, when there is suspicion for intracranial hemorrhage, hydrocephalus, extra-axial fluid collection, or midline defects. A good tool to follow the course of a hemorrhage and to assess for secondary obstructive hydrocephalus in the neonatal period.

Computed Tomography (CT)

Primarily limited by radiation dose in pediatrics, as children have a higher likelihood of developing radiation-associated diseases.[1] Utility is in the speed of acquisition and ability to image without sedation. Prior to ordering a CT scan, ask whether the same or higher-quality information can be obtained either through ultrasonography or through MRI techniques. This must be balanced against the potential need for sedation in children <5 to 7 y of age. Primary utility of CT in pediatrics is in acute trauma as well as for evaluation of blood products, increased ICP, pneumocephalus, or fractures.

CT Angiography (CTA)

Intravenous contrast study that provides high-resolution images of cerebral and neck vasculature. Depending on timing, the arterial or venous phase can be visualized. Utility in aneurysms, vascular disease (e.g., moyamoya), venous sinus thrombosis, and in acute setting of stroke (e.g., to visualize location, morphology, and extent of clot or narrowed vessel). CTA is complicated in children by small patient size, an inability to hold still and hold their breath, and smaller-caliber IVs making a timed bolus less accurate. These difficulties can be partially overcome by using multidetector CT, sedation, faster scanners, hand injection of contrast, and narrow reconstruction intervals with overlapping maximal intensity projections (MIPs).

Magnetic Resonance Imaging (MRI)

Primary benefits include lack of radiation and the availability to choose multiplanar sequences tailored to answer specific diagnostic questions. The primary disadvantage is the time required to obtain each sequence, which increases the likelihood that sedation will be needed to obtain high-quality images without motion artifact. However, recent advances enable more rapid sequences and motion correction techniques to mitigate the motion-related artifact. MRI is superior in evaluating the posterior fossa and detecting early cerebral edema, ischemia, and microhemorrhages. Further, MRI is able to characterize tissue better than do other imaging modalities.

Myelination Patterns

In general, myelination is associated with an increase in signal (i.e., white) on T1-weighted images and a decrease in signal on T2-weighted images. MRI myelination patterns follow a predictable course in the developing brain (Fig. 3.1 and Table 3.1), and correlate well with pathologic and

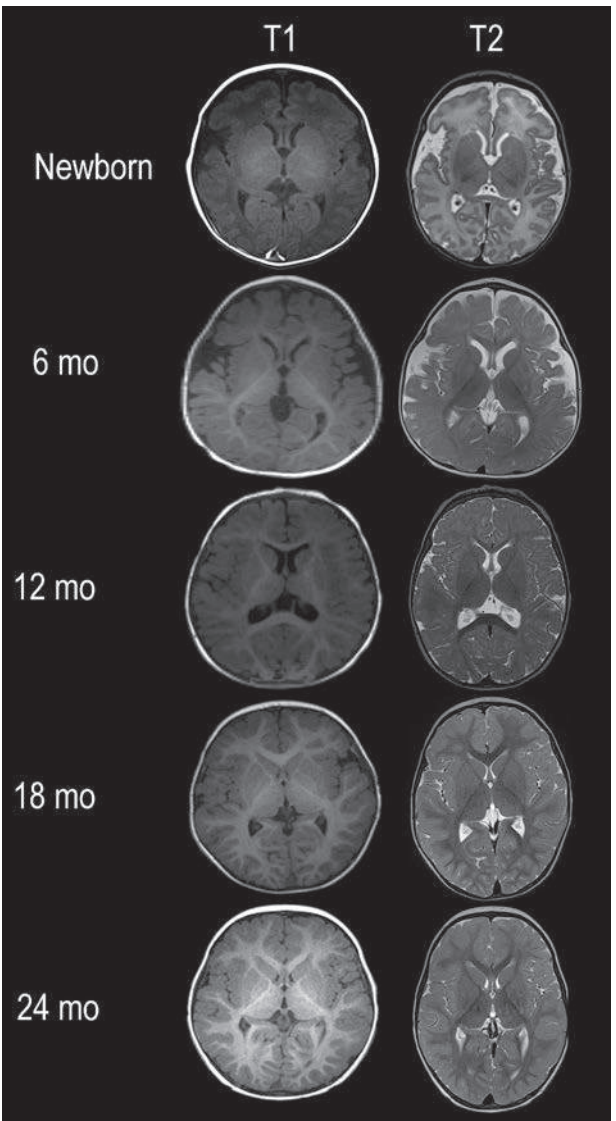


FIGURE 3.1 Developmental Myelination Patterns. Normal progression of myelination, as seen in T1- and T2-weighted images, from birth to 24 mo. Myelination occurs in a deep to superficial, caudal to cranial, and dorsal to ventral fashion.[25]

TABLE 3.1 Progression of Key Myelinated Structures

	Age (mo)				
	Neonate	**0–2**	**3–8**	**7–11**	**11–16**
Myelinated structures	Dorsal brainstem Ventrolateral thalami	Middle cerebellar peduncle	Cerebellar white matter Anterior limb of internal capsule Corpus callosum	Central semiovale Occipital lobes	Peripheral white matter of occipital lobes Central white matter of frontal lobes

Adapted from Kinney HC, Brody BA, Kloman AS, et al. Sequence of central nervous system myelination in human infancy. II. Patterns of myelination in autopsied infants. *J Neuropathol Exp Neurol.* 1988;47(3):217–234.[26]

developmental milestones.[2] T1-weighted images are preferred up to 8 mo of age, when the myelinated white matter will have high signal. T2-weighted images are preferred for assessing myelination after 8 mo of age, when the myelinated white matter will have low signal. Myelination is generally seen 2 to 4 mo earlier in T1 images than in T2 images.

T1-Weighted

Gray matter is darker than white matter, CSF is dark. All MRIs should include a sagittal T1 sequence: it assesses midline structures such as corpus callosum, pituitary, hypothalamus, and cerebellum.

T2-Weighted

White matter is darker than gray matter, CSF is bright.

Gradient Echo (GRE or T2*)

Changes in susceptibility can represent iron (e.g., hemosiderin from old bleeds), blood, and calcium; so these sequences are used in stroke, trauma, or a search for calcifications (note that CT is superior for detection of calcifications).

Fluid-Attenuated Inversion Recovery (FLAIR)

Another T2-weighted sequence, but suppresses the CSF signal. Useful for delineating many pathologies; sensitive but not specific.

Diffusion-Weighted Imaging (DWI)

Useful for delineating areas of decreased diffusion. Most common cause of decreased diffusion is ischemia, although it can also be seen in tumors, abscesses, encephalitis, traumatic brain injury, metabolic disorders, and intracerebral hemorrhage. This modality is very useful in the acute setting, as decreased diffusivity can often be seen within minutes to hours of the insult. Decreased diffusion is DWI bright (beware of "T2 shine through," a phenomenon in which the underlying T2 signal in the area is so bright that it crosses into the DWI. You can assess by just looking at the associated T2 image).

Apparent Diffusion Coefficient (ADC)

Used in combination with DWI images to show areas of decreased diffusion. Decreased diffusion is ADC dark.

Diffusion Tensor Imaging (DTI)

Useful for evaluating the integrity and direction of white matter bundles. Water diffusion is generally restricted to the axis parallel to the direction of white matter bundles (called anisotropy).[3] Fractional anisotropy (FA) (i.e., the amount of signal due to anisotropy) can be used to evaluate white matter tracts, and disruption is associated with a decreased FA. In several neurological disorders, the FA appears to correlate with diagnosis, management, or prognosis.[4,5]

Perfusion-Weighted Imaging

Evaluates cerebral perfusion dynamics, including relative cerebral blood volume, relative cerebral blood flow, and mean transit time. Currently, use is limited to evaluation of new tumors and for investigational purposes.[6–8]

Susceptibility-Weighted Imaging (SWI)

Uses paramagnetic property of blood products to increase the visibility of microhemorrhages. This technique is useful in evaluating intracerebral hemorrhage, venous thrombosis, and vascular malformations.

Arterial Spin Labeling (ASL)

An MR perfusion measurement that allows the clinician to estimate cerebral blood flow. Valuable in pediatric stroke and hypoxic-ischemic injury. A useful tool in pediatrics, as CT perfusion studies in adults involve a timed bolus of contrast, which is technically difficult in children.

Magnetic Resonance Spectroscopy (MRS)

Measures the concentration of various metabolites within a given region. *N*-acetylaspartate (NAA) measures cell membrane integrity, creatine (Cr) measures cellular metabolism, lactate measures cellular metabolism, and choline (Ch) measures cell membrane synthesis. Standard samples (voxels) are placed in gray matter, deep white matter, and basal ganglia. Additional voxels can target abnormal imaging areas, for example, in metabolic causes of stroke (e.g., mitochondrial disease).

High-Resolution T2-Weighted Images (i.e., FIESTA or CISS)

Excellent visualization of small soft-tissue structures, can be used to identify individual cranial nerves.

Magnetic Resonance Angiography (MRA)

Increasing utility in the emergency setting. A good screening for intracranial aneurysms, arteriovenous malformations (AVM), and dissections.[9] Note that this is (typically) not an intravenous contrast study, as a time-of-flight (TOF) technique reconstructs the vessels. Therefore, MRA cannot distinguish between slow flow and absence of flow, and CTA may be superior in some clinical scenarios.

Magnetic Resonance Venography (MRV)

Becoming the modality of choice for assessing dural venous sinus thrombosis. Beware in neonates that increased flow gaps in the venous sinuses, particularly affecting the posterior aspect of the superior sagittal sinus,

can cause an equivocal picture for a thrombus.[10,11] In this case it has been recommended to consider postcontrast 3D-FSPGR (fast-spoiled gradient echo images) or MPRAGE (magnetization prepared rapid acquisition gradient echo) sequences.

Functional MRI (fMRI)

Used predominantly in research setting and at times clinically as part of presurgical assessment of eloquent areas of, e.g., motor and language functions. Neural activity is mapped by blood-oxygen-level-dependent (BOLD) contrast, based on hemodynamic changes related to changes in local energy demand, implicating changes in tissue activity. By comparing a task to a control task the condition of interest is isolated. Resting-state fMRI provides information about neural activity that is not task related.

SPECIFIC CONDITIONS

Headache

Chronic Headache without New Features

General: 0.4% chance of finding a lesion that can be treated.[12] **1st Choice:** Usually none needed. **Alternative:** MRI with and without contrast (MRI W&WO). **Key Findings:** Incidental versus symptomatic Chiari malformations. **Follow-up:** Varied, although unlikely to need any unless concern is raised following initial study.

Chronic Headache with New Features

General: Significantly higher yield than for imaging chronic headache with unchanging characteristics.[13] **1st Choice:** MRI W&WO. **Alternative:** CT if hemorrhage is suspected or MRI is contraindicated. **Key Findings:** Tumors with variable imaging characteristics. Hemorrhage may be seen with GRE (or T2*) sequences on MRI. **Follow-up:** MRA/CTA/angiography if vascular lesion. MRS if neoplastic lesion suspected.

Sudden Onset Severe Headache

General: Primary concern is for ruptured aneurysm causing a subarachnoid hemorrhage (SAH). Less commonly may encounter an AVM. **1st Choice:** CT without contrast, with vascular imaging (MRA vs. CTA). **Alternative:** MRI, angiography. **Key Findings:** Hyperdense blood on CT, SAH may track into parenchyma, ventricles, along sulci. **Follow-up:** CTA or MRI/A.

Sudden Onset Unilateral Headache

General: Primary concern is for dissection.[14,15] **1st Choice:** MRI or CT with MRA (with T1 fat saturation) or CTA. **Alternative:** Doppler ultrasound (not useful for vertebral dissection) or angiography. **Key Findings:** Tapering of vessel lumen. T1 fat-saturation may show thrombus within false lumen. **Follow-up:** Angiography is the gold-standard but carries a 1% risk of stroke.

New Headache in the Immunocompromised

General: Primary concern is for treatable infectious etiologies and then neoplasms. **1st Choice:** MRI W&WO. **Alternative:** CT W&WO (lower yield). **Key Findings:** Bacterial meningitis with meningeal enhancement, FLAIR bright in subarachnoid space. Empyema is DWI and T2 bright, enhances. *Cryptococcus* may cause meningitis with concurrent T2 bright lesions of the midbrain and basal ganglia. Toxoplasmosis may cause T2 bright deep nuclei with ring enhancement. **Follow-up:** As indicated by findings.

New Headache with Suspected Meningo-Encephalitis

General: MRI preferable to CT in most instances. Rule out elevated ICP, with concern for impending herniation. **1st Choice:** Screening CT or MRI prior to LP. **Alternative:** MRI; may consider MRS if concerned for encephalitis. **Key Findings:** Meningeal enhancement (may be seen following an LP in normal individuals). Different distributions of FLAIR and T2 hyperintensities are seen with various encephalitides. **Follow-up:** Repeat imaging if no improvement with intervention, or new signs suggesting impending herniation.

Epilepsy and Seizures

Simple Febrile Seizure

1st Choice: Usually none needed. **Alternative:** EEG, consider LP if concerned for meningitis or encephalitis. **Key Findings:** See below (1st seizure). **Follow-up:** PCP follow-up with neurological consultation if concerned for focal findings.

Complex Febrile Seizure

1st Choice: Usually none needed unless focality is seen on EEG. **Alternative:** Consider MRI for focal findings on exam during postictal period. **Key Findings:** See below (1st seizure).

First Generalized or Focal Seizure

General: Lower yield of abnormalities for generalized seizures than in 1st afebrile focal seizures. 3T much better than 1.5 T. [16] **1st Choice:** MRI with fine temporal cuts and coronal views. **Alternative:** CT if concerned for hemorrhage or elevated ICP, may be quicker to obtain. **Key Findings:** Prior infarct/hemorrhage, heterotopias (ectopic gray matter), cortical dysplasias, pachygyria (abnormally thick cortex), polymicrogyria (abnormal folding of cortex), lissencephaly (lack of normal gyral pattern), porencephaly (cavity lined by white matter), neoplasms, infections, stroke. **Follow-up:** Static lesions may not warrant repeat imaging.

Postconcussive Seizure

1st Choice: If seizure occurs after 24 h or has focal features, then consider CT for hemorrhage. MRI if late postconcussive (often months after the injury), as in 1st afebrile seizures. **Key Findings:** Diffuse axonal injury (DAI) may be seen on MRI-GRE sequences as microhemorrhage at gray–white junction. MRI-DTI may also demonstrate abnormalities in diffusivity along white matter tracts in DAI. Otherwise, look for evidence of old infarct or blood products due to prior head injury. **Follow-up:** As indicated by findings.

Ataxia and Dysmetria

Slowly Progressive

General: CT significantly less useful because of poor visualization of posterior fossa. MRI superior for cerebellum, brainstem, vestibular nuclei, thalamic nuclei, and frontal lobes. **1st Choice:** MRI W&WO. **Alternative:** Consider MRI spine if concerned that ataxia is due to proprioceptive deficit. **Key Findings:** Expanding mass lesions, may be intracranial or extra-axial. **Follow-up:** Strongly consider contrast if not used in original study.

Acute <3 Hours

General: Primary concern is for vascular etiologies. **1st Choice:** MRI head and MRA head and neck. **Alternative:** CTA may alternatively be performed

of the head and neck, although less commonly used in pediatrics. MRV if concerned for central or dural venous thrombosis. May consider angiography if dissection strongly suspected but not seen on MRA or CTA. **Key Findings:** Vertebral dissections, brainstem or cerebellar infarct, hemorrhage from neoplastic lesions. **Follow-up:** As indicated by findings.

(Sub)Acute Suspect for (Post)Infectious Process

General: 1st Choice: MRI W&WO. **Alternative:** CT not indicated unless MRI unavailable. **Key Findings:** Cerebellitis with FLAIR, T2 hyperintensity, and enhancing lesions. Acute cerebellar ataxia (parainfectious) with T2 hyperintensity in cerebellar hemispheres and associated mass effect. **Follow-up:** Repeat MRI may demonstrate atrophic changes. **Rare:** Bickerstaff encephalitis (T2 intensity and restricted diffusion within pons, medulla, and cerebellum). Miller Fisher variant of Guillain–Barré syndrome may show T2 hyperintensity within cerebellum/brainstem, may also see enhancement of cranial nerves and spinal nerve roots.

Acute Following Head Trauma

General: May be a normal component of concussive syndromes without any radiologic abnormalities. **1st Choice:** MRI with GRE and DTI. **Alternative:** CT temporal bone (if concerned for skull base or middle ear injury). **Key Findings:** May have injury to frontopontocerebellar tract with frontal lobe injuries. Similar etiologies as other acute ataxias. **Follow-up:** May require later imaging if progressive ataxia to evaluate for expanding cyst or extra-axial hematomas, or perilymph fistula. **Note:** Metabolic stroke is DWI bright but less dark on ADC, and abnormalities may not follow vascular territory. The extent of abnormalities may be greater than suggested clinically. Consider MRS.

Stroke and Focal Deficits (see Fig 3.2)

New Focal Deficit, Fixed or Worsening, <3 Hours

General: Great speed is critical to reduce stroke-to-needle time for thrombolytic therapy (please refer to Chapter 18). **1st Choice:** CT head noncontrast unless a rapid protocol MRI with SWI/GRE imaging is available in your institution. MRI needs to include T2, DWI, ADC sequences. **Alternative:** CT or MR perfusion studies to delineate "ischemic penumbra," i.e., areas at risk for infarction. **Key Findings:** Hemorrhage on CT excludes tPA. Infarction on CT can manifest as (1) hypodensity, (2) blurring of grey–white matter junction, (3) edema, (4) by presence of a white dot referred to as the "dense vessel sign", and (5) by hemorrhage. Acute infarct is bright on DWI, dark on ADC, T1 and T2 sequences often isointense. **Follow-up:** Once lack of hemorrhage is identified, and decision has been made whether patient qualifies for tPA, consider MRI with MRA of head and neck. **Caveat:** T2 shine-through is an artifact of ADC imaging. If the area of interest is bright on both DWI and ADC, it is likely artifact.

New Focal Deficit, Fixed or Worsening, 3 to 24 Hours

General: 1st Choice: MRI head without contrast (with DWI and ADC), may add MRA head and neck if a vascular lesion is suspected. **Alternative:** CT head with perfusion and CTA head and neck. **Key Findings:** Same DWI/ADC characteristics as those of acute infarcts. T1 becomes dark around 6 h, and T2/FLAIR will become bright. **Follow-up:** Consider venous imaging (MRV) if infarcts do not follow an arterial distribution. **Caveat:** TOF MRA may overestimate stenotic lesions and does not distinguish between "slow flow" and "no flow."

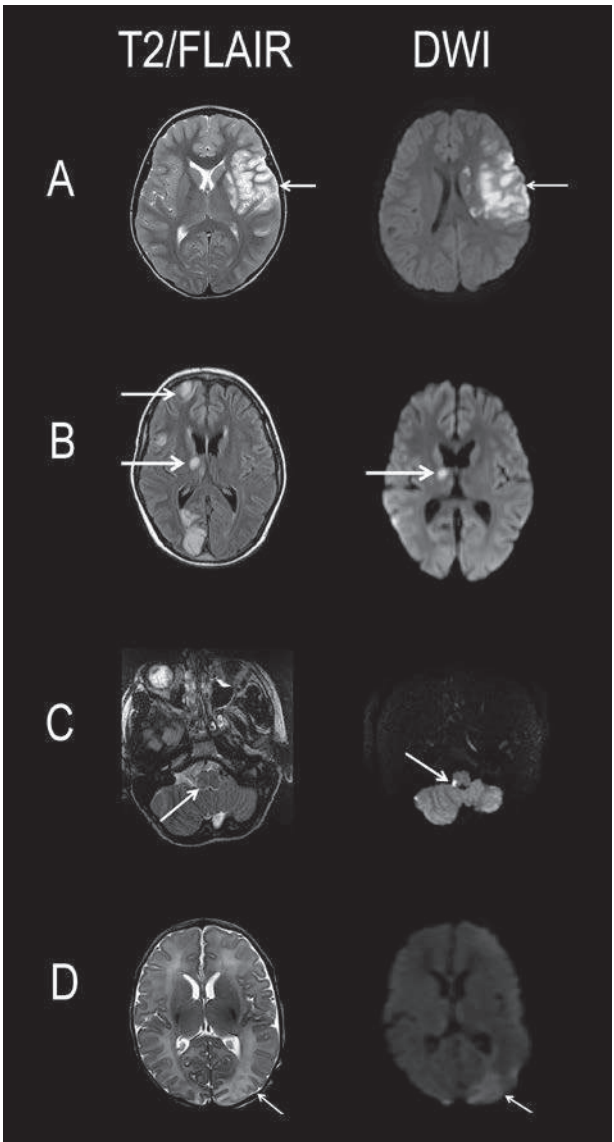


FIGURE 3.2 Selected Strokes. Representative T2 or FLAIR images, contrasted to their DWI correlate, of selected strokes. **A:** Left middle cerebral artery (MCA) infarct. **B:** Right acute thalamic and subacute anterior cerebral artery (ACA) infarct. **C:** Right lateral medullary infarct in the posterior inferior cerebellar artery (PICA) vascular territory. Note that there is no evidence of infarct on T2, whereas DWI shows a discrete area of decreased diffusivity. **D:** Left posterior cerebral artery (PCA) infarct.

Suspected Subarachnoid Hemorrhage

General: Vascular imaging is done in all cases of SAH. **1st Choice:** CT head without contrast. **Alternative:** MRA with SWI. **Key Findings:** Blood tracking into parenchyma, along gyral folds, into ventricles, cisterns and along tentorium. **Follow-up:** Lumbar puncture (looking for xanthochromia). Vascular imaging (MRA or CTA) if concerned or evidence for an aneurysm causing SAH. Angiography (1% stroke risk) if there is a strong suspicion for an aneurysm but it has not been seen on MRA/CTA.

Suspected Parenchymal Hemorrhage

General: MRI may be more sensitive than CT, but slower. **1st Choice:** CT head noncontrast. **Alternative:** MRI with SWI/GRE images (can overestimate size of hemorrhage). **Key Findings:** Associated mass effect is the primary concern initially. **Follow-up:** May need to reimage in the acute phase if there is any clinical worsening (may be expanding hemorrhage). May need to reimage 6 to 8 wk after blood has cleared to evaluate for potential sources underlying the hemorrhage. MRA/CTA if a vascular malformation is suspected.

Cranial Neuropathy of Suspected Central Origin

General: Consider a central origin if multiple cranial nerves involved or if motor or sensory involvement in other areas of the body. **1st Choice:** MRI with high-resolution T2-weighted sequences (i.e., FIESTA or CISS) and fine cuts through brainstem. **Alternative:** Consider adding contrast if multiple cranial neuropathies. **Key Findings:** Infarction/hemorrhage of cranial nerve nuclei, injury along the cranial nerve tract, or peripherally. **Follow-up:** As indicated by findings.

Head Trauma

Closed Head Injury, GCS >13, without Risk Factors or Focal Deficit

General: Imaging is of low yield in this setting, may be needed in patients <2 y of age given difficulty examining.[17,18] **1st Choice:** None. **Alternative:** MRI. **Key Findings:** Evaluate for signs of elevated ICP (midline shift, obliteration of cisterns. **Follow-up:** MRI with SWI/GRE and/or DTI to evaluate for microhemorrhages and/or diffuse axonal injuries. CT skull with bony reconstructions if concerned for fractures.

Closed Head Injury, GCS ≤13, with Risk Factors or Focal Deficit

General: Use of MRI in acute setting still limited by availability and longer imaging times. DTI may also be useful if DAI is suspected. **1st Choice:** CT head without contrast. **Alternative:** MRI head without contrast, with DWI/ADC/GRE/SWI/DTI. **Key Findings:** Evaluate for signs of elevated ICP (midline shift, obliteration of cisterns). Focal contusions and diffuse axonal injuries often show restricted diffusion. **Follow-up:** Consider vascular imaging if there is a suspicion for pseudoaneurysm formation, dissection, or considering need for intervention on uncontrolled hemorrhage. Vascular injury is more common with basal skull fractures, injury to the neck, or penetrating injuries.[19–21]

Subacute Closed Head Injury with Cognitive or Focal Deficits

General: Almost no role for CT in the evaluation of deficits related to a remote injury. **1st Choice:** MRI with DWI/ADC/SWI/GRE. **Alternative:** Consider single-photon emission computed tomography (SPECT) or functional imaging, may pick up focal areas discordant with abnormalities on MRI or CT.[22] **Key Findings:** Looking for areas of encephalomalacia, small infarcts that may have been missed with an acute-setting cranial CT. **Follow-up:** Consider neuropsychiatric/cognitive testing.

Closed Head Injury with Concern for Carotid or Vertebral Dissection

General: In addition to concern for dissection, image other head injuries as indicated above. **1st Choice:** MRI with MRA head and neck if available quickly. If there are equivocal focal areas of suspicion, consider fat saturation sequences. **Alternative:** CT head without contrast and CTA head and neck. **Key Findings:** Luminal tapering, intraluminal flap, clot formation. **Follow-up:** Consider angiography (1% stroke risk) as gold standard.

Cranial Neuropathies and Painful Visual Loss

Cranial Neuropathies

General: These include anosmia, visual field deficits, gaze restriction, facial sensory or motor phenomenon, vertigo, hearing loss, deficits in palate or tongue. **Anosmia** should exclude abnormalities of anterior skull base. **Gaze restrictions** should always include evaluation of skull base and brainstem. **Visual field deficits** can be seen in many intracranial processes, as the course of the optic nerves to the occipital cortex is a long one. Evaluation of **weakness of masticatory muscles or abnormalities of facial sensation** should include cerebellopontine angle, central skull base, orbits, and masticator space. If there is **facial pain**, high-resolution T2-weighted sequences and angiography may help show vascular compression. **Weakness of facial expression** should include imaging of the central and posterior skull base, brainstem, temporal bones, and parotid glands. **Vertigo** should include imaging of the internal auditory canal. Hearing loss may be due to conductive or sensorineural deficits, with **conductive hearing loss** best evaluated with CT of the temporal bones. **Vestibular neuritis** may show MRI gadolinium enhancement of the labyrinthine structures or vestibular nerves during the acute phase.[21] **Palatal weakness**, **vocal cord paralysis**, **tongue weakness/deviation**, **or weakness of the sternocleidomastoids/trapezii** should all include evaluation of the skull base and brainstem. **1st Choice:** MRI W&WO. **Alternative:** CT of orbits/temporal bones may be better at evaluating osseous pathologies causing neuropathies. **Key Findings: Olfaction** may be interrupted by cribiform plate trauma, tumors (squamous cell, meningioma, esthesioneuroblastoma), inflammatory disorders (Wegener's granulomatosis, sarcoidosis), and congenital disorders (Kallmann syndrome, cephaloceles). **Gaze palsies** may be due to lesions along the entire course of the 3rd, 4th, or 6th nerves. **Abnormal mastication and sensation** may be due to lesions along the entire complex and branching course of the trigeminal nerve. **Facial expression** may be compromised with involvement of central or peripheral portions of the facial nerve. Patients with classic Bell palsy do not need to be imaged unless duration of symptoms is >2 mo.[23] **Vertigo** may be caused by a cholesteatoma or labyrinthine fistula, more readily visible on CT of temporal bone.[24] Consider MRA or CTA of head and neck if concerned for vertebral dissection/occlusion or if evidence is seen of a cerebellar infarct. **Sensorineural hearing loss** may be caused by vestibular schwannoma/acoustic neuroma, transection following head injury, cholesteatoma, labyrinthine fistula. **Follow-up:** As indicated by findings.

Painful Visual Loss

General: Consider intraocular abnormalities vs. inflammatory conditions (i.e., optic neuritis). **1st Choice:** MRI head and orbits, with and without contrast. **Alternative:** CT orbits if visual loss is subsequent to trauma. **Key Findings:** Optic neuritis best seen as focal or diffuse enlargement of the

optic nerve, increased T2 signal, and/or enhancement. **Follow-up:** If concerned for optic neuritis, consider MRI head and spine with and without contrast to establish whether there are demyelinating lesions.

Neurocutaneous Disorders and Cerebral Dysgenesis

Cerebral dysgenesis is discussed in Chapter 11, and neurocutaneous disorders in Chapter 12. Figure 3.3 illustrates a few common conditions described in Chapters 11 and 12.

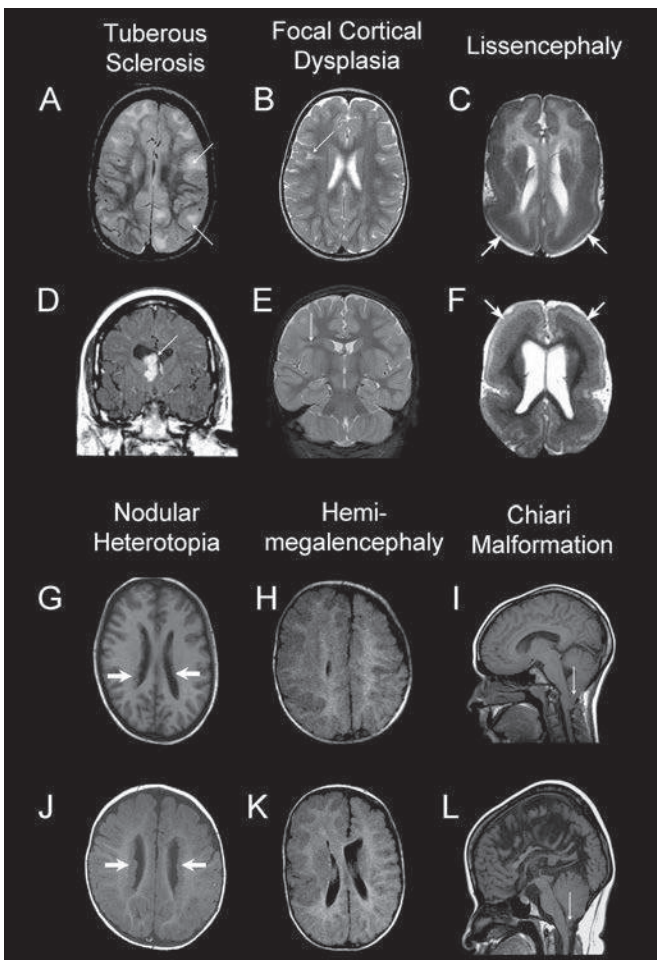


FIGURE 3.3 Selected Dysgenesis Syndromes. A and D: Cortical tubers and subependymal giant cell astrocytoma (SEGA) in tuberous sclerosis complex (TSC). **B and E:** Focal cortical dysplasia. **C and F:** Lissencephaly due to *Lis1* mutation with posterior involvement greater than anterior, and due to *DCX* mutation with anterior involvement greater than posterior. **G and J:** Periventricular nodular heterotopia. **H and K:** Hemimegalencephaly. **I and L:** Chiari 1 and Chiari 2 malformations.

Myelopathy

Traumatic Myelopathy

General: First priority is assessing spinal stability. **1st Choice:** CT spine without contrast. **Alternative:** XR spine to assess stability if CT will be delayed. MRI spine if deficits not explained by fracture on CT. **Key Findings:** CT is adequate in assessing spinal fractures, herniated disks, bone fragments, or hematomas. MRI is better if assessing for direct neural or ligamentous injury, as well as relation of injury to the cord. **Follow-up:** As indicated by findings.

Nontraumatic Myelopathy

General: If local or radicular pain is present, consider spondylosis, tumor, or infection. Demyelinating disease may be painful, but is more frequently painless. MRI provides better distinction between solid and cystic masses than does CT. **1st Choice:** MRI spine with and without contrast. **Alternative:** CT and/or CT myelography. **Key Findings:** If accompanied by local or radicular pain, often caused by compression, tumor, or infection. Painful myelopathy may less frequently be caused by demyelinating lesions or syrinx (i.e., anesthesia dolorosa). **Follow-up:** As indicated by findings.

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ONLINE RESOURCES

http://www.acr.org/Quality-Safety/Appropriateness-Criteria – Valuable resource for choice of appropriate imaging based on clinical indication.

http://www.seattlechildrens.org/healthcare-professionals/education/radiology/pediatricbrainatlas/ – Pediatric Neuroimaging Brain Atlas for download and installation.

http://www.ajnr.org – Links to review papers and a fellow's page with links to recommended articles for education and review (sorted by imaging modality, by indication and by anatomy). Also has a list of journals that accept imaging case reports.

General Reference

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4 Pediatric Neurology in the Emergency Department

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GENERAL APPROACH

This chapter provides information on the emergency department (ED) presentation/management of these topics. Each topic is covered in more detail in subsequent chapters.

WORDS OF ADVICE: In the ED, three questions need to be answered with a good history and physical exam: (1) Is there a neurological problem/symptom? (2) Is there an urgent medical treatment needed? (3) What are the pertinent and first-line diagnostic tests needed to determine a disposition plan for the patient?

GOAL: Not to make a full neurologic diagnosis but to determine disposition: (1) Admission due to life-threatening neuro emergency and/or for further workup. (2) Needs basic labs/imaging and is safe to be discharged with a neurologic follow-up.

NEUROIMAGING: Consider noncontrast head CT (NCHCT) for evaluation of intracranial hemorrhage, skull fracture, changes in mental status, concern for new tumor, herniation, or possible midline shift. If time allows, consider brain MRI over NCHCT except when intracranial blood is of concern. CT exposes the child to ionizing radiation, while MRI does not.

SEIZURES IN THE EMERGENCY DEPARTMENT[1–4]

Febrile Seizures

DIFFERENTIAL: (1) CNS infection especially if the child has had fever for 1 to 2 d and then develops seizures. (2) Underlying seizure disorder where fever triggered an event. (3) Febrile seizure: an age-limited, genetic epilepsy in which seizures occur only with fever.

DEFINITIONS: Simple febrile seizure: brief (<15 min), generalized (nonfocal), once in 24 h. Complex febrile seizure: duration >15 min (hard to define for parents; good rule of thumb is whether still seizing after the parents have left the house), focal or secondarily generalized, or > once in 24 h. **EPIDEMIOLOGY:** Most common between ages 6 mo to 6 yo. Risk factors: close relative with a hx of a febrile seizure. Roseola and AOM are common precipitants. **EXAM:** Simple febrile: normal exam. Meningitis: headaches ± stiff neck. Encephalitis: altered mental status (AMS) before the seizure (somnolence, not following commands, not acting appropriate, and irritable). Children with meningitis/encephalitis do not tend to wake up after a seizure. Other: If focality on exam consider stroke, infection, or Todd paralysis (see "Weakness/Gait Difficulties" section below).

DIAGNOSTIC STUDIES: (1) Fever workup: strongly consider LP: if <12 mo (meningismus frequently absent); 12 to 18 mo where meningismus is subtle; >18 mo if recently on antibiotics (partially treated meningitis) or meningeal

signs. (2) EEG: not recommended for first simple febrile seizure. EEG indicated for complex febrile seizure. Also consider if child not neurologically normal at baseline, has developmental delay, or family history of epilepsy. (3) Neuroimaging: not recommended for first simple febrile seizure. For complex febrile seizure, brain MRI is indicated to evaluate for a mass, hemorrhage, or CNS dysgenesis.

TREATMENT: (1) Around-the-clock antipyretics not shown to decrease risk of recurrent seizures, can be discussed with the family as they may feel more comfortable knowing about this option; remember that antipyretics can mask a serious infection. (2) Simple febrile seizure: no need for long-term treatment with anticonvulsive medication. Consider giving family rectal diazepam prescription for seizure lasting >5 min (0.5 mg/kg if <5 y; 0.3 mg/kg if 6–11 y; 0.2 mg/kg if >11 y). (3) Complex febrile seizure: consider prophylactic AEDs if family history of epilepsy, child does not recover rapidly, or frequent complex febrile seizures. Consider Depakote (avoid in children <2 yo due to risk of liver failure), levetiracetam, topiramate; needs follow up with neurologist, brain MRI, and EEG. If a child presents with frequent complex febrile seizures, consider Dravet syndrome, which is associated with developmental delay in the first 1 to 2 years.

PROGNOSIS: Good. Risk of epilepsy: 1% after simple febrile seizure (same as general population), ~2% if recurrent febrile seizures, abnormal neurologic exam or developmental delay is an important predictor of epilepsy risk. **RECURRENCE RISK:** Febrile seizures tend to recur (30% if first seizure occurs in >12 mo; 50% if <12 mo). Simple febrile seizures tend to decrease in frequency as the child gets older. Risk increases with family history of febrile seizure or history of low temperature with seizure onset.

First Nonfebrile Seizure[5–7]

DEFINITIONS AND CONSIDERATIONS: Non-febrile seizure, non-provoked (not due to trauma, illness, or other medical condition) in a child not known to have seizures. Characterize seizure type: preserved or AMS, focal vs. generalized, increase tone (tonic), jerking (clonic, myoclonic), or loss of tone (atonic). **MAJOR RISKS:** Congenital malformations (cortical dysplasia, TORCH infection), neonatal seizures, or family history of epilepsy (genetic). If a child presents with partial seizures, *strongly consider* focal brain lesion. Intractable seizures in children <2 yo are associated with mental retardation. Greatest probability of mental retardation in descending order is myoclonic > tonic-clonic > complex partial > simple partial. **HISTORY:** Decide if seizure vs. non-seizure paroxysmal event. Until the event is proven to be a seizure, better to define the event as "spell." Of importance: What happened *before* the event (more important than what happened after)? What do the parents believe is the cause? What time did it happen? Was there an aura? Has this happened before? **SEMIOLOGY:** Changes in behavior, cry (seizure cry is usually at the beginning and then stops), slurred speech, head/eye deviation (eyes should look away from the seizure focus), posturing, jerking, automatism, generalized or focal movements, apnea/cyanosis, and autonomic signs (pupil size, drooling, heart rate, incontinence, pallor, vomiting, LOC). Postictal period: amnesia of the event, confusion, lethargy, sleepiness, headache, and transient focal weakness (Todd paralysis).

Common Non-Epileptic Paroxysmal Events

(1) Without prominent alteration of awareness: benign neonatal sleep myoclonus (infant already asleep), GERD, shuddering attacks, hyperekplexia (marked susceptibility to startle), benign paroxysmal torticollis, benign

paroxysmal vertigo, self-gratification phenomena ("infantile masturbation"), tics, behavioral stereotypies, hyperventilation and anxiety attacks, paroxysmal dyskinesias (kinesigenic, non-kinesigenic), and migraine. (2) With alteration of awareness: syncope, breath-holding spells, daydreaming, nonepileptic attacks (pseudoseizures), and narcolepsy/catatonia. **EXAM:** Special focus on vital signs—elevated BP (posterior reversible encephalopathy syndrome/PRES), head circumference in children <3 yo, skin exam, including hypochromatic or café au lait spots (neurocutaneous syndromes), evidence of trauma.

DIAGNOSTIC STUDIES: Depends on history: if back to baseline, >6 mo, and history not suggestive of seizure, generally not necessary. (1) LP: if possibility of meningitis/encephalitis. (2) EEG: used to define an epilepsy syndrome, *sometimes* when there is difficulty determining if spell was seizure by history. Normal EEG associated with favorable outcomes, can be done as outpatient; sleep deprivation increases the sensitivity. If high suspicion of seizures and EEG negative, consider repeating. (3) Neuroimaging: emergent NCHCT if prolonged focal deficit. MRI (outpatient OK) with seizure protocol if: focal seizure, history of developmental delay, cognitive problems, abnormal neurologic exam, abnormal EEG, or <1 yo. **TREATMENT:** AEDs not indicated after first nonfebrile seizure, normal EEG, and imaging. If abnormal EEG and/or brain MRI, consider starting AEDs. Will need neurologic follow-up. **COMPLICATIONS:** Most children with 1st unprovoked seizure have no or few recurrences (30% to 50% recurrence within 2 y after 1st seizure). Epilepsy risk increased if abnormal EEG findings or history/findings of remote brain injury.

Status Epilepticus (SE)[3,8]

DEFINITION: Seizure lasting > 30 min or > two sequential seizures with no return to baseline, medical emergency. Current understanding: recurrent seizures become harder to treat, most seizures last 2 to 3 min; therefore, current recommendation is to treat seizures lasting >5 min. **Classification:** Generalized SE and focal SE (epilepsia partialis continua, aura continua, limbic SE, and hemiconvulsive status with hemiparesis). **Epidemiology:** Most common age group is <3 yo. ⅓ is initial presentation of epilepsy, ⅓ have preexisting epilepsy, and ⅓ are acute symptomatic. If seizure lasts >60 min, it is defined as refractory SE. **ETIOLOGY:** Febrile seizures account for >⅓ of all SE in childhood. Other causes: Epilepsy, withdrawal or change in AEDs, CNS infection, cerebral hypoxia/metabolic disturbance, and acute insults (stroke, trauma). **EXAM ON PRESENTATION:** Vital signs: BP/HR—bradycardia (increased ICP?), hypertension may be the cause of seizures (hypertensive encephalopathy, PRES). Body temperature: cold/clammy (sepsis, hypoglycemia), warm (meningitis/encephalitis). Head: otorrhea, rhinorrhea (skull fracture, trauma). Skin: rash (sepsis). Brief neuro exam: pupils/posture - decorticate/decerebrate posturing may be confused with tonic seizure, focality (mass, herniation). **DIAGNOSTIC STUDIES:** (1) Labs (before giving any treatment): glucose, Chem 20, CBC/diff, U/A, blood/urine cultures (if febrile), toxicology (full serum and urine), AED levels on patients (asses compliance; for phenytoin/phenobarbital level corresponds with efficacy). (2) LP: if concern for CNS infection. (3) Neuroimaging: NCHCT, when unclear reason for SE, concern for trauma. EEG, when patient stable, or for SE lasting >30 min, may need LTM. **INITIAL TREATMENT:** ABCs: O_2 by mask, CV monitor, correct metabolic derangement. **MEDICATION PREPARATION**: Always be one step ahead: when med is given, order the next med, hold in case needed. Do not wait to find out whether the 1st med is effective or not before ordering the next. Time is of the essence! Maintain

euglycemia (start normal saline with dextrose), treat pyrexia; when safe, place nasogastric tube to empty stomach contents.

MEDICATIONS:

- First-line (benzodiazepines): lorazepam 0.1 mg/kg (max 2 mg). Diazepam can also be used IV or IM (IM effect slow, not recommended). No IV access: diazepam PR (0.5 mg/kg if <5 yo; 0.3 mg/kg if 6 –11 yo; 0.2 mg/kg if >11 yo). Repeat either benzodiazepine if no response in 5 min. Lorazepam preferred for longer half-life (12–24 h; diazepam 1–4 h), produces less respiratory depression.
- Second-line: If still seizing, fosphenytoin IV 20 phenytoin equivalents (PE)/kg loading dose. Another 10 PE/kg can be repeated. If not available, give phenytoin 20 mg/kg slow IV push over 20 min (monitor EKG and BP).
- Third-line: If still seizing, use phenobarbital 20 mg/kg IV push. Consider intubation before administering, high likelihood of respiratory depression; another 10 mg/kg can be given if needed.
- *In neonates: phenobarbital is first-line and fosphenytoin is second-line.*

Alternative medications: *Can be used instead of fosphenytoin or phenobarbital if patient is already known to be taking them.* (1) Valproic acid: 30 mg/kg load, caution if liver or mitochondrial disease. (2) Levetiracetam: 20 to 40 mg/kg load. *(preferred given little interaction with other AEDs, good side effect profile, no need for monitoring drug levels).*

If refractory SE: Intubate (if not already), EEG to monitor for burst suppression. (1) Pentobarbital: load 20 mg/kg IV push, maintenance dose 1 to 2 mg/kg/h. Titrate to burst suppression. (2) Midazolam: load 0.15 to 0.3 mg/kg IV push, maintenance dose 0.1 mg/kg/h, but may need to increase due to tachyphylaxis, titrate to burst suppression. **Disposition:** Admit to ICU. **Complications:** Cardiac arrhythmia, cerebral edema, hypotension, pneumonia, rhabdomyolysis, and dehydration. Outcome is etiology-dependent.

Nonconvulsive SE (NCSE)

The diagnosis is based on EEG, the common cause of coma in the pediatric ICU. Consider NCSE when a known epileptic patient presents with persistent AMS, or after the patient presents with GTC, movement stops after AEDs are administered but patient not back to baseline after reasonable time (related to dose/type of medication given). **CLASSIFICATION AND TREATMENT:** (1) Subtle SE: following cessation of motoric convulsions but mental status not back to baseline. Most common, needs to be treated as SE with same medications, typically needs burst suppression on EEG for at least 24 to 48 h. Prognosis depends on time between onset and diagnosis as well as underlying etiology. (2) Absence SE: presents with confusion, disorientation, and decreased speech. Can present with minor motor disturbances including jerks, head drops, automatism, and autonomic features. Typically does not have long-term sequelae even if it lasts for days. Treat as SE. Valproic acid used over fosphenytoin, as later can exacerbate SE. Levetiracetam currently being studied. (3) Complex partial SE: fluctuating, with or without automatism or eye deviation, no significant sequelae after resolution. Treat as SE. Good response to benzodiazepines and fosphenytoin. (4) Epileptic encephalopathy: early myoclonic encephalopathy, infantile spasms, Otahara, Dravet, or Lennox-Gastaut syndromes, myoclonic status in nonprogressive encephalopathy, Landau-Kleffner syndrome, and epilepsy with continuous spike and wave during slow wave sleep (ECSWS). EEG needed for diagnosis and to direct therapy. Consider in children with developmental regression including autistic regression (see Chapter 5 for extended discussion).

HEADACHE (HA)/MIGRAINE[9–13]

CONSIDERATIONS: Headaches are either primary (migraine, tension, cluster, and other variants) or secondary to other multiple medical conditions. Headaches are common in children and most parents are seeking reassurance (that HAs are not due to a serious cause). Determine whether: acute HA presents in a child without a history of HAs (worrisome), recurrent acute HA (reassuring), chronic nonprogressive HA (reassuring), or chronic progressive HA (worrisome).

ETIOLOGY: Acute HA: Consider - viral illness, sinusitis, meningitis, spontaneous SAH (will usually present with signs of meningismus), hydrocephalus, dental abscess, arterial hypertension, and head trauma. **Chronic HA:** (1) Nonprogressive: consider primary HA. (2) Progressive: consider mass, increased ICP. If prior history of migraine with same quality but increasing frequency, consider chronic daily HA (is there an exacerbating factor?).

Worrisome signs

- Any acute HA located in back of head (posterior fossa mass, hemorrhage)
- Early morning HA that awakens child, with/without nausea/emesis (brain mass)
- HA that worsens during Valsalva - exercise, coughing, laughing, defecating (Chiari I malformation, increased ICP)
- Optic disc edema (increased ICP)
- Change in mental status (intracranial bleed, meningitis/encephalitis, and midline shift)
- History of trauma (SDH, epidural hemorrhage, midline shift, and parenchymal bleed)
- Dental pain (brain abscess)
- Meningismus (meningitis, SAH)
- Any focal neurological deficit
- Elevated BP (arterial hypertension), if associated with bradycardia (increased ICP)

QUESTIONS TO ASK IF CONCERN FOR MIGRAINE: General: Car sickness when younger; HA associated with nausea/emesis; aura preceding the attack (visual, paresthesias, weakness); photo- or phonophobia; aggravated with stress, fatigue, lack of sleep, certain foods, menstrual cycle; alleviated with sleep/dark room. **Family history:** Do not ask, "Does anyone in your family have migraines?" Ask instead, "Does anyone suffer from HAs?" Some parents consider "sinus HAs" different from migraines or don't realize family members' HAs are classified as migraines (because infrequent, mild, uncomplicated, etc.).

Migraine and Migraine Variants (not all-inclusive)

MIGRAINE: Presents in children with either uni- or bi-hemispheric HA, pulsating/throbbing pain, and free interval time during attacks. Common migraine has no aura; classic migraine has an aura (prodrome). Can present without HA, e.g., nausea and brainstem signs ("Alice in Wonderland" syndrome, opthalmoplegia). **BASILAR MIGRAINE:** HA associated with nausea/emesis and either vertigo, nystagmus, visual disturbances, ataxia, diplopia, decreased level of consciousness, decreased hearing, tinnitus, dysarthria, or other bulbar symptoms. **FAMILIAL HEMIPLEGIC MIGRAINE (FHM):** Usually presents with HA followed by slowly (over few minutes) migrating pattern of weakness or sensory deficits (e.g., weakness starts in the face and migrates to the arm/leg). Differentiate from stroke where weakness is complete at onset (however, there are exceptions including stuttering lacunar stroke). Be cautious of diagnosing hemiplegic migraine on first presentation without ruling out stroke if history

unclear. **PRECURSORS OF MIGRAINE:** Cyclic vomiting, benign paroxysmal vertigo of childhood, and abdominal migraine/nausea (car sickness).

TENSION HA: Usually presents as symmetric head pain, band-like, typically with almost no free interval period and constant ache. **CLUSTER HA:** Intense HA occurring for a period of weeks/months, with long pain-free intervals (years), often unilateral, associated with rhinorrhea, tearing, congestion, eyelid edema, myosis, and ptosis.

HISTORY: Time pattern, frequency, duration, warning signs, location, quality, associated symptoms, alleviating/aggravating factors, and degree of debilitation. **EXAM:** BP, temp, sinuses, teeth, fundoscopic examination (presence of venous pulsations implies normal ICP; however, absent in ~10% of the population), visual fields, cranial nerve exam, signs of meningismus (neck pain, Kernig and Brudzinski signs), strength, gait. **DIAGNOSTIC STUDIES:** *None needed* if history classic for migraines, family history of migraines, and nonfocal neurologic exam. **NEUROIMAGING:** If any neurologic deficit with acute presenting HA, worrisome signs, or changes in HA characteristics. Consider NCHCT for head trauma, acute weakness, or signs suggestive of stroke; SDH; SAH; epidural hemorrhage; and acute changes in mental status. Consider MRI for chronic progressive HA to rule out brain mass or other subtle etiology. **LP:** if history of fevers or changes in mental status and neuroimaging is negative. If needed, consider performing LP *after* MRI to avoid leptomeningeal enhancement (however, use clinical judgment).

Treatment

MIGRAINE: (1) Acute: IV fluids, ibuprofen (10 mg/kg), ketorolac (0.5–1 mg/kg) in the ED. Consider prochlorperazine (2.5–10 mg), metoclopramide (1–2 mg/kg; max 10 mg) if emesis/nausea. Sumatriptan (4–6 mg SC, may repeat ×1 after 1 h if HA recurs), contraindicated if cardiovascular disease, cerebrovascular syndromes, use of MAO-I, uncontrolled hypertension, hemiplegic or basilar migraine, and peripheral vascular disease. (2) Prophylaxis: can start in the ED, but will need follow up for titration. Consider starting if significant disability/school day loss, inability to participate in joyful experiences, >2 HAs/wk, or HA lasting >48 h. Consider cyproheptadine (2–4 mg q.h.s.) if young or history of allergies; amitriptyline (1 mg/kg/d, start at 10 mg and slowly increase) often good 1st choice; propranolol (<35 kg, 10–20 mg t.i.d; >35 kg, 20–40 mg t.i.d.) also common 1st choice, effective for tension HAs, cyclic vomiting, avoid if history of asthma, monitor for hypotension/bradycardia; topiramate (start at 25 mg q.h.s. and increase to 25 mg b.i.d. in 1 wk) if overweight; gabapentin (10–15 mg/kg/d b.i.d.); verapamil (start low 20 mg b.i.d.–t.i.d.) can be used in older children (see Chapter 14 for additional details). (3) Rescue medication (at home): ibuprofen (10 mg/kg), sumatriptan (*oral*: 25–100 mg; may repeat ×1 in 2 h if HA recurs; max 200 mg/24 h. *Nasal:* dose 5 to 20 mg in one nostril ×1; may repeat ×1 in 2 h if HA recurs; max 40 mg/24 h, butalbital/acetaminophen/caffeine (age >12 yo: 50–100 mg butalbital; max 300 mg/d, avoid long-term use due to dependence), prochlorperazine (2.5–10 mg) or metoclopramide (1–2 mg/kg; max 10 mg) if emesis/nausea.

CHRONIC DAILY HA: Amitriptyline (1 mg/kg/d, start at 10 mg and slowly increase).

STATUS MIGRAINOSUS: HA lasting >72 h (true HA vs. secondary gain). Rescue meds: sumatriptan, metoclopramide, prochlorperazine, valproic acid (10 mg/kg IV, max 500 mg over 5 min, can be repeated ×1), magnesium sulfate (25 mg/kg, max 1g IV), and dexamethasone (0.3–0.6 mg/kg IV, max 8 mg).

CLUSTER HA: Acute: high flow O_2, sumatriptan, ibuprofen, ketorolac. Prophylaxis: consider calcium antagonist like verapamil.

SECONDARY HA: Treatment based on the underlying cause.

WEAKNESS/GAIT DIFFICULTIES[14]

LOCALIZATION AND DIFFERENTIAL DIAGNOSIS: If a previously walking child presents with weakness/inability to walk, consider localization-based etiologies (Table 4.1).

KEY QUESTIONS: (1) Timing: Acute or rapidly progressing weakness suggests motor unit disorder (nerve, anterior horn cell), involvement of face

TABLE 4.1 Localization and Differential Diagnosis of Weakness/Gait Difficulty[46]

Localization	Etiologies
Cortex and basal ganglia	Stroke, hemiplegic migraine, alternating hemiplegia (epilepsy), postictal Todd paralysis, multiple sclerosis, tumor/mass, primary dystonia (generalized torsion dystonia; DYT1), and secondary dystonia
Cerebellum and brainstem	Infection/postinfection (EBV, HSV, VZV, measles, mumps, and mycoplasma), meningitis, cerebellar abscess, multiple sclerosis, hemorrhage/hematoma, basilar migraine, stroke (vertebrobasilar occlusion), spinocerebellar ataxia, EA1, EA2, metabolic (mitochondrial disease, urea cycle defects, organic acidurias, MSUD, pyruvate dehydrogenase deficiency, and Hartnup disease), thyroid disorder, drug/intoxication (heavy metals/lead, AEDs, benzodiazepines or other sedatives, alcohol, and methotrexate); hydrocephalus, opsoclonus-myoclonus syndrome (neuroblastoma), and posterior fossa mass (ependymoma, medulloblastoma, and hemorrhage)
Spinal cord	Trauma/transection, cord compression, anterior spinal artery occlusion (paresis and loss of pain and temperature), vascular malformation, epidural hematoma (s/p trauma, hemophilia), transverse myelitis, abscess, bony compression (fracture, dislocation in Down syndrome), tumor (neurofibroma, glioma, ependymoma), metastasis (leukemia/lymphoma, neuroblastoma), hydromyelia/syrinx, Cu deficiency, and subacute combined degeneration (vit. B_{12}, E)
Anterior horn cell	Polio, spinal muscular atrophy, Kennedy disease
Peripheral nerve	GBS/AIDP, acute intermittent porphyria, toxic (vincristine, cisplatin, lead, mercury, and arsenic), hereditary neuropathies (CMT), sarcoid, infectious (lyme, syphilis), and vitamin deficiency (B_6, B_{12}, thiamine)
Neuromuscular junction	Botulism, myasthenia gravis, Eaton-Lambert syndrome, tick paralysis, ICU weakness (corticosteroid myopathy, critical illness myopathy, critical illness polyneuropathy), familial hypokalemic/hyperkalemic/ normokalemic periodic paralysis, and organophosphate poisoning
Muscle	Rhabdomyolysis, transient acute myositis, viral myositis, dermatomyositis, medication-induced myopathy (corticosteroid, statin), muscular dystrophies, endocrine myopathies (thyrotoxic, hypothyroid, Cushing syndrome), and metabolic (hypophosphatemia, hypokalemia)
Other	Functional/psychogenic, labyrinth disease, atrophy from disuse/bed rest

and/or arm suggests a lesion above the highest area of deficit; progressive weakness suggests genetic cause. (2) Precipitating factors: trauma, abnormal movements, fever; back pain, ascending paresthesias (Guillain–Barré syndrome [GBS]); and recent infection, vaccination (infectious/postinfectious cerebellitis, GBS). (3) Fear of walking: ataxic, severe muscle/bone pain. (4) Back pain: transverse myelitis, cord compression, and GBS. (5) DD: genetic/metabolic causes. (6) Recurrent: episodic ataxias. (7) Refusal to use one limb: bone, joint, or muscle pain. (8) Proximal weakness: consider myopathy.

EXAM: (1) Check temp, heart rate, murmurs, skin lesions, and full neuro exam. (2) Peripheral nerve: distal weakness, areflexia, and sensory loss. (3) Spinal cord: distal weakness, hyperreflexia, and sensory level. However, acute spinal shock presents with areflexia, no sensory loss, and a motor level. (4) Hemiplegia/quadriplegia: weakness with increased tone, Babinski reflex, and hyperreflexia (upper motor signs). Acute hemiplegia is usually epileptic in infants and toddlers (who were otherwise normal), but with vascular cause in older children. Consider: sudden onset (ischemic, hemorrhagic stroke) vs. slow progression (migraine) vs. stuttering course (lacunar infarct, infrequent in children). (5) Myasthenia gravis: weakness without paralysis. (6) Brainstem/cerebellar: associated with nausea/emesis/nystagmus.

DIAGNOSTIC STUDIES: (1) Laboratory: CBC w/ diff, Chem20, PT/INR, PTT, D-fiber, fibrinogen, CK. Additional labs pending most likely cause based on information in Table 4.1. (2) Neuroimaging: brain and/or spine MRI depending on most likely localization (urgently if considering spinal cord compression). (3) Consider LP: contraindicated if suspicion of epidural abscess due to risk of introducing infection to CSF.

Guillain–Barré Syndrome (GBS)[15,16]

DEFINITION: Immune-mediated polyneuropathy; typically refers to acute inflammatory demyelinating polyradiculoneuropathy (AIDP), most common form, although other variant forms also fall under syndrome of GBS (see below). **PRESENTATION:** Usually presents after infection (most commonly GI/URI). Most common preceding organisms: *Campylobacter jejuni*, mycoplasma, CMV, EBV, VZV, measles, mumps, hepatitis A/B, rubella, influenza, coxsackie, and echovirus. Classic symptom presentation: low back pain, symmetric ascending paresthesias (can be painful)/weakness (but can start asymmetrically), areflexia (starts distally at ankles), and absence of fever. Can present with autonomic dysfunction (orthostasis, tachycardia, urine retention) and transient sphincter dysfunction. Respiratory weakness/failure may occur. Neck flexion strength correlates well with diaphragmatic weakness (good bedside exam technique). Bulbar weakness can cause difficulty handling secretions. **VARIANTS:** (1) Miller Fisher Syndrome (MFS): ophthalmoplegia, ataxia, muscle weakness, and areflexia. (2) AMAN: acute motor axonal neuropathy. (3) AMSAN: acute motor and sensory axonal neuropathy with prominent sensory features. **COURSE:** Worsens over 2 to 4 wk, may involve respiratory compromise at presentation, or later on plateau and then recovery phase. **DIAGNOSTIC STUDIES:** (1) CSF: albumin-cytologic dissociation (elevated protein with a normal/low cell count); most dramatic after first week, initially can be absent/mild. (2) EMG/NCV: (not urgent) demonstrates demyelinating pattern, except in axonal variant. (3) Serology: Anti-CG1b if MFS, Anti-GM1 if AMAN. (4) MRI spinal cord: consider if doubtful and clear sensory level, explosive/rapid onset. GBS may show enhancement of spinal nerve roots (anterior > posterior). (5) Baseline pulmonary functions: normal values: negative inspiratory force (NIF) > −20, forced vital capacity (FVC) > 15 mL/kg. **TREATMENT:** (1) Admit: if quickly

progressing; poor respiratory function: needs ICU admission. (2) Monitor: respiratory function (if NIF < –20 or FVC < 15 mL/kg consider intubation) q2–4h initially, increase interval if stable or improving; bulbar function (ability to clear secretions, concern for aspiration); vital signs (concern for autonomic dysfunction). (3) IVIG (0.4 g/kg/d ×5 d). Adverse effects: proteinuria, aseptic meningitis, anaphylaxis if IgA deficient (check serum IgA level), HA, rash, and thromboembolic events. (4) Plasmapheresis (alternative to IVIG): exchange 200 to 250 mL/kg of plasma in—4 to 6 treatments q.o.d. (5) Pain control: NSAIDs, narcotics if severe, consider neuropathic agents (gabapentin, duloxetine, nortriptyline).

SPINAL CORD COMPRESSION[17,18]

PRESENTATION: (1) Sensory level (check both back and abdomen: pinprick, light touch, temperature). (2) Motor weakness level. (3) Bladder/bowel involvement. (4) No CNS involvement. (5) May have back pain or tenderness. (6) Reflexes either brisk or, if very early, hyporeflexic. **DIAGNOSTIC STUDIES:** Spinal cord MRI with and without contrast, including susceptibility sequence (blood). **TREATMENT:** (1) Dexamethasone 0.25 mg/kg IV, max 10 mg. (2) Neurosurgical consult (may need decompression). (3) Spinal shock in traumatic spinal cord injury necessitates methylprednisolone (30 mg/kg bolus over 15 min, 45 min pause, then maintenance 5.4 mg/kg/h for 24 h, consider for 48 h if initiated 3–8 h after injury). (4) Supportive care: bladder and bowel care, prevention of pressure sores. (5) PT/OT evaluation.

Transverse Myelitis[19,20]

See Chapter 17 for more details.

DEFINITION: Acute focal inflammation of spinal cord, usually affects children >5 y.

CAUSES: (1) Common: post-infectious (EBV, mumps, mycoplasma, rubella, and rubeola); autoimmune demyelination (first presentation of MS); and compression. (2) Infectious: viral (HSV, VZV, CMV, HHV6, EBV, HTLV, HIV, influenza A, measles, mumps, rubella, coxsackievirus, enterovirus, and echovirus); bacterial (abscess, mycoplasma, Lyme, syphilis, TB); fungal (actinomyces, blastomyces, coccidioides, aspergillus); and parasitic (neurocysticercosis, schistosoma). (3) Less common: vascular, neoplastic, and paraneoplastic process.

PRESENTATION: Onset over days, sometimes hours, preceded by nonspecific viral illness. Sensory level present, symptoms depend on level. High cervical: quadriplegia, respiratory paralysis (C3–5). C2–T1: weakness (weak and flaccid, hyporeflexic initially) in upper extremities. T1–T12: spastic paraplegia. L1–S5: bowel/bladder dysfunction. Back pain (common), fever, and malaise.

DIAGNOSTIC STUDIES: (1) MRI spine with/without contrast: if demyelinating (enhancing) lesion documented, also obtain brain MRI with/without contrast to evaluate for demyelinating lesion(s) in the brain (high suspicion for MS). (2) CSF: pleocytosis (lymphocytes) with normal to moderately increased protein, normal glucose; send for IgG index, cytology, oligoclonal bands. (3) Serum studies: SPEP, ESR, CRP, RF, ANA, ANCA, anti-Ro, anti-La, vitamin B_{12}, folate, copper, methylmalonic acid. (4) Viral/infectious workup: pending presentation and suspicion.

INITIAL TREATMENT: (1) IV steroids: methylprednisolone, dexamethasone. (2) Supportive care: bladder and bowel care, prevention of pressure sores. (3) PT/OT evaluation and treatment.

MYASTHENIA GRAVIS/CRISIS[21,22]

See Chapter 6 for more details.

DEFINITION: Neuromuscular disorder due to abnormal function or absence of acetylcholine receptors in neuromuscular junction (NMJ). Antibodies against AChR are common.

CLASSIFICATION: (1) Transient neonatal: transfer of maternal anti-AChR antibodies. Usually presents in first few hours after birth, very unusual after 3 d, lasts 2 to 4 wk. (2) Congenital: inherited genetic defect of NMJ proteins, antibody negative. (3) Juvenile: similar to adult, association with thymomas, remitting/relapsing course. (4) Myasthenic crisis: life-threatening. Presents with inability to clear secretions or maintain oxygenation. Precipitated by infection, surgery, stress, menses, medication change.

PRESENTATION: (1) General signs/symptoms: fever, drooling, cough, difficulty clearing secretions, increased work of breathing or shallow breathing, decreased O_2 saturation, ptosis, diplopia, difficulty swirling tongue in the mouth, dysphonia, dysphagia. Check how high the patient can count in a single breath (concern if <20), sustained upgaze (concern if <20 s). Evaluate neck flexion/extension (correlates well with diaphragmatic weakness), fatigable, proximal weakness, DTRs normal or brisk. (2) Cholinergic crisis (due to overmedication): diarrhea, cramps, sweating, muscle weakness, bradycardia, pupil dilation, and fasciculations. **TREATMENT:** Hold anticholinesterases, consider atropine. **DIAGNOSTIC STUDIES:** If new presentation: (1) Ice pack for evaluation of ptosis (if myasthenia, should improve ptosis as it slows down acetylcholinesterase activity). (2) Antibodies (anti-AChR, anti-MuSK). (3) EMG shows decrement in compound muscle action potential on repetitive nerve stimulation. If known diagnosis: CBC/diff, Chem20, serologies depending on probable cause of infection (if febrile), FVC, NIF. **MANAGEMENT:** (1) Admission (if not going to the ICU, also let the ICU know as may decompensate easily). (2) Cardiac telemetry. (3) Monitor: up gaze time, digits said in single breath, FVC, NIF. Intubate for FVC <15 mL/kg and NIF < −20). (4) Pharyngeal suction, nasogastric tube. (5) Methylprednisolone: 1 to 2 mg/kg/d, max 60 mg q.d. (may worsen it before making it better, monitor closely). (6) IVIG (0.4 g/kg/d ×5 d). Adverse effects: proteinuria, aseptic meningitis, anaphylaxis if IgA deficient (check serum IgA level first), HA, rash, thromboembolic events. (7) Plasmapheresis (alternative to IVIG): exchange 200 to 250 mL/kg of plasma q.o.d. until improvement, usually 5 to 6 exchanges. (8) Drugs to avoid: β-blockers, procainamide, lidocaine, aminoglycosides, tetracycline, ciprofloxacin, clindamycin, phenytoin, lithium, magnesium, procainamide, trimethadione, chloroquine, and D-penicillamine.

STROKE[23,24,25]

See Chapter 18 for complete details.

DEFINITION: Acute onset of a neurologic deficit due to disturbance in blood supply to the brain. Can be ischemic (decreased perfusion) or hemorrhagic. Several other conditions can present similarly, but must rule out stroke as it is medical emergency. While the frequency of stroke is high in the neonatal period, frequency in older children is less than adults. **PRESENTATION:** Acute onset of focal neurologic deficit, seizures (more common in children than adults, especially in the newborn). Important history: febrile illness, otitis media, mastoiditis, tonsillitis, recent varicella infection, known cardiac disease, neck trauma (dissection), sickle cell disease, family history of early stroke (<45 yo). Consider cerebral venous sinus

thrombosis: if dehydration, HA, optic disc edema. **DIAGNOSTIC STUDIES:** (1) NCHCT: to exclude hemorrhage, perform urgently in ED. Avoid CTA (vascular imaging) in children due to high radiation dose, consider of MRI/MRA, if available, and acute onset focal deficits localized to vascular territory. (2) Brain MRI/MRA with stroke protocol: perform urgently in ED. Includes DWI/ADC, FLAIR, T2, T1, susceptibility sequence, ± contrast if suspicious of a mass, and MRA head *and* neck. If suspicious for dissection, add fat saturation sequence. If suspicious for cerebral venous sinus thrombosis (HA, optic disc edema), or suspicious of stroke in neonate, add MRV (gold standard is CTV, but radiation dose is high). (3) Serum Labs: CBC/ w diff, Chem20, lipid panel, ESR/CRP, VDRL, HbA1C, B_{12}, folate; coagulation labs: fibrinogen, D-dimer, PT/INR and PTT, lipoprotein(a), homocysteine, Factor V Leiden, protein C and S, activated protein C resistance, prothrombin gene 20210G>A mutation, antithrombin III, beta-2-glycoprotein, antiphospholipid antibodies (anticardiolipin and lupus anticoagulant), vWF antigen. (4) Transthoracic echocardiogram (TEE): look for cardiac source (e.g., intracardiac clot). If neg and high suspicion or inconclusive, get TEE (not urgent). (5) In newborn: add to the above: placental pathology, lactate, pyruvate, serum amino acids, ammonia, urine organic acids, and ABG. **ACUTE MANAGEMENT:** (1) airway, breathing, and circulation. (2) BP control: during first 24 h, allow BP to autoregulate (allow compensatory hypertension). (3) PICU admission and neurosurgical consult: If changes in mental status, >⅓ of cerebral hemisphere involvement (might need surgical decompression); cerebellar stroke; brainstem stroke. (4) Treat seizures: consider fosphenytoin, levetiracetam. (5) Keep normoglycemic, normothermic. (6) Emergency thrombolysis by IV or endovascular infusion (e.g., tPA) is being studied. Strongly consider in patients >15 yo. Discuss with a referral center experienced in pediatric stroke.

ACUTE ATAXIA[26,27]

ETIOLOGY: In children, usually represents cerebellar dysfunction (vs. sensory ataxia). Most common causes in previously healthy children are: (1) Drug ingestion/intoxication: benzodiazepines, antihistamines, AED, alcohol; less commonly, heavy metals. (2) Acute cerebellar ataxia: most commonly post-infectious (no fever at presentation), previously up to 26% s/p varicella (less common now with vaccination), preceding illness 5 to 21 d before onset, typically young children (2–4 yo) but also older children/adolescents. (3) Autoimmune demyelination: explosive onset with gradual recovery. (4) Less common: direct cerebellar infection (i.e., cerebellitis), more concerning HA, vomiting, and systemic signs. **EXAM:** temperature, vital signs. Mental status: Concern for compression of brainstem due to cerebellar hemorrhage or mass effect. Cerebellar exam: speech ("scanning" with fluctuations in volume), finger-nose-finger and heal-to-shin (dysmetria), mirroring, rapid alternating movements (dysdiadochokinesia), intention tremor, tone, gait/tandem walk (ataxia), posture when sitting (titubation of trunk and/or head), pendular DTRs, symptoms unchanged with eyes open or closed. **EXAM LOCALIZATION:** (1) Cerebellar hemisphere: ipsilateral limb dysmetria and hypotonia (gait veers toward side of lesion), ocular dysmetria (over/undershoot saccade), dysdiadochokinesis, dysarthria. (2) Midline (vermis): truncal ataxia/titubation, difficulty with tandem gait. (3) Posterior cerebellum (flocculo-nodular lobe): eye movement disorder (nystagmus), postural and gait dysfunction. (4) Deep cerebellar nuclei: resting tremor, palatal (rare) and extremity myoclonus, opsoclonus.

OTHER CAUSES OF ATAXIA: (1) Sensory ataxia: GBS (broad-based gait, +Romberg sign, decreased DTRs). (2) Epileptic pseudoataxia. (3) Brain

tumors most likely present with slowly progressing ataxia (and other focal deficits); if truly acute, consider secondary hemorrhage or hydrocephalus. (4) Opsoclonus-myoclonus syndrome: dancing eyes, dancing feet syndrome; sometimes presents with ataxia, followed by eye movement abnormalities, then myoclonus; due to paraneoplastic autoimmune phenomenon (e.g., neuroblastoma). (5) If intermittent ataxia, consider episodic ataxia type 1 (EA1) or episodic ataxia type 2 (EA2), basilar migraine, metabolic disease (DD, severe vomiting/diarrhea, lethargy, unusual odors). (6) Functional/psychogenic (astasia-abasia gait).

DIAGNOSTIC STUDIES: (1) NCHCT and/or MRI with contrast: To evaluate for hemorrhage (CT better). MRI ideal to evaluate mass in the posterior fossa or signs of cerebellitis/edema. (2) Serum titers (acute and chronic): EBV, varicella, measles, mumps, echovirus, Coxsackie B. (3) LP (if normal scan): protein, glucose, cell count and differential, Gram stain/culture, EBV, VZV, enterovirus, and CMV. (4) Urine and serum toxicology. (5) EEG: consider if suspicious for seizures. (6) Metabolic work-up: if clinical suspicion: CBC, LFTs, ammonia, lactate, pyruvate, ketones, acid/base balance, urine organic acids, and serum amino acids. (6) EMG/NCS, if sensory ataxia suspected. (7) Urine catecholamines: VMA, HVA, if opsoclonus-myoclonus syndrome is suspected. **TREATMENT:** Depends on etiology. (1) Brain tumors: consult neurosurgery, hematology/oncology team. (2) Acute postinfectious cerebellar ataxia: admit, supportive treatment, serial neuro exam q4h. (3) Episodic ataxias: no need for admission. EA1: some patients respond to anticonvulsive medication. EA2: acetazolamide 125 mg b.i.d. in young children, 250 mg b.i.d. in older children.

BELL PALSY[28,29,30]

DEFINITION/ETIOLOGY: *Idiopathic* acute lower motor neuron facial palsy. Usually, the main portion of the facial nerve affected is at the temporal bone portion. Respiratory illness usually antecedes its presentation, can be associated with viral inflammation (HSV, VZV, HIV, EBV, hepatitis, Lyme [25%–40% in endemic areas]).

OTHER CAUSES OF LOWER MOTOR NEURON FACIAL PALSY (NOT BELL'S): (1) Trauma: instrumental delivery, facial fractures. (2) Infiltrative: brainstem tumor (pontine glioma, cerebellopontine angle tumor), TB, leukemia, parotid tumor. (3) If bilateral neonatal/congenital: consider Moebius syndrome (aplasia of facial nerve nuclei/muscles; often involves multiple CN), muscular dystrophies, congenital myasthenia syndromes, myotonic dystrophy. (4) If recurrent: consider Melkersson–Rosenthal syndrome (recurrent paralysis with facial/lip swelling and fissured/furrowed tongue). (5) Vascular: hypertension, diabetes, and other vascular (rare in children). (6) Metabolic: hypothyroidism (often bilateral), hyperparathyroidism.

PRESENTATION: Unilateral upper and lower facial weakness: unable to furrow forehead, close eyelid, puff cheeks, whistles; asymmetric smile; and drooling. Usually presents with pain/numbness around ear and impairment of taste (also from CN VII). **EXAM:** BP, otoscopy, mouth evaluation, parotids, motor exam of upper and lower face, taste of anterior ⅔ of tongue (if cooperative); exclude other cranial nerve involvement, especially CN V (looking for cerebellopontine lesion).

DIAGNOSTIC STUDIES: (1) Generally not required if considering Bell palsy. (2) If in an endemic area: Lyme serology. (3) If neck pain, fever, HA: strongly consider LP to rule out meningitis. (4) If presenting with other signs: consider brain MRI with contrast. Also recommend MRI if no improvement after 1 mo. **TREATMENT/PROGNOSIS:** Patch eye closed when sleeping,

artificial tears during the day q1 to 2 h. If <7 d since onset, give prednisolone 1 mg/kg/d for 7 d with 7-d taper (still controversial, benefits of steroids in children not definitively proven). Use of Acyclovir has not shown benefit. Generally have good prognosis with or without treatment.

TRAUMATIC BRAIN INJURY (TBI)[31,32,33]

See "Coma and Disorders of Consciousness" below.

COMMON CAUSES: Motor vehicle accidents and sports (hockey, football, lacrosse, and horse riding).

CLASSIFICATION: Mild TBI ("concussion") (GCS 13–15); moderate TBI (GCS 9–12); severe TBI (GCS 3–8). **Concussion:** Complex pathophysiologic process affecting the brain, induced by traumatic biomechanical forces. Cognitive changes ± loss of consciousness (LOC).

GRADES: I: No LOC, symptoms <15 min. **II:** No LOC, symptoms >15 min. **III:** Any LOC.

SPORTS-RELATED CONCUSSION: Grades II–III need neurologic evaluation. Return to play guidelines: (1) Grade I: rest 15 min, return to play. (2) Multiple Grade I, any Grade 2, or Grade 3 (LOC seconds): rest 1 wk. (3) Multiple Grade II, any Grade III (LOC minutes): 2 wk. (4) Multiple Grade 3: ≥1 mo. Always return to play gradually. **PRESENTATION:** (1) Acute symptoms: HA, dizziness, confusion, amnesia (anterograde > retrograde), nausea/emesis, and seizure. (2) Chronic symptoms: HA, light sensitivity, worsening migraines, confusion, mental slowness, poor attention and concentration, fatigue, irritability, and sleep disturbances. **Exam:** BP, HR. Evaluate for depressed cranial fracture, pain, or fracture in any other part of body. Otoscopic examination (otorrhea suggests CSF leak), nasal leak (consider CSF). Look for battle sign (bruising temporal/posterior auricular area), raccoon eyes (base of the skull fracture). Mental status exam, GCS, CN exam: CN I (anosmia-cribriform plate injury), III, IV, VI (diplopia, orbital fracture, cavernous sinus injury, and stretching/compressing nerve against skull base), VII (facial palsy, hearing loss from fracture of petrous portion of temporal bone), and motor exam.

DIAGNOSTIC STUDIES: (1) Canadian CT head rule[34]: *(a) High risk for neurologic intervention:* GCS <15, 2 h post trauma, suspected open or depressed skull fracture, any sign of basal skull fracture, >2 episodes of emesis. *(b) Medium risk (brain injury on CT):* retrograde amnesia for events >30 min prior to trauma, dangerous mechanism of injury including fall >3 feet or 5 stairs. Obtain NCHCT to evaluate for intraparenchymal hemorrhage, subdural hematoma, epidural hematoma, IVH, bone fracture, and midline shift. (2) Head/neck CTA/MRA: if dissection is considered. (3) Brain MRV: if displaced skull fracture adjacent to venous sinus. CTV is gold standard, but concern for significant radiation. (4) Neck CT ± spine MRI: if unconscious or cannot clear the spine medically. (5) Brain MRI: non-emergent to better determine extent of lesion and diffuse axonal injury. (6) EEG: if seizure or suspicion of seizure. (7) Test for presence of CSF: if fluid from nose, check glucose (mucus has no glucose); beta-2 transferrin.

ACUTE MEDICAL MANAGEMENT[35]: (1) Airway, breathing, and circulation. Always consider internal bleeding if hemodynamically unstable. Use crystalloids for resuscitation. (2) C-spine immobilization. (3) ICU admission: if GCS <8 and neurosurgical consult required (hemicraniectomy, ICP monitoring). (4) Keep head of the bed elevated to 30°C. (5) Seizure prophylaxis: fosphenytoin load 20 PE/Kg and continue with phenytoin PO/PNGT

5 to 10 mg/kg/d t.i.d. with phenytoin goal of 15 to 20 mcg/mL for 7 d.[36] AEDs are shown to decrease frequency of early post-traumatic seizures, not shown to decrease incidence of late post-traumatic seizures. (6) If presented with seizures, treat with (fos) phenytoin or levetiracetam. Continue AED ×6 mo with repeat EEG. (7) Start D5 NS IV infusion (watch for SIADH and cerebral salt wasting), Na^+ goal 140 to 150. (8) Keep room well lit, quiet setting. (9) Try to avoid benzodiazepines (can produce agitation and can cloud neurologic exam). (10) Treat pain with acetaminophen/opioids. (11) Aim for normoglycemia, normothermia.

ALTERED MENTAL STATUS (AMS)[37]

General Approach

DEFINITION: Any change from the baseline mental status; multiple causes, most important to treat underlying etiology. **ETIOLOGY:** (1) Infection: intracerebral (meningitis, encephalitis), extracerebral (pneumonia, UTI), and parainfections: ADEM. (2) Withdrawal: alcohol, benzodiazepines, opioids, and other sedatives. (3) Metabolic: hypoxia, electrolyte derangement (especially hyponatremia), hypoglycemia, and renal/pulmonary/hepatic insufficiency. (4) Trauma: head injury, burns, and heat stroke. (5) Heavy metals: lead, mercury. (6) Toxins or drugs: steroids, anticonvulsants, narcotics, and recreational drugs. (7) Vascular: TIA, stroke, intraparenchymal bleed, and hypertensive encephalopathy. (8) Endocrine: thyroid, adrenal, and parathyroid dysfunction. (9) Deficiency: thiamine, folate, and B_6. (10) CNS pathology: mass lesion, epilepsy, and paraneoplastic encephalopathies. (11) Psychiatry: psychosis, bipolar (mania), and catatonia. **EXAM:** Vital signs. Signs of mastoiditis, otitis media, evidence of drug use, and new heart murmur (cardioembolic events). Full neurologic exam (attention to: level of alertness, CN deficits, preference for using single extremity, withdrawal to pain, and finger-nose-finger exam).

DIAGNOSTIC STUDIES: (1) Labs: CBC w/ diff, Chem 20, full toxic screen (blood, urine), TSH, free T_4, and thiamine. (2) Brain MRI ± contrast. (3) LP, if history of fever, recent fevers ± use of antibiotics (partially treated meningitis). (4) EEG, if concerns of NCSE.

TREATMENT: Tailored to the likely cause of the AMS. (1) If agitated: use medications when necessary. Benzodiazepines and antipsychotics are the 1st choice but can also aggravate delirium, exacerbate underlying causes, cloud neurologic exam and cause adverse reactions (acute dystonic reactions). (2) Benzodiazepines: preferred when concern for NCSE or withdrawal symptoms are present; if history of liver insufficiency or long QT syndrome that prevents use of antipsychotics (e.g., lorazepam 0.05–0.1 mg/kg q4h), watch for respiratory depression.(3) Antipsychotics: atypical agents (risperidone, olanzapine) preferred in children due to fewer side effects than typical medications. If no response, can try haloperidol, check baseline and daily EKG to monitor for prolonged QTc. Consider standing dose with p.r.n dosing instead of chasing the acute agitation. (4) Environmental changes: keep room well lit, decrease environmental noise, allow mobilization to the extent consistent with safety, and have familiar people present.

AMS with Fever (Meningitis/Encephalitis)[38,39]

See Chapter 22 for additional details.

MENINGITIS: Inflammation of the meninges, esp. arachnoid and pia mater ("leptomeninges") (Table 4.2).

TABLE 4.2 CSF Findings in Meningitis

	Cells	Cell Count	Protein (mg/dL)	Glucose
Bacterial	PMN	>500	>250	<½ serum
Viral	Lymph	50–1,000	<100	>½ serum
Fungal	Lymph	100 +	25–500	<½ serum
TB	Lymph	100–500	50–500	<½ serum

Newborn CSF WBC: 1 d old: up to 30 cells/field; 2 wk old: 15 cells/field; 1 mo old: <5 cells/field. Up to 50% PMN can be considered normal.

Acute Bacterial Meningitis

ETIOLOGY: (1) By age:

- *Neonates:* GBS, *E. coli*, gram-negative rods, and *L. monocytogenes*.
- *Infant 1 to 3 mo old:* GBS: late onset, *S. pneumoniae*, *L. monocytogenes*, *H. influenza* type B, *N. meningitidis*, and *Salmonella* sp.
- *3 mo to 12 y old: S. pneumoniae*, *N. meningitidis*, and *H. influenza* type B (rare due to vaccination).
- *12 yo to adult: N. meningitidis*, *S. pneumoniae*.

(2) Rarely due to *S. pyogenes* and *S. aureus*. (3) Always have TB in differential if immunocompromised, from an endemic area or multiple CNs involved. (4) Almost all cases due to blood-borne dissemination, low proportion caused by local spread (mastoiditis, skull trauma), particularly pneumococcus. (5) CSF leaks → *S. pneumoniae*, *S. epidermitis*, *S. aureus*, and Corynebacterium. (6) VP shunt → *S. epidermitis*, Corynebacterium. (7) Lyme in endemic areas. (8) Functional/anatomic asplenia (sickle cell disease, nephrotic syndrome, IgG deficiency)→ encapsulated organism (*S. pneumoniae*, *H. influenza* type B, *N. meningitidis*). **KEY HISTORY POINTS:** HAs, seizures, vaccine history, recent infections (sinusitis, otitis media), exposure to patients with meningitis, immunological status, HIV+, travel history, recent head trauma/craniotomy, VP shunt, and history of recent antibiotic use. **Exam:** (1) *Classic signs seen in ages >2 y:* fever, HA, neck stiffness, Brudzinski and Kernig signs. (2) *Neonates and infants <2 y old:* absent/indeterminate neck stiffness; will present with irritability, poor oral intake, lethargy, bulging fontanelle, seizures, and vomiting. (3) Seizures (usually after fever), CN involvement, especially CN VI (if multiple: TB), and other focal neurologic signs. (4) Petechial/purpuric rash/septic shock in meningococcal infection. (5) If new changes or focal exam consider vasculitis → thrombosis and infarction. (6) Increased ICP (check optic discs), secondary vasogenic or cytotoxic edema.

DIAGNOSTIC STUDIES: (Do not delay antibiotics for LP or imaging!) (1) Blood*:* CBC/diff, Chem20 (especially looking for hyponatremia/SIADH), ESR, CRP, blood culture, and Lyme serology (where endemic). (2) LP: Opening pressure (do not forget to measure this!), Gram stain/culture, protein, glucose, cell count, VZV, HSV, and CMV PCR assays. If TB is considered, ask for TB culture. Save extra CSF for future studies if needed. (3) NCHCT before LP: immunocompromised, history of CNS disease (mass lesion, stroke, and focal infection), new onset of seizures, seizure >30 min (concern for increase ICP), papilledema, AMS, and focal deficit. (4) MRI with/without contrast and MRA (after LP ± NCHCT, start of antibiotics): if focal deficit, AMS (looking for abscess, vasculitis, stroke). Contrast to look for meningeal enhancement. If LP done before MRI, leptomeningeal enhancement may be seen (even without meningitis). Use clinical judgment. **TREATMENT:** Choice depends on age and local resistance patterns. (1) First line*:* Third-generation cephalosporin

(Ceftriaxone or Cefotaxime) + vancomycin and acyclovir (for 48 h until HSV PCR comes back negative). (2) If <3 mo: add ampicillin for *Listeria*. (3) When pathogen identified, tailor the treatment pending sensitivities. (4) Duration of treatment: 7 d for *N. meningitides*; 10 to 14 d for HiB and *S. pneumonia*; 14 to 21 d for other organisms (consult ID when LP is consistent with meningitis). (5) If persistent fever after treatment started: consider repeat MRI w/ contrast to look for abscess and hygromas (both pneumococcus and HiB can → hygroma). Repeat LP if concerned for resistant organism. (6) ID consult*:* involve early. (7) Steroids: controversial. Studies show ↓ CSF inflammation and ↓ auditory complications, pathogen specific, maximum benefit seen with HiB (which rarely presents after immunization). Adverse effects may cause ↓ CSF penetration of antibiotics due to ↓ blood-brain barrier inflammation. Can use: dexamethasone (ideally before first antibiotic treatment) at 0.15 mg/kg/d q.i.d. for 2 to 4 d. Do not use in neonatal meningitis. (8) If hyponatremia: obtain serum and urine osmolarity; assess Na^+ concentration if SIADH. If SIADH, restrict fluids. If not definitive SIADH, do not jump to restrict fluids as fluids are needed to maintain cerebral circulation. **ACUTE COMPLICATIONS**: Effusions, empyema, hydrocephalus (all need neurosurgical evaluation), seizures, hypoglycemia, septicemia, DIC, metastatic infection, cerebral edema, increased ICP, tonsillar herniation, and stroke.

Aseptic/Viral Meningitis/Encephalitis[39,40]

PRESENTATION: (1) Meningitis: common in children, presents with HA, fever, and neck stiffness following a flu-like illness. Children don't look toxic and somnolence is uncommon (yet hard to differentiate from early bacterial meningitis without LP). (2) Encephalitis: HA, fever, and encephalopathy. Possibly focal neuro signs, seizures, or behavioral issues (may confuse with psychiatric illness). ~50% due to virus. **ETIOLOGY:** See Tables 4.3 and 4.4.

TABLE 4.3 Viral Causes of Meningitis/Encephalitis

Virus	Distinguishing Features
Enteroviruses	Highest incidence (includes echovirus, coxsackievirus, and poliovirus) Diffuse body rash
Coxsackie	Hand, foot and mouth disease Myocarditis, pericarditis, pleurisy
Echovirus	Myopathy and conjunctivitis
Polio	Very infrequent now due to vaccination Can present with meningitis before paralysis
HSV1, HSV2	Either primary infection or reactivation After neonatal period HSV1 more common In newborn, HSV2 can be blood-borne and cause multiorgan failure
Mumps	Parotitis, orchitis, pancreatitis
CMV	Abnormal LFTs and retinitis
EBV	Pharyngitis, lymphadenopathy, splenomegaly Atypical lymphs, abnormal LFTs
VZV	Typical skin rash Small vessel encephalitis usually occurs in the immunosuppressed
Measles	Typical rash, lymphadenopathy, conjunctivitis
Arboviruses	Due to mosquito bites West Nile virus, eastern equine encephalitis, Japanese encephalitis (S/SE Asia)
Adenovirus	Conjunctivitis, vomiting, diarrhea

TABLE 4.4 Nonviral Causes of Infectious Encephalitis

Bacterial	TB, Syphilis, *Mycoplasma pneumoniae, Salmonella typhi, Tropheryma whippeli*, Legionella, Brucellosis, Leptospirosis, *Borrelia burgdorferi, Listeria monocytogenes* (common in transplant patients)
Rickettsial	*Rickettsia rickettsii* (Rocky Mountain spotted fever), Ehrlichiosis, *Coxiella burnetti* (Q fever)
Fungal	Cryptococcus, aspergillosis (common in transplant and immunosuppressed patients), candidiasis, and hystoplasmosis
Parasitic	Cerebral malaria, toxoplasmosis, schistosomiasis, human African trypanosomiasis

DIAGNOSTIC STUDIES: Same studies as for bacterial meningitis above with additional ones:

1. CSF: usually lymphs, but may have PMNs in the first 48 h. HSV can cause bloody tap.
2. MRI findings:
   - HSV 1,2: abnormal signal in temporal lobes (mainly hemorrhage), insular cortex, frontal lobes, and thalamus. May show cerebellar involvement and leptomeningeal enhancement after gadolinium.
   - VZV: gray and white matter abnormalities representing vasculitis and infarction.
   - Enteroviruses: may have abnormalities in brainstem and thalamus.
   - Arboviruses: may have abnormalities in basal ganglia and thalamus.
3. EEG: indicated when AMS with MRI lesion to correlate; diffuse slowing, may show focal abnormalities and periodic lateralizing epileptic discharges (PLEDS—seen mainly in HSV 1,2).

TREATMENT: (1) Admit. (2) Antibiotics and acyclovir: for 48 h (pending CSF cultures and HSV PCR*).* (3) *If+HSV PCR:* acyclovir 10 mg/kg q8h for 21 d (discuss with ID). Monitor renal function, liberal IVF, PO. (4) Treat seizures and raised ICP per usual.

Coma and Disorders of Consciousness[37,41]

DEFINITION: State of unarousable unresponsiveness, absent sleep/wake cycle, no auditory response, and no visual function. **Etiology**: (1) *Trauma:* accidental or non-accidental (retinal hemorrhages, bulging fontanelle). (2) *Infectious:* sepsis, meningitis, meningoencephalitis, abscess, ADEM (onset 1–2 wk after viral/other infections or vaccination producing encephalopathy, including coma, ± focal neuro signs), cerebellitis. (3) *Metabolic:* hypoglycemia, DKA, renal/adrenal/liver failure, hyperammonemia, hypo/hyper Na^+, inborn error of metabolism, myxedema-thyrotoxicosis, hypo/hyperparathyroidism, hypo/hyper Mg^{2+}. (4) *Epilepsy:* postictal, SE, NCSE. (5) *Hydrocephalus:* 1st episode (post IVH, CNS infection, tumor), shunt failure. (6) *Toxic:* heavy metal, drug overdose, suicide attempt. (7) *Vascular:* IPH, SDH, SAH, EDH, hypertensive encephalopathy, cerebral venous sinus thrombosis, stroke. (8) *Hypoxia-ischemia:* cardiac/respiratory arrest, suffocation, drowning, recent gastroenteritis in hemolytic-uremic syndrome. (9) *Structural:* tumor, prion disease, pituitary tumor, and paraneoplastic syndromes. **Exam:** GCS and modified GCS for children. (If age <12 yo or worsening mental status,

look for signs of increased ICP (hypertension, bradycardia, papilledema, upgaze deficit, and CN VI palsy), examine CNs looking for herniation). Look for nonreactive pupil with *no direct or consensual response*, CN III palsy suggesting uncal herniation, oculocephalic response (if no concern for cervical cord injury), corneal response, nose tickle, gag/cough, head turn to pinch, decerebrate/decorticate posturing. *Fundoscopic examination:* papilledema (increased ICP) and macula star (hypertensive encephalopathy). **EMERGENCY MANAGEMENT:** See Tables 4.5, 4.6, and 4.7.

First Episode Psychosis[42–45]

DEFINITION: Gradual emergence of unusual behavior and/or social withdrawal and failing school performance, auditory hallucinations >> visual hallucinations, paranoia.

EVALUATION: History of seizure disorder? Is there hard evidence of true cognitive decline or is this baseline? Family history of schizophrenia and psychosis? Fluctuating mental status, presence of pyramidal, extrapyramidal, or cerebellar signs - incompatible with primary psychosis.

TABLE 4.5 Emergency Management of Coma/Disorders of Consciousness

ABCs	*A*irway, *b*reathing, *c*irculation
Labs STAT before treatment	CBC w/ diff, Chem20, finger stick, PT/PTT, INR, U/A, CRP, ESR, TSH, free T4, ABG, ammonia, lactate, blood cultures, urine cultures, full toxicology screen, and hold tube
EKG	Check for associated arrhythmia, ischemia
Intubate	If GCS <8, evidence of herniation on exam or unable to protect airway
Neuroimaging	STAT NCHCT MRI brain with contrast when stable; consider MRA/MRV according to the presentation
Mannitol	1 g/kg bolus if evidence of herniation
Treatment of status	Assume subtle motor status epilepticus if tonic eye deviation or nystagmus
LP & Antibiotics	
If fever, child <12 mo, no obvious source	Ceftriaxone, vancomycin, acyclovir; LP for opening pressure, cell count/diff, Gram stain/culture, glucose, protein, HSV, CMV, VZV PCR, enterovirus, and oligoclonal bands if ADEM suspected
If GCS <12 and deteriorating	Defer LP and start antibiotics
Neurosurgery consult	If evidence of herniation, posterior fossa hemorrhage, significant mass, or raised ICP
Urine catheter and arterial line	Consider if needed
EEG/LTM	If question of NCSE (asymmetry on EEG suggests focal pathology, PLEDs in herpes encephalitis)
Other	Tailor fluids based on initial labs/herniation syndrome Normalize body temperature Correct electrolyte and acid–base imbalances
Admit	ICU admission

TABLE 4.6 Specific Emergency Management of Increased ICP[35]

ICP & cerebral perfusion	Goal ICP <20 mm Hg and cerebral perfusion > 60–70
Head position	Head midline and elevated 30°C
Mannitol	Bolus 1 mg/kg bolus over 10–20 min and then Q6h. Contraindicated with low BP, anuria. Hold further doses if osmolar gap < 12 (osm gap = measured − calculated serum osm), serum osmolarity >320, serum Na^+>160
Hypertonic saline	Goal serum Na^+ 145–155 For 23% NS, give 15–30 cc via central line and then q6h For 3% NS, up to 50 cc/h per peripheral line up to 12 h, a central line required.
Hyperventilate	pCO_2 goal of ~30 mm Hg
Labs	Chem 7, serum osmolarity, fluid balance q6h
Neurosurgery consult	Hydrocephalus, persistent increased ICP, mass effect, large stroke, and posterior fossa mass/hemorrhage
Treat seizures	Seizures will further increase ICP
Temp	Maintain normothermia
ICP monitor	Consider in severe trauma

DIFFERENTIAL DIAGNOSIS: (1) *Neurologic:* head trauma, infections, brain tumors, seizures, multiple sclerosis, metachromatic leukodystrophy, Huntington disease, Wilson disease, vCJD, SSPE, autoimmune disease (anti-NMDA receptor encephalitis, Hashimoto encephalopathy), late onset GM2-gangliosidosis, Niemann–Pick disease (type C) , inborn error of metabolism (urea cycle disorders, homocysteine remethylation defects/cobalamin metabolism defects, cystathione b-synthase deficiency, cerebrotendinous xanthomatosis, nonketotic hyperglycinemia, and succinic semialdehyde dehydrogenase). (2) *General medical conditions:* endocrinopathies (thyroid, adrenal, pancreatic), autoimmune disorders (SLE), vitamin deficiencies (B_{12}), hepatic or erythropoietic disorders of metabolism (acute intermittent porphyria). (3) *Adverse reaction to prescribed medication:* steroids, l-dopa, anticholinergics, and H_2 blockers.

TABLE 4.7 Emergency Management of Suspected Inborn Errors of Metabolism[47, 48]

Labs (in addition to above)	Pyruvate, urine organic acids, plasma amino acids, coQ10
Nutrition	Stop feeds Start dextrose 10% with electrolytes to prevent tissue catabolism
Acid/base & electrolytes	Follow frequently (q4–6h)
Bicarb	Up to 20–40 mmol/kg to correct metabolic acidosis
Na benzoate	250 mg/kg load, then 250 mg/kg/d infusion, to treat hyperammonemia
Supplements	Vit. B_{12} 1 mg IM Biotin 10 mg QD Thiamine 50 mg QD L-carnitine 25 mg/kg/d q6h

INITIAL INVESTIGATION (RULE OUT SECONDARY CAUSES): (1) Labs: CBC/diff, Chem 20, ESR, CRP, TSH, free T4, TPO, anti-TSH, ANA, ceruloplasmin, serum copper, 24 h urine collection for copper, HIV, VDRL/RPR, full serum/urine toxicology, Vit. B_{12}, folate, urinary porphobilinogen, and cholesterol panel. Consider paraneoplastic panel (e.g., anti-NMDA Ab). (2) Additional labs, if concern for inborn error of metabolism: plasma amino acids, urine organic acids, homocysteine, lactate, pyruvate, and ammonia. (3) LP: if signs of meningismus; cell count/differential, glucose, protein, Gram stain/culture, HSV, CMV, VZV, and 14-3-3 protein. Consider CSF paraneoplastic studies if concern for limbic encephalitis. (4) EEG. (5) MRI brain with contrast. **TREATMENT:** (1) Psychiatric consultation. (2) Treatment based on initial investigation results. (3) Antipsychotics: second generation (olanzapine, risperidone, quetiapine) preferred initial antipsychotics.

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5 Epilepsy and Paroxysmal Events

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Definitions

Epilepsy and paroxysmal events are among the most common reasons to seek consultation from a pediatric neurologist. Definitions are listed in Table 5.1.

Diagnostic Approach[1]

(1) General: The common general neurology approach implies: (1) description of signs and symptoms, (2) localization, and (3) etiological investigation. Specific combinations of as well as related medical information may provide information on a possible (4) epilepsy syndrome.

(2) Temporary management: (a) **Recurrent paroxysmal event of uncertain etiology** is a neutral term that allows for later adjustment of the diagnosis, and often patients can be managed temporarily without a more specific diagnostic label. (b) **First, do no harm.** A false-positive diagnosis may be more harmful than a delayed diagnosis. A wrong diagnosis does not address the true condition, and may result in parental anxiety, patient stigmatization, and exposure to unnecessary testing and potentially harmful treatment. (c) **Treatment trials with antiepileptic drugs** (AED) are discouraged as they are often false-positive, as less events on AED may be due to inherent low frequency or natural evolution. Patients with frequent, threatening events of unknown etiology may be admitted for urgent diagnosis and therapy. (d) **Make a clinical diagnosis**. EEG and auxiliary tests have limitations.

Step 1: Structured History and Physical (What are the clinical features?)

(1) History: Analyze the event in sequence: (1) setting, (2) onset, (3) core presentation, (4) end and postictal features.[1] Describe the presentation in the patient's or family's own words, and obtain a history from both the patient and a witness of the event (Table 5.2).

(2) Physical examination: See Chapter 1 of this book. Skin examination by Wood's lamp and hair examination, ophthalmologic exam, and presence of dysmorphic features may provide important clues. Check for injuries sustained during or after an event (e.g., burns from hot drinks, open fire, radiator). Activation procedures (e.g., hyperventilation) can be performed in office-based outpatient setting, provided appropriate safety measures are in place.

Step 2: Epileptic vs. Nonepileptic Event (Is it an Epileptic sz?)

Nonepileptic paroxysmal events: Key clinical features of the event assist in formulating a differential diagnosis (see Table 5.15 [by age] and Tables 5.16–5.20 [by key feature]).

Psychogenic nonepileptic szs (PNES): Spells that resemble epilepsy but have psychogenic rather than physiologic origin. Usually somatoform

TABLE 5.1 Definitions of Epilepsy and Seizures

Seizure (sz): Transient occurrence of signs and symptoms due to excessive or synchronous neuronal activity in the brain.

Epilepsy: Two or more unprovoked epileptic szs (status epilepticus and multiple szs in 24 h are both considered a single event, only febrile szs do not qualify as epilepsy).

Epilepsy syndrome: A complex of signs and symptoms that define a unique epilepsy condition. This may include sz type, age at onset, gender predominance, etiology, behavioral or cognitive comorbidity, diurnal variation or association with sleep, precipitating factors (sleep deprivation, photic stimulation), family history. A syndromic diagnosis has implications for management, developmental prognosis and epilepsy outcome, genetic testing, and heritability.

Adapted from Vendrame M, Loddenkemper T. Approach to seizures, epilepsies and epilepsy syndromes. In: Grigg-Damberger MM, Foldvary-Schaefer N. Sleep-related Epilepsy and Electroencephalography. *Sleep Med Clin.* 2012;7(1):59–73.[1]

TABLE 5.2 Structured History and Physical Examination

History Taking: Key Elements	
General	• Patient: development, birth Hx, PMH (e.g., cardiac, neurologic, psychiatric, immunologic, infectious, trauma) • Family: szs, febrile convulsions, tics, ADHD, behavioral problems, developmental delay, significant learning disabilities, neurological or genetic syndromes, including neurocutaneous disorders, psychiatric or mental health diagnoses, unexplained or early death, malignancies • Exposures, psychosocial: insect bites, travel (e.g., malaria, cysticercosis), stressors, life events
(1) Setting	• Who witnessed the sz? Who is the source of the history? Always question the patient and a witness if possible • Where (environment): home, school, bed, in- or outside, cross-situational, alone or witnesses present • What (activity engaged at time of onset): awake, asleep, active, sitting, standing, TV/computer • When (triggers, circumstances immediately prior): feeding (timing, certain foods, missed meals), medication, drugs, alcohol, or toxins (intake, ingestion, recent change), sleep, sleep transitions, or sleep deprivation, menstruation, exercise, auditory and visual stimuli, headache, head trauma, emotions, fever, other triggers and reflex epilepsies (e.g., hot water) • How: frequency, duration, time course (worsening, decreasing, stable), diurnal pattern or time of day; if clusters, interval and duration
(2) Onset	• Aura: premonitory experiential sz symptom of sensory, gustatory, olfactory, auditory, abdominal, or more complex experiences, frequently providing localizing clues

TABLE 5.2 Structured History and Physical Examination (Continued)

History Taking: Key Elements

Aura	Symptom
Somatosensory	Burning, tingling, pain, numbness
Visual	Simple fixed objects, complex, moving
Auditory	Sounds, voices
Olfactory, gustatory	Smell, taste without external source (usually bad smell or taste)
Epigastric	Rising abdominal sensation
Déjà vu, jamais vu	Sensation of familiarity, unfamiliarity
Derealization	Sensation out of body, seeing self "like on camera"
Cephalic	Unspecified, unexplainable feeling in head
Autonomic	Palpitations, (cold) sweat, shivers, piloerection, urge to urinate or defecate

Note: Prodromal symptoms in syncope—cold sweat, lightheadedness, graying or blackening of vision "like a curtain," palpitations, chest pain, weakness or buckling of legs, sensation of voices and sounds being distant

(3) Core presentation, evolution	Feature	Poor Descriptors	More Accurate
	Motor	Shaking, twitching, seizing, grand mal	Tonic activity/dystonic posturing (tense unnatural posture) Myoclonic movements (fast flexion, rapid relaxation) Clonic movements (recurrent biphasic, rhythmic, synchronous motor movements) Tonic–clonic (first posturing, then clonic movements) Head version (forcible slow deliberate head and eye deviation, often with clonic movements) Epileptic spasms (rapid forward hip/abdomen flexion with extension of arms, brief tonic moment, then relaxing, often clustering; more subtle or extension, or a combination can also be seen) Eye movements (nystagmus, forced sustained deviation)
	Impairment of consciousness	Out of it, zoned/blanked out, nobody home, lost it, out, gone	Unconscious, unresponsive, loss of awareness, loss of memory, attempting to answer, eye contact, response to voice, touch, or noxious stimuli, agitation or fending people off

(continued)

TABLE 5.2 Structured History and Physical Examination (Continued)

History Taking: Key Elements

	Feature	Poor Descriptors	More Accurate
	Fall	Fall, went down	Found down, helped to ground, slumped, buckled, partial loss of tone while sitting or standing, sudden total loss of tone and posture, forced brisk forward motion with trunk and head, injury
	Automatisms	Weird motions with hands or lips	Simple repetitive movements or natural-looking sequence of movements, including picking movements, hand washing or -rubbing, lip smacking or tongue licking, chewing
	Autonomic system	Off color, wet, sweaty	Piloerection, flushing, pallor, cyanosis, diaphoresis, vomiting, sensation of cold or feeling hot, loss of urine, fecal incontinence
	Oral, language	Making strange sounds	Gagging, choking, guttural sound, swallowing, drooling, vocalization (scream, moan, grunt, hum, mumble), verbalization (speech, gibberish), aphasia (speech impaired) or anarthria (speech motor control impaired)
	Note: Qualitative descriptors include rhythmicity, frequency, synchrony, amplitude, symmetry, quality (fast-and-slow phase or oscillatory, violent (jerks, thrashing), subtle (tremulous, trembling, shivering), sequence (body parts involved, tonic phase, clonic phase)		
(4) End	Todd's paresis		Postictal weakness of arm, leg, or face, typically resolves in 24–48 h
	Vision		Hemianopia
	Language		Aphasia or dysphasia
	Mental status		Combativeness, agitation more diagnostic than brief bewilderment or mild confusion, rapidly alert/oriented after loss of consciousness suggests syncope
	Posture		Are events position related; i.e., do they always occur while standing (syncope)?

ADHD, attention deficit hyperactivity disorder; Hx, history; PMH, past medical history; sz, seizure.
Table in part based on,[1,2,39] in addition to own data.

(conversion more often than somatization disorder, rarely factitious, malingering). Ten percent to thirty percent of patients with PNES also have epileptic szs. Poor prognosis of PNES with significant disability is associated with longer duration and prolonged course of symptoms and with late diagnosis and psychotherapy. Better prognosis with early diagnosis, no psychiatric comorbidity, less dramatic features (e.g., limpness rather than thrashing). In children respectfully and carefully assess for psychosocial stressors, sexual abuse, and mood disorders (Table 5.3).

Step 3: Localization (What regions in the brain are involved?)

Localization of sz focus assists in (1) classification and (2) etiology (e.g., focused high-resolution imaging of the temporal lobe) and (3) determining candidacy for epilepsy surgery. Semiology may reflect only the symptomatogenic zone (area of the cortex that is generating the symptoms) but epileptic activity may have originated in and spread from a "silent" cortical area.[3] Different aspects from the semiology provide information about lateralization (in which hemisphere) and localization (in which area) (Table 5.4)[1].

TABLE 5.3 Psychogenic Nonepileptic Seizures—Diagnostic Considerations

A. Features suggestive of PNES (most differentiating features are in bold):
History: **clinical presentation and features can be influenced by others,** multiple normal EEGs, resistance to multiple AEDs, unusual triggers (stress, pain, specific movements, sounds, lights), antecedent of sexual trauma or conversion disorder, occur only around others or only when alone, extensive positives on review of systems, vague somatic symptoms suggesting somatization, coexistence of poorly defined diagnosis (e.g., fibromyalgia, chronic pain, fatigue), depression, anxiety, inappropriate affect or lack of concern ("la belle indifference"), or inducibility by suggestion

Semiology: Side-to-side head shaking, bilateral asynchronous movements, crying, moaning, stuttering, back arching, pelvic thrusting, presence of stuffed animals ("teddy bear sign") in adolescent or adult patients, **eye flutter** or eye closing (with eyes rolling to back on passive eye-opening, aka Bell sign), prolonged spells (10–30 min), **preserved awareness** despite generalized motor involvement, waxing and waning pattern with fluctuating responsiveness (rather than clear onset, core presentation, and end with postictal phase in epileptic szs)

B. Features against PNES (most differentiating features are in bold): eye opening or widening, abrupt onset, arise during verified sleep (DDx panic attacks, OSAS, sleep disorder), injuries sustained, tongue bite (especially lateral), incontinence, **postictal confusion, depressed mental status** or agitation (more so than confusion)

C. Pitfalls[6] and pearls: (1) Movements not suppressible by the examiner do not necessarily imply epilepsy and do not exclude PNES or movement disorders. (2) Response to pharmacologic intervention is not specific to epileptic szs; e.g., benzodiazepines will also suppress PNES or motor spasticity. (3) Rage attacks and psychosis are uncommon presentations of epilepsy, as opposed to postictal agitation and memory problems. **Pearls** include lateral tongue bite (highly suggestive of epileptic origin) and forced eye closure against resistance (highly suggestive of PNES)

PNES, psychogenic nonepileptic szs.

Adapted from Westover MB, Peters JM, Bromfield E. Seizures and other spells. In Greer DM, ed. *Pocket Neurology*. Philadelphia, PA: Lippincott, Williams & Wilkins; 2010:57–79, with permission.

TABLE 5.4 Lateralization and Localization from Seizure Semiology

Feature		Lateralization	Localization
Aura	Unilateral sensory aura	C/L	PL (Brodmann area 1–3)
	Hemifield visual aura	C/L	OL (Brodmann area 17–19, adjacent areas)
	Abdominal aura	None	Usually mesial TL
Motor	Head version	C/L	FL (Brodmann area 6 and 8)
	Clonic movements	C/L	FL (Brodmann area 4 and 6)
	Tonic activity	C/L	FL (SMA, possibly others)
	Unilateral dystonic posturing	C/L	Basal ganglia activation
	Figure-of-four (asymmetric tonic limb posturing in early tonic phase before generalization: arm flexed, other extended, head version to extended arm)	C/L of ext. arm	FL
	Fencing posture (abduction, external rotation, and partial flexion of arm at the shoulder, head and eyes "look at" the abducted arm. Other arm extends downward and backward, feet may be apart to support partially rotated trunk)	None	FL (SMA)
	Unilateral eye-blinking	I/L	Unknown
	Nystagmus	C/L	FL, PL
Impairment of Consciousness		**Complex**	**TL, FL, B/L**
Automatisms	With preserved consciousness	N/D	TL
	With impaired consciousness	D or B/L	TL, hippocampus
	With unilateral dystonic posturing	I/L	TL, BG
Autonomic	Ictal emesis/urination/defecation	N/D	TL
	Cold sensation	D	TL
Speech	Ictal speech	N/D	TL
	Ictal aphasia	D	TL, sometimes FL
	Ictal anarthria	D	Rolandic/Sylvian fissure
Postictal	Todd paresis	C/L	Brodmann 4 and 6
	Hemianopia	C/L	Brodmann 17–19, adjacent areas
	Aphasia or dysphasia	D	Language areas

B/L, bilateral; C/L, contralateral; BG, basal ganglia; D, dominant; FL, frontal lobe; I/L, ipsilateral; N/D, nondominant; PL, parietal lobe; TL, temporal lobe.

Adapted from Loddenkemper T, Kotagal P. Lateralizing signs during seizures in focal epilepsy. *Epilepsy Behav*. 2005;7:1–17.[40]

Step 4: Etiology (What is causing the clinical presentation?)

In many patients no cause can be found. In others, history, physical exam, and auxillary test may provide guidance.[1] **(1) EEG:** Recommended by AAN in the evaluation of a first unprovoked sz.[4] Assists in determination of sz type, localization, potential syndrome, and estimate of recurrence risk. Activation procedures include hyperventilation, photic stimulation, and recording sleep and may provoke epileptiform discharges and increase yield of routine outpatient EEG. Routine EEG is 20 min. Ambulatory monitoring can be done at home or in-hospital with continuous video recording, up to several days in duration. Sleep, the transition to sleep, and sleep deprivation itself increase sensitivity increase by 25%. EEG performed <24 h after event increases sensitivity by 15%. EEG's sensitivity in predicting recurrence is 48% to 61%, specificity 71% to 91%. EEG findings should always be placed in clinical context.[5] **Interpretation in clinical context:** (1) A **normal EEG** does not rule out epilepsy. (2) An **abnormal EEG** with epileptiform discharges by itself does not constitute a diagnosis of epilepsy unless a sz is captured during the recording. Up to 3.5% of normal school-aged children may have epileptiform spikes in EEG, with higher numbers in children with ADHD (6%) and autism (18%–64%). An epileptiform EEG therefore may indicate (a) a genetic trait, (b) a lowered sz threshold, or (c) a higher recurrence risk if the event in question was indeed a sz. An abnormal EEG is more predictive of epilepsy if the prior clinical suspicion of a sz is high.[6] (3) **Variations in subjective interpretation** (i.e., over- or under-reading) contribute to variability in sensitivity and specificity of EEG as a test. **(2) Neuroimaging:** MRI is recommended by AAN in the evaluation of first unprovoked sz, to assess for underlying etiology such as structural abnormality (e.g., tumor, stroke, infection, arteriovenous malformation, cortical malformation, or cerebral dysgenesis).[4] Persistent focal deficits and altered mental status prompt urgent imaging with CT. In classic presentations of genetic or developmental epilepsies (e.g., juvenile myoclonic epilepsy, childhood absence epilepsy, or benign Rolandic epilepsy of childhood), imaging may not be needed. **(3) Laboratory studies:** Basic metabolic panel includes sodium, potassium, calcium, magnesium, phosphate, and bicarbonate. Serum &urine toxicology screen. For suspected infection extend workup (e.g., to include CSF examination). In case of known epilepsy, consider AED levels. **(4) Genetic testing:** Please refer to later paragraphs in this chapter. **(5) ECG:** May be indicated to assess for QT prolongation and to rule out other cardiac causes.

Step 5: Classification[1] (Which category does this presentation fit best?)

(1) Utility: To (a) understand the sz type(s) and epilepsy of a patient, (b) localize the clinical presentation, (c) identify the potential etiology, (d) elicit related medical conditions important for the diagnosis (in part reiterative from Steps 1 to 4). Classification improves communication and allows tailored treatment and prognosis assessment. **(2) Several classifications** have been evaluated by the International League Against Epilepsy (ILAE) each serving different functions, e.g., practical clinical vs. research-driven applications. **(3) The 1989 ILAE classification of epilepsies** (Table 5.5) is still current. Strengths include ease of use and, in some cases, guidance for choice of AED. Weaknesses include the neglect of more complex conditions, genetic and structural metabolic etiologies, the limited description of sz semiology, and the assumption of a strict relationship between etiology, localization, and sz type (Steps 1–4). **(4) The 2010 Revised Terminology and Concepts for Organization of Szs and Epilepsies**[7] (Table 5.6) attempts to reconcile ongoing controversies and address weaknesses of previous

TABLE 5.5 The 1989 International League Against Epilepsy (ILAE) Classification of Epilepsies

Etiology

(a) Idiopathic: unknown cause (with age-related onset), now often genetic epilepsies
(b) Symptomatic: known cause
(c) Cryptogenic: a cause is suspected but not demonstrated yet

Localization

(a) Localization-related (focal, partial) epilepsies and syndromes
(b) Generalized epilepsies and syndromes
(c) Epilepsies and syndromes underdetermined whether focal or generalized
(d) Special syndromes

Note: Still current, novel proposals have not been formally adapted.

Proposal for revised classification of epilepsies and epileptic syndromes. Commission on Classification and Terminology of the International League Against Epilepsy. *Epilepsia*. 1989;30:389-399.[41]

schemes. It allows for further description within each category of sz type(s), localization, cause, age of onset, and comorbid conditions. Etiology is divided into (a) known genetic (without significant structural abnormalities), (b) structural/metabolic, or (3) unknown. Epilepsy syndromes and etiologies by subgroups are outlined in Tables 5.7 to 5.11. **(5) Ongoing critical interpretation** of novel data allows for ajustment of a diagnosis and the therapeutic approach.[1]

TABLE 5.6 2010 ILAE Proposal for Classification of Epilepsies

I(a) Electroclinical syndromes with age-related onset

Neonatal period
- Benign familial neonatal epilepsy (BFNE)
- Early myoclonic encephalopathy (EME)
- Ohtahara syndrome (EIEE)

Infancy
- Epilepsy of infancy with migrating focal szs (MMPEI)
- West syndrome (IS)
- Myoclonic epilepsy in infancy (MEI)
- Benign (familial or nonfamilial) infantile epilepsy
- Dravet syndrome (SMEI)
- Myoclonic encephalopathy in nonprogressive disorders

Childhood
- Febrile szs plus GEFS+
- Epilepsy with myoclonic atonic (previously astatic) szs (Doose syndrome)
- Benign epilepsy with centrotemporal spikes (BECTS)
- Autosomal-dominant nocturnal frontal lobe epilepsy (ADNFLE)
- Early-onset childhood occipital epilepsy (Panayiotopoulos syndrome)
- Late-onset childhood occipital epilepsy (Gastaut-type)
- Epilepsy with myoclonic absences (EMA)
- Lennox–Gastaut syndrome (LGS)
- Epileptic encephalopathy with continuous spike and wave during sleep (CSWS)
- Landau–Kleffner syndrome (LKS)
- Childhood absence epilepsy (CAE)

TABLE 5.6 2010 ILAE Proposal for Classification of Epilepsies (Continued)

Adolescence and Adulthood
- Juvenile absence epilepsy (JAE)
- Juvenile myoclonic epilepsy (JME)
- Epilepsy with generalized tonic–clonic szs alone (EGTCO)
- Progressive myoclonus epilepsies (PME)
- Autosomal-dominant epilepsy with auditory features (ADEAF)
- Other familial temporal lobe epilepsies

Less-specific age relationship
- Familial focal epilepsy with variable foci
- Reflex epilepsies

I(b) Electroclinical syndromes with structural–metabolic cause
- Mesial temporal lobe epilepsy with hippocampal sclerosis (MTLE with HS)
- Rasmussen syndrome
- Gelastic szs with hypothalamic hamartoma
- Hemiconvulsion–hemiplegia–epilepsy

I(c) Electroclinical syndromes of unknown cause

I(d) Conditions with epileptic szs that are traditionally not diagnosed as a form of epilepsy per se
- Benign neonatal szs (BNS)
- Febrile szs (FS)

II Nonsyndromic epilepsies with structural–metabolic cause
- Malformations of cortical development (hemimegalencephaly, heterotopias, etc.)
- Neurocutaneous syndromes (tuberous sclerosis complex, Sturge–Weber, etc.)
- Tumor, infection, trauma, vascular malformation, perinatal insults, stroke, inflammatory/autoimmune conditions

III Epilepsies of unknown cause

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.* 2010; 51:676–685, with permission.[7]

SELECTED EPILEPSY SYNDROMES

Conditions with Epileptic Seizures that are Traditionally not Diagnosed as a form of Epilepsy

Febrile Seizures

DEFINITION: Sz in a neurologically healthy child between 6 mo and 5 y of age associated with fever (>38.4°C) without evidence of central nervous system (CNS) infection, electrolyte imbalance, or other defined cause and without history of a febrile seizure (FS).[8,9] **Simple** FS are brief generalized szs that do not recur within 24 hrs and without postictal neurologic abnormalities.[8,10] **Complex** FS are szs that occur for a duration of more than 15 min, recur multiple times within 24 hrs, or have focal features.

EPIDEMIOLOGY: Prevalence rates are 2% to 5% in children in the United States, and genetic predisposition often plays a role.[9] Half the children present between 12 and 30 mo of age, and it is unusual to present for the first time at the upper end of the age range.[10]

TABLE 5.7 Neonatal Period: I(a) Electroclinical Syndromes with Age-Related Onset

Syndrome	Prev	Onset	Sz Type	EEG	Rx	Prognosis, Remarks
BNC (benign [idiopathic] neonatal convulsions, 5th-day fits)[42]	Rare <1% of pediatric epilepsy	Day 1–7 (most day 5)	Brief, 1–3 min. Clonic, partial tonic, or subtle (e.g., apnea). May start on one side, then affecting other side. Often repeated or clustering, leading to status epilepticus	Interictal normal or asynchronous rhythmic theta "theta pointu alternant," ictal rhythmic usually focal sharp or slow waves, or spikes	PB, PHT, BDZ	**Excellent prognosis**. Remission after 24–48 h. Dx often after resolution and normal outcome. Some data suggest mild developmental deficits in 50% of cases, and ↑ risk epilepsy later. Hypotheses have included Zn^{2+} def., rotavirus (unconfirmed). Decreased frequency, no case series reported since 1990s
BNFC (benign neonatal familial convulsions)[43]	Rare, unknown	Day 2–7, but can be up to 3 mo	Focal tonic and clonic, formally still categorized as generalized (new classification not adopted yet)	Normal interictal EEG. Ictal generalized flattening, next generalized spike-and-wave or focal discharges	PB	**Spontaneous remission** by 2–3 mo, normal neurological exam. Autosomal-dominant defect in voltage-gated potassium channel KCNQ2, 3 with incomplete penetrance. Later childhood epilepsy 11%–16%

EME (early myoclonic encephalopathy)[44]	Rare, <1%	Neonatal period	Segmental & erratic myoclonic, generalized myoclonic, evolve into infantile spasms w/ atypical hypsarrhythmia, which may persist into late childhood	Suppression-burst: Bursts of spike and sharp waves alternate with periods of voltage attenuation, more pronounced in sleep	Steroids, BDZ, VPA, VGB, KGD	**Malignant epilepsy syndrome**: poor neurological outcome 100%, mortality 50% <1 y. Nonstructural, metabolic disorders common (e.g., NKH). Similar genetic associations as EIEE (below). MRI with atrophy and delayed myelination DDx: EIEE occurs in 1st mo, tonic szs main type, EEG has longer bursts and brain malformations are common, earlier transition to IS and LGS
EIEE (Ohtahara) (early infantile epileptic encephalopathy)[45]	Rare, <1%	(Early) neonatal to 1st mo	Tonic szs main type, occur during wake, sleep, and typically not in clusters. Also partial motor, focal motor szs, hemiconvulsions, GTCs	Suppression-burst (see above), but during wake and sleep, longer bursts	See above	**Malignant epilepsy syndrome:** Poor outcome in most. Structural brain abnormalities from encephaloclastic events, cerebral dysgenesis, even in cryptogenic cases, rarely metabolic. Genetic association with *CDKL5*, *STXBP1* and *ARX* mutations (reviewed in[46] and see genetics table)

TABLE 5.8 Infantile Period: I(a) Electroclinical Syndromes with Age-Related Onset

Syndrome	Prev	Onset	Sz Type	EEG	Rx	Prognosis, Remarks
MMPEI (malignant migrating partial epilepsy of infancy)[47]	Very rare, <<1%	<6 mo	At first occasional focal szs with rapid secondary generalization and autonomic symptoms, weeks to months followed by multiple clinical sz types in the second phase. Late 3rd phase w/ occasional breakthrough sz but prolonged sz-free intervals	1st phase: multifocal spikes, migrating patterns of focal slowing. 2nd & 3rd phase: migrating and expanding focal discharges, complicated multifocal EEG with near-merger of ictal and interictal patterns. Frequent status epilepticus and subclinical szs warrant prolonged inpatient video-EEGs	Any combination of multiple AEDs	Usually **markedly drug-resistant** to any combination of older and newer AEDs. KGD variable success. **Outcome severe** with progressive deterioration of psychomotor development, microcephaly, mental retardation, and death. **MRI** typically negative with later atrophy, some w/ mesial temporal sclerosis. Extensive genetic and neurometabolic **workup typically negative**.
IS (infantile spasms, West)[48]	Uncommon, 1%–5%	3–14 mo (peak 4–9)	Brief tonic or clonic spasms, typically clustering, many times daily (on arousal). Flexor (arms, neck) and extensor (legs), or flexor (jackknife) or extensor. Can be subtle, e.g., head nods only. 50%–60% have szs in later life, frequently LGS	Disorganized high-voltage multifocal polymorphic slowing with interspersed epileptiform discharges. Initially may be during (light) sleep only. Ictal generalized high-voltage slow wave with electro-decrement or diffuse fast beta-range activity	Steroids, VGB, TPM, Vit B6, LTG, RFA, KGD	**West syndrome**: Triad of clusters of IS, psychomotor deterioration, and hypsarrhythmia on EEG. >**85%–95% symptomatic**: prenatal, perinatal, and postnatal insults, e.g., hypoxic ischemic injury, perinatal infections, tuberous sclerosis, cerebral malformations and dysgenesis, chromosomal (trisomy 21, del1p36), gene mutations (*ARX*, *CDKL5*, *STXBP1*), metabolic (untreated PKU, tetrahydrobiopterine def, Menkes), and mitochondrial (*NARP* mutation). **Poor prognosis**, rarely good outcome with *cryptogenic* etiology ~5%.

BMEI (benign myoclonic epilepsy of infancy)[49]	Rare, <1%	3 mo–4 y	Brief generalized myoclonic, mainly head and upper part of body, awake, upon falling asleep, or during slow sleep. Multiple daily, in isolation or nonrhythmic recurring, some subtle	Generalized (poly-) spike (and wave), with normal interictal EEG	VPA, BDZ, LTG	**Normal neurological outcome** (reportedly some with developmental delay). Reflex form is common variant with excessive sleep startle, photosensitivity, earlier onset, and usually good outcome. Other idiopathic generalized epilepsies may occur in adolescence.
Benign infantile (non)familial szs[50]	Rare, <1%	<2 y	Behavioral arrest with staring, and then focal clonic, focal tonic, or secondarily GTC. May cluster	Interictal normal, ictal with focal discharges, may generalize	VPA, CBZ, PB	**Sporadic, in some cases familial. Good response to Rx, good neurological outcome.** Some are associated w/ familial paroxysmal choreoathetosis. Some associated with *SCN2A* mutations. *PRRT2* is also identified in families with benign familial infantile convulsions and choreoathetosis (not yet clinically testable in the US).
SMEI (Dravet) (severe myoclonic epilepsy of infancy, some related syndromes with different phenotypes)[51]	Rare, <1%	1st y or life, peak 3–8 mo	Prolonged febrile sz (or status), next recurrent 1–2/mo, generalized and alternating unilateral clonic or tonic–clonic szs, often prolonged and w/ fever. Later myoclonic, atypical absence, complex, partial, atonic, and unilateral szs, nonconvulsive status epilepticus. Tonic szs are rare	Generalized spike and wave complexes, focal and multifocal spikes. Whole body myoclonic szs associated with generalized spikes and waves or occasionally without EEG Δ. Atypical absences: generalized 2–3.5-Hz irregular spike waves	Refractory to most AEDs. LTG and CBZ worsen	**Malignant epilepsy syndrome.** Recurrent febrile hemiclonic status epilepticus between 6 and 12 mo, w/ developmental arrest after 1st y of life and regression with recurrent status. **Early control may lead to better neurological outcome.** Positive FHx for (febrile) szs in 25%. MRI normal at 1st, later hippocampal sclerosis. *SCN1A* (and *GABRG2*) mutations in >70%. MRI normal and later with nonspecific atrophy and gliosis, hippocampal atrophy.

TABLE 5.9 Childhood: I(a) Electroclinical Syndromes with Age-Related Onset

Syndrome	Prev	Onset	Sz Type	EEG	Rx	Prognosis, Remarks
GEFS+ (generalized epilepsy w/ febrile szs plus)[52]	Common, >5%	Febrile Szs <5 y, others later childhood	Marked phenotypic diversity: typical febrile szs in early childhood. GTC, absence, myoclonic, (a)tonic, focal motor or continuing brief, generalized febrile szs follow	Normal or as in Idiopathic generalized epilepsies: generalized epileptiform discharges	Standard AEDs based on sz type	**Autosomal dominant with incomplete penetrance** 70%–80%. *SCN1A*, *SCN2A*, *SCN1B*, and *GABRG2* gene mutations. Strong family history with variable phenotypes, including partial szs ~15%. Variable outcome ranging from remission at 10–12 y to ongoing refractory epilepsy
Panayiotopoulos (early-onset benign childhood occipital epilepsy)[53]	Common, 6%	1–13 (peak 3–6) y	Long (30+ min), mainly autonomic szs/status, often from sleep: (1) feeling sick, headache, pale, vomiting, pallor, flushing, cyanosis, eye deviation, mydriasis, cardio- & thermoregulatory sensations, incontinence, hypersalivation, ictal syncope (unresponsive, limp). Next may have (2) complex partial features and/or (hemi)clonic convulsions, brief	Multifocal spike and wave, Rolandic morphology, frequently with occipital predominance or with multifocal spikes	As in Rolandic Some: rectal DZP only	**Better defined than Gastaut-type** (see below), reported to be common, but this depends on inclusion criteria. Despite autonomic status epilepticus usually benign prognosis, even if frequent szs: remission <2 y. Most have infrequent szs, 25% have only 1, 50% have total <5. No increased risk later epilepsy in adulthood. **Misdiagnosis is common**, DDx with migraine, gastroenterologic (-itis, cyclic vomiting, abdominal migraine), syncope, sleep d/o. Cardiac arrest has been described, but is rare.

EMAS (Doose) (epilepsy with myoclonic astatic szs, myoclonic astatic epilepsy)[54]	Uncommon, 1%–5%	7 mo–6 y	Generalized myoclonic, astatic, or myoclonic–astatic szs, leading to falls. Also short absences, generalized tonic–clonic szs and nonconvulsive status; no tonic szs or tonic drop attacks during daytime	Generalized EEG patterns ([poly-] spike and wave, photosensitivity, 2–3/s rhythms), no multifocal spikes	VPA, ESM, BDZ, LTG, TPM, LEV, RFA	**Criteria**: (1) Szs as outlined on left; (2) genetic predisposition (high incidence of szs and/or genetic EEG patterns in relatives 15%–40%); (3) normal development and neurologic exam prior to onset; (4) EEG as outlined on left; (5) exclusion SMEI, BMEI, and LGS. **Differences with LGS:** in Doose myoclonic predominant type, genetic basis, outcome usually better, but variable: at times fair with sz control and (near-) normal cognition.
BECTS (Rolandic) (benign childhood epilepsy with centrotemporal spikes, benign Rolandic epilepsy of childhood)[55]	Most common epilepsy of childhood (10%–15%)	3–13 (peak 7–9) y	Nocturnal unilateral, tongue, lips, cheek, larynx, pharynx (anarthria), occasionally arm, preserved consciousness. May generalize during sleep. Sensory aura common but underreported by patient	Interictal unilateral or bilateral centrotemporal triphasic spikes with horizontal anterior–posterior dipole, prominent sleep activation, nl background	OXC, CBZ,LTG, TPM, GZP, LEV	**Excellent outcome**, szs almost always remit by puberty. May be frequent initially. Consider not treating if infrequent, nocturnal, or partial only. Learning and behavioral difficulties can be present, in part related to frequency of interictal discharges. Atypical BECTS associated with language and developmental delay. Genetic etiology suspected (*ELP4*). Age-related penetrance suspected.

(continued)

TABLE 5.9 Childhood: I(a) Electroclinical Syndromes with Age-Related Onset (Continued)

Syndrome	Prev	Onset	Sz Type	EEG	Rx	Prognosis, Remarks
ADNFLE (autosomal-dominant nocturnal frontal lobe epilepsy)[56]	Rare	0–50 y (85% <25, mean 12, median 8)	Frequent (multiple per night), very stereotyped, brief, sudden onset and end, during non-REM sleep stage II: sudden arousal with complex, motor features, automatisms, (dys-)tonic posturing and hypermotor activity (e.g., leg pedaling), no postictal phase, may have daytime szs. Often preserved awareness	Routine EEG is normal, rarely frontal epileptiform or nonspecific abnormalities. Ictal EEG: frontal rhythmic beta frequency epileptiform abnormalities	CBZ, OXC, LTG, TPM	**Challenging electroclinical diagnosis.** Autosomal dominant with high degree of penetrance. Different mutations in several genes (20q13.2, 1p21) (nicotinic acetylcholine receptor, changes in presynaptic NT release), similar phenotype. Sleep deprivation and stress worsen or precipitate. Behavioral problems common until sz control. Previously was considered a paroxysmal nocturnal dystonia.
Gastaut (Late-onset) Idiopathic benign childhood occipital epilepsy[57]	Rare, <1%–2%	3–16 (peak 8) y	Brief, seconds to several min. Frequent, many times a day in awake patient. Visual aura (blindness, colored luminous discs, formed visual hallucinations). At times eye deviation, eyelid flutter, and postictal headache (50%) and vomiting (5%) can occur	High-amplitude spike-and-wave occipital discharges with eyes closed or during sleep. Ictal pattern consists of fast, occipital spikes	As in Rolandic	**Overall, rare.** "Idiopathic" is speculative as genetic etiology is not proven. Frequency, nature, and brevity of the visual symptoms should help distinguish from migraine with aura. **Fair prognosis**: 60% remit within few years. Migraines in 20%, family Hx(+) epilepsy in 50%.

Syndromes with absence szs and myoclonus or micturition[58]			**MAE (Tassinari)** (myoclonic absence epilepsy): ictal 3-Hz myoclonus, arms "ratcheting" upward. Usually mental retardation, resistant to Rx **EMA (Jeavons)** (epilepsy with myoclonic absences): marked ictal eyelid, more subtle facial or upper arm jerking. AD inheritence, resistant to Rx **MA** (micturational absence epilepsy): ictal detrusor contraction with urination. May be resistant, prominent social implications			
LGS (Lennox–Gastaut syndrome)[59]	Uncommon, 1%–5%	<8 y, peak 3–6 y	Tonic szs (required for Dx, not at onset, more in sleep), variable severity and semiology. Atypical absences (2nd most common, gradual onset and ending), tonic and atonic szs (>50%) may be preceded by myclonus and lead to injury, (non)convulsive status (50%–70%), myoclonic, and others. ≥20% preceded by IS	Wake: bursts of diffuse slow 1–2.5-Hz spike and wave. Sleep: bursts of diffuse or bilateral fast rhythm patterns ≥10 Hz or "polyspikes," aka generalized paroxysmal fast activity. Ictal: tonic diffuse fast bursts, atypical absence 1–1.5-Hz spike-and-slow waves, atonic or myoclonic diffuse spikes or polyspikes and slow waves	Refractory to most AEDs. VPA, BDZ, TPM, ZNS, LTG, LEV, FBM, RFA, steroids	**Triad of multiple sz types, typical EEG, cognitive impairment.** Tonic szs (hallmark) not present at onset, EEG not pathognomonic. Progressive developmental delay, regression, often psychosis. Causes (see IS) heterogeneous: cerebral malformation, tuberous sclerosis, in LGS less commonly acquired destructive lesions or metabolic diseases. Genetics less important. **Rx:** (1) AEDs; (2) nonpharmacological management: epilepsy surgery (callosotomy, VNS, others), KGD[60]; (3) comorbid psychiatric, behavioral d/o: neuropsychiatric and psychiatric assessment; (4) monitor side effects (coordination, cognition, behavior, sz aggravation).

(continued)

TABLE 5.9 Childhood: I(a) Electroclinical Syndromes with Age-Related Onset (Continued)

Syndrome	Prev	Onset	Sz Type	EEG	Rx	Prognosis, Remarks
CSWS (continuous spike and wave during slow-wave sleep)[61]	Rare, 0.2%–0.6% Male:female 3:2	Sz onset: 2–4 y. Onset of regression, ESES pattern, and worsened szs: 5–6 y	Before regression: infrequent and mostly nocturnal szs, predominantly unilateral motor szs After regression: much more frequent szs of different types: atypical absence of szs, motor szs, generalized tonic–clonic szs Tonic szs never present	ESES EEG pattern: near-continuous spike-waves during non-REM sleep More focal during wakefulness and REM sleep	DZP, VPA, LEV, steroids, IVIG, epilepsy surgery Avoid CBZ, PHT, PB	**Severe epileptic encephalopathy with an age-related evolution.** Global and profound developmental delay. Spontaneous improvement of szs and EEG abnormalities before puberty but severe residual neuropsychological deficits.
LKS (Landau–Kleffner syndrome)[61,62]	Rare, 0.2% Male:female 2:1	Receptive aphasia around 3–5 y	Infrequent szs, mostly partial motor. One third never have szs	Bilateral centrotemporal, posterior temporal, and parieto-occipital spikes much more diffuse during non-REM sleep, leading to near-continuous spikes and waves	See above, ESM, CLB	**Severe age-related language regression**, frequent associated behavioral symptoms, improvement of EEG and szs before puberty, severe residual language deficits.

CAE (childhood absence epilepsy, formerly called petit mal)[63]	Common, 5%–12%	School age (peak 6–7 y)	Several to innumerable absences per day, 5–15 s. May have motor manifestations (facial) myoclonic, tonic, and atonic components alone or in combination), automatisms and autonomic disturbances	Interictal 3–4-Hz generalized (poly-) spike and wave, normal background	ESM, VPA, LTG, LEV	Neurologically normal children, often with positive FHx of idiopathic generalized epilepsies. Not always "benign": only 60% respond to 1st AED, in some patients lifelong (cognitive and) learning disabilities, 15% will develop JME later, may affect long-term psychosocial outcome. **Hyperventilation** frequently provokes absence in the office or during EEG.

TABLE 5.10 Adolescents and Adults: I(a) Electroclinical Syndromes with Age-Related Onset

Syndrome	Prev	Onset	Sz Type	EEG	Rx	Prognosis, Remarks
JAE (juvenile absence epilepsy)[63]	Less common than CAE	7–16, peak 10–12 y	Absences, GTCs (awakening), and myoclonic jerks	Mildly faster than CAE: generalized 2.5–4.5-Hz (poly-) spike and wave, but EEG does not differentiate	See CAE	**Overlap syndrome between CAE & JME.** Prognosis not as favorable, lifelong disorder, although absences may become less severe. The EEG may show asymmetry, and the partially preserved awareness may lead to a false Dx of focal epilepsy and wrong Rx, e.g., CBZ will aggravate JAE.
JME (Janz) (juvenile myoclonic epilepsy)[64]	Common, 5%–11%	8–26, peak 12–16 y	Bilateral, single or multiple myoclonic szs, predominantly in arms, more often on awakening. Also GTCs 90% and JAE-type absences in 10%–30%	Generalized (poly-) spike and wave, 3–6 Hz. Photosensitivity in 40%–70%	VPA, LTG, BDZ, TPM, LEV	**Sz-precipitating factors** (sleep deprivation, fatigue, alcohol, photosensitivity, stress). **Genetics:** see paragraph on genetics. Absences can appear during childhood, later followed by myoclonic jerks and GTCs in mid-teens. Lifelong condition, milder in 3rd or 4th decade, but withdrawal of AEDs may lead to recurrence. 70% control w/ VPA. Avoid PHT, CBZ: aggravation.

EGTCA (epilepsy with GTCs on awakening): GTCs soon after awakening or when relaxing. Aberrant wake–sleep cycle; unstable sleep.[65] This syndrome has recently been abandoned as an isolated syndrome, in favor of EGTCO (below).

EGTCO (epilepsy with GTCs only): Less strictly defined—includes random and nocturnal GTCs. No absences or myoclonic szs.[66]

Progressive myoclonic epilepsies (PME)		Group of rare myoclonic epilepsies with onset during childhood in which generalized or fragmentary myoclonic szs (and other types) are associated with neurological deterioration, including cerebellar impairment and cognitive dysfunction. Most are progressive, neurogenerative		**Typically** p/w PME: Lafora dz, Unverricht–Lundborg syndrome, sialidosis type 1 and 2, mucolipidosis type 1, juvenile neuropathic Gaucher's dz (type 3), juvenile neuroaxonal dystrophy **Occasionally** p/w PME: neuronal ceroid lipofuscinosis (NCL), MERRF, Huntington's dz, Wilson's dz, Hallervorden–Spatz **Atypically** p/w PME: NKH, infantile hexosaminidase def (Tay–Sachs, Sandhoff's), biopterin deficiency, sulphite oxidase deficiency		
FMTLE (familial mesial temporal lobe epilepsy)[67,68]	Rare	Mean onset at 10 y	Aura only: prominent psychic and autonomic features, only rare complex partial szs (CPS), and even more rare secondary GTC szs With MTS: CPS with oral or manual automatisms, rare secondary GTC szs	Interictal: normal or with focal slow waves or epileptiform abnormalities in the temporal regions	CBZ, OXC, LTG, TPM	**Only positive FHx distinguishes** from nonfamilial TLE (at least 2 family members with TLE in absence of being part of other epilepsy syndrome). Heterogeneous phenotype with mild to severe epilepsy and variable association with MTS and febrile szs. Genetics unclear.
ADTLE (autosomal-dominant lateral temporal lobe epilepsy)[67,68]	Rare, <1%	1–60 y, mean 18	Simple partial szs, often auditory auras (humming, buzzing, ringing), which may be triggered by external noises. Also aphasic, complex visual, psychic, autonomic, and other auras. High propensity to generalize	Interictal: normal or with focal slow waves or epileptiform abnormalities in the temporal regions	CBZ, OXC, LTG, TPM	**Aka autosomal-dominant partial epilepsy with auditory features,** penetrance 70%–80%. Normal conventional MRI, good response to antiepileptic treatment, and overall benign outcome. The same phenotype is shared by sporadic and familial cases with complex inheritance. *LGI1* mutations in about 50% of families.

TABLE 5.11 I(b) Electroclinical Syndromes with Structural–Metabolic Cause

Syndrome	Prev	Onset	Sz Type	EEG	Rx	Prognosis, Remarks
MTS (mesial temporal sclerosis)[69]	Uncommon in children (1%–5%)	Childhood–adolescence	Initial recurrent or prolonged **febrile szs** at 0–4 y of age may occur. **CPS**, 1–2 min; oral, hand, verbal automatisms with semipurposeful behavior and decreased responsiveness, and secondary generalization. Common auras include rising epigastric sensation, psychic auras, e.g., déjà vu	Uni- > bilateral anterior to mid-temporal spikes, ictal patterns with 5–9-Hz temporal sharp waves. May need depth electrodes	CBZ, TPM, LTG, LEV. See panel on right	MRI with uni- > bilateral MTS. Children have higher proportion of dysplasia and low-grade glioma. **60% fair control with AEDs, surgery with >75% excellent outcome** (anterior temporal lobe, selective amygdalohippocampectomy). Progressive behavioral and memory dysfunction common.
Rasmussen encephalitis (chronic progressive epilepsia partialis continua of childhood)[32,70]	Rare, <1%	<10 y	Progressive and intractable focal szs and cortical deficits, including hemiparesis, visual field cut, and expressive aphasia when the dominant hemisphere is involved. Cognitive decline is common. Szs remain (multi-) focal and unilateral; epilepsia partialis continua is common	Very frequent focal fronto- and mid-temporal epileptiform discharges with focal slowing, and later widespread slowing	Any. See panel on right	**Progressive primarily T cell-mediated** autoimmune multifocal encephalopathy. Clinical Dx, see references 32, 70 for clinical criteria. MRI w/ progressive (initially peri-insular) atrophy and gliosis. Immunomodulatory treatments may provide temporary relief. Early hemispherectomy improves outcome, yet considerable neurological sequelae.

HHE (hemiconvulsion–hemiplegia–epilepsy syndrome)[71]	Very rare, $<<1\%$	0–4 y	Initial prolonged hemiclonic szs, followed by hemiparesis of variable duration (may be permanent). Several years later CPS from temporal lobe	Ictal pattern with 2–3-Hz bilateral slow waves, unilateral fast ictal discharges. Later EEG as in TLE	Early abortive: BDZ. Status Epilepticus—see paragraph below	**Hemiclonic convulsions provoked by fever**. Later uni- > bilateral atrophy similar but worse than MTS. Poor outcome in past but now better Rx of prolonged febrile szs and (febrile) status epilepticus (BDZ). Idiopathic (fever—now thought to be autoimmune), or symptomatic (trauma, vascular malformation, infection).
HH (hypothalamic hamartoma)[72]	Very rare	Extremely variable. Can be associated with TSC complex or Pallister–Hall syndrome	Laugher is brief, stereotyped, and mechanical, without a sense of mirth and without or little loss of consciousness; autonomic signs, such as facial flushing and pupillary dilation are frequent. Refractory focal or generalized epilepsy develops in most	Multiple complicated patterns have been described, specificity and diagnostic yield are unknown (see full ref.)	Any AED, KGD. Surgery best	**Wide spectrum**, ranging from mild urge-to-laugh szs and no cognitive involvement to a catastrophic encephalopathy with early-onset gelastic szs, precocious puberty, behavioral problems, and mental retardation. **Surgery** may be followed by (incomplete, delayed) recovery.

WORKUP: Complex FS are associated with an increased risk of epilepsy, and may require additional evaluation, including evaluation for fever source, blood chemistries, EEG, and neuro-imaging.[11] Workup is generally not indicated in the case of simple FS. LP if meningoencephalitis is suspected or in young children (<12 mo) who may show little symptoms.

PROGNOSIS: Cognitive and developmental outcomes are generally excellent with FS except in rare cases of prolonged FS. Recurrence risk after first FS is ~30% to 40%.[8] Risk factors for recurrence include young age at onset (<15 mo), family history of FS, height of temperature (lower risk of recurrence with higher peak temperature), and duration of fever (higher risk of recurrence with shorter duration of fever).[9] Risk of development of epilepsy after simple FS is minimally higher than in the general population, 1% to 2.4% compared to 0.5% to 1.4% in children without FS.[8,10] The risk is higher with complex FS and varies depending on type and number of complex features, up to a maximum of 49% with all three complex features (prolonged, multiple, and focal features). Prolonged FS increase the frequency of epilepsy to 21%.[10] Other risk factors for the development of epilepsy in children with FS include neurological abnormalities, a family history of epilepsy, and short duration of fever (<1 h) before the sz.[10]

TREATMENT: Generally not required for simple FS.[8,9] Prophylactic antipyretics are *not* effective in preventing szs (based on available data), although fever control should be encouraged. The risk of daily AEDs generally outweighs the benefits, although PB and VPA are effective. For frequent FS, prophylactic BDZs (e.g., DZP [1 mg/kg/d divided bid to tid]) around the time of febrile illness are effective. **MISC:** Similar szs also occur in children with mild gastroenteritis, even in the absence of fever or electrolyte abnormalities.[10] Compared with children with FS, these children have less of a family history of szs, a lower recurrence rate, and more clustering of szs.

Acute Symptomatic Seizures

Seizures can be provoked in the setting of alcohol or BDZ **withdrawal**. They can also occur acutely in the setting of **intoxication** from alcohol or illicit drug use. They can also be provoked if antiepileptic medications are withdrawn too quickly. **Certain medications** lower the sz threshold, listed on www.epilepsy.com. Of the antidepressants, buproprion is most prone to lower the sz threshold. In practice the use of stimulants for treatment of ADHD rarely causes sz exacerbation. Seizures can occur in the setting of **acute symptomatic insults** such as infarction, trauma, hemorrhage, meningoencephalitis, or **electrolyte disturbances** (hyponatremia, hypomagnesemia, and hypocalcemia) and may not persist after the acute insult. In most such scenarios there are no data to suggest temporary (prophylactic) treatment with AEDs alters the chance of developing epilepsy (e.g., in traumatic brain injury); that is, they are not antiepileptogenic (Table 5.12).

Immune-Mediated Epilepsy

There is mounting evidence for a causal role of immunity and inflammation in epilepsy, for example, from seizure exacerbation in the setting of fever and infection due to proinflammatory molecules, the increased frequency of seizures in systemic autoimmune disease, and the rapidly expanding field of autoantibodies in previously unexplained epilepsies.[11] Autoimmune encephalitis is discussed in detail in Chapter 17.

TABLE 5.12 Medications that can Lower Seizure Threshold

Category	Drug	Comment
Antiasthmatics	Aminophylline, theophylline	Especially but not exclusively above therapeutic levels
Antibiotics	Isoniazid, lindane, *metronidazole, **nalidixic acid, penicillins	*Vitamin B_6 supplement may protect. **Especially with renal failure
Antidepressants	Tricyclics, serotonin-specific agents, bupropion	Rarely a practical problem, desipramine may be preferable
General anesthetics	Enfluraneketamine	
Hormones	*Insulin, **prednisone, ***estrogen	By means of *hypoglycemia, **hypocalcemia. ***Especially without progesterone
Immunosuppressants	Chlorambucil, cyclosporin A	
Local anesthetics	Lidocaine, bupivacaine, procaine	
Narcotics	Fentanyl, meperidine, pentazocine, propoxyphene, some inhalation narcotics	
Psychostimulants	Amphetamines, cocaine, methylphenidate, phenylpropanolamine	
Neuroleptics	*Clozapine, **phenothiazines, butyrophenones	*1%–4% of patients, dose-dependent, ** molindone, thioridazine, fluphenazine least likely
Other	Anticholinergics, anticholinesterases, antihistamines, baclofen, heavy metals, hyperbaric oxygen, *lithium, mefenamic acid, oral hypoglycemic, oxytocin	*By means of water intoxication

From Bromfield EB. Drugs that may lower seizure threshold [online]. Available at http://professionals.epilepsy.com/page/table_seniors_drugs.html. Accessed January 12, 2013.[73]

Anti-NMDA Receptor Encephalitis: Most common form of autoimmune encephalitis in children (Table 5.13). Prodromal phase of fever, headache, viral-like symptoms, followed in days to weeks by a wide range of marked psychiatric and behavioral problems, which progress to decreased level of consciousness, seizures, dyskinesia and choreoathetoid movements and posturing, and breathing and autonomic instability. In younger children, abnormal behaviors include tantrums, agitation and aggression, mood and personality changes, and regression of speech with mutism, echolalia, or perseveration. Seizures typically involve the temporal lobe, and EEG shows diffuse (or more rarely focal) slowing. Electrographic seizures are common and status epilepticus (SE) may occur. For further details see Chapter 17.

TABLE 5.13 Nonsyndromic Epilepsies with Structural–Metabolic Cause

Disorder	Brief Description	Comments/Examples
Neurocutaneous d/o	See Chapter 12	E.g., tuberous sclerosis, Sturge–Weber, neurofibromatosis, hypomelanosis of Ito, epidermal nevus syndrome
Cerebral malformations	See Chapter 11	E.g., Miller–Dieker, X-linked lissencephaly, subcortical band heterotopia, periventricular nodular heterotopia, hemimegalencephaly, polymicrogyria, schizencephaly, focal cortical dysplasias
Tumors	See Chapter 12	DNET, gangliocytoma, ganglioglioma, cavernous angioma, astrocytoma, hypothalamic hamartoma
Chromosomal abnormalities[74]	See Chapter 10	Wolf–Hirschhorn, trisomy 12p, inversion duplication 15, ring 20
Monogenic diseases	See Chapter 10	Fragile X, Angelman, Rett
Metabolic disorders[75]	See Chapter 7	NKH, D-glyceric acidemia, propionic acidemia, sulphite oxidase def, fructose 1,6-diphosphatase def, other organic acidurias, pyridoxine deficiency, aminoacidopathies, urea cycle d/o's, d/o of carbohydrate metabolism, d/o of biotin metabolism, d/o of folic acid and B_{12} metabolism, glucose transport protein deficiency, Menkes dz, glycogen storage d/o's, Krabbe dz, fumarase def, peroxisomal d/o, Sanfilippo syndrome, mitochondrial dz, lysosomal dz, NCL
Acquired static infectious and ischemic encephalopathies[42]	Heterogeneous group of disorders acquired in the antenatal, perinatal, or postnatal period. See Chapter 19	Porencephaly, periventricular leukomalacia, microcephaly, calcifications and lesions from TORCHS infections, HSV encephalitis, bacterial meningitis, head injury, maternal alcohol and drug abuse, stroke
Fever-induced Refractory Status Epilepticus (FIRES)[76]	A catastrophic epileptic encephalopathy of childhood of unknown etiology	Suspected to be infectious or immune mediated. Other names include devastating epileptic encephalopathy in school-aged children (DESC), acute encephalitis with refractory, repetitive partial szs (AERRPS), severe refractory status epilepticus due to presumed encephalitis, idiopathic catastrophic epileptic encephalopathy, or new-onset refractory status epilepticus (NORSE). No intervention efficacious in shortening the acute phase except possibly ketogenic diet

TABLE 5.13 Nonsyndromic Epilepsies with Structural–Metabolic Cause (Continued)

Disorder	Brief Description	Comments/Examples
Autoimmune channelopathies[31]	Includes NMDA receptor encephalitis, voltage-gated potassium channel antibodies (LGI1 and Caspr2), AMPA receptor antibodies, $GABA_B$ antibodies, and GAD-65 antibodies	Each antibody is associated with a syndrome typically including szs, encephalitis, and in some cases movement disorders, psychiatric manifestations, and autonomic dysfunction. Immunomodulatory treatments are typically indicated (see treatment section)
Limbic encephalitis[77]	Rare disorder, in early childhood and later. Typically immune mediated, may be paraneoplastic or non-paraneoplastic. Antibodies include VGKC antibodies and GAD antibodies among others	Temporal lobe szs, typically with loss of consciousness, some with secondary generalization. EEG with temporal region epileptiform activity or slowing. AEDs for focal szs or immunomodulatory treatment. Mediotemporal lobe symptoms, including memory impairment, affective disturbances, and temporal lobe szs
Miscellaneous	NA	Celiac dz (epilepsy with occipital calcifications and celiac dz), Huntington disease, Alpers dz

Limbic Encephalitis (LE): Autoimmune or paraneoplastic LE is extremely rare in children. No dyskinesias or central hypoventilation. MRI and EEG findings are restricted to the temporal lobe.

Fever-Induced Refractory Epileptic Encephalopathy Syndrome (FIRES): Several devastating epilepsy syndromes with some degree of overlap, including FIRES, acute encephalitis with refractory, repetitive partial seizures (AERRPS), devastating epilepsy of school-aged children (DESC), and new-onset refractory status epilepticus (NORSE). These share an onset with fever or inflammation, a biphasic clinical course suggesting an infection-triggered autoimmune process, negative laboratory studies (including CSF), and SE refractory to conventional pharmacotherapy. Various autoantibodies have been reported but their clinical significance is unclear, and these patients are typically refractory to immunomodulatory therapy as well. Outcome is poor with mesial temporal sclerosis (MTS), temporal lobe epilepsy, and long-term developmental delays.

Opsoclonus-myoclonus syndrome and Rasmussen encephalitis are discussed in the tables.

Epilepsy Genetics

EPIDEMIOLOGY: Genetic mechanisms play an important role in the pathophysiology of epilepsy in many cases. In Western countries about 5% of patients with epilepsy have a 1st-degree relative with epilepsy.[12]

The recurrence risk ratio is ~2.5 in 1st-degree relative as compared with that in the general population. In idiopathic generalized epilepsy the risk among 1st-degree relatives is even higher, 8% to 12%.[13] In twin studies, the concordance for monozygotic twins is 40% to 50% and for dizygotic twins is 10% to 15%.[12]

SINGLE GENE DISORDERS: Many single gene models of epilepsy have been identified both for lesional and for nonlesional epilepsy ranging from early-onset epileptic encephalopathies (EOEE) to generalized and focal epilepsy syndromes in older age groups. The channelopathies (e.g., *SCN1A*, associated with GEFS+ and Dravet syndrome) were the first described and best known. Examples of other mechanisms include a transcription factor (*ARX*), cytoskeletal proteins (*SPTAN1*, *CASK*), serine/threonine protein kinase (*CDKL5*), DNA repair enzyme (*PNKP*), and a protein involved in synaptic transmission (*STXBP1*). Both nuclear and mitochondrial genes may be involved.

For discussion of genes associated with malformations of cortical development, see Chapter 11. Some genetic syndromes with identified single gene association are commonly associated with epilepsy (e.g., tuberous sclerosis [*TSC1*, *TSC2*] and classical Rett syndrome [*MECP2*]). Examples of clinically available and useful epilepsy genes in early-onset epilepsies are included in Table 5.14; however, it is not intended to be a comprehensive list. Metabolic disorders and mitochondrial causes of epilepsy are discussed in Chapters 7 and 8, respectively.

COPY NUMBER VARIANTS (CNVs): Well-identified examples of CNVs causing syndromes with associated epilepsy include congenital Rett syndrome (14q12 microdeletions, including *FOXG1*), Sotos syndrome (5q35 deletion), Wolf–Hirschhorn syndrome (partial deletions of 4p), and Miller–Dieker syndrome (deletions of 17p13.3, including *LIS1*). Some single gene disorders, including *KCNQ2* mutations in benign familial neonatal szs, were identified first through identification of a microdeletion, followed by a search for candidate genes.[14] CNVs have been identified in up to 8.9% of a larger series of patients with idiopathic epilepsy, with hot spots including 1q21.11, 5q11.2, 15q13.3, 16p13.11, 16p13.11, and 22q11.2.[15–17] They may be more likely in patients who also have intellectual disability and/or autism spectrum disorder.

COMPLEXITY IN EPILEPSY GENETICS: In most cases the genetics of epilepsies are complex and not straightforward Mendelian inheritance patterns. With both single gene disorders and CNVs there are frequently variable penetrance and expressivity, with wide variability in phenotypic presentations. This may relate to epigenetic and environmental factors, other susceptibility genes, imprinting, single nucleotide polymorphisms, or, in the case of deletions, CNVs on the remaining hemizygous allele.

WHEN TO TEST: Consider a genetic workup in cases with features that suggest a specific syndrome, dysmorphic features and/or congenital anomalies, intellectual disability or autism. Testing is also often indicated for the EOEEs and progressive myoclonic epilepsies without a clear metabolic etiology. Although genetic testing is available in other situations, the decision of whether or not to pursue genetic testing depends on a balance of clinical suspicion and benefit to the family. It some cases a genetic diagnosis may be helpful in predicting outcome (i.e., benign familial neonatal seizures) or in genetic counseling for the family. Sequencing and/or duplication or deletion testing should be considered if a specific gene abnormality is suspected. Larger gene panels may be indicated in other cases such as EOEEs without features pointing toward a specific gene. Chromosomal microarray studies

TABLE 5.14 Clinically Testable Epilepsy Genes, by Subgroup[13,106–108]

Early-Onset Epileptic Encephalopathy (EOEE) or Infantile Spasms (IS)			
ARX	Aristaless-related homeobox, X-linked	Xp21.3	EOEE, EOEE-SB, OS, or WS, especially if corpus callosal and/or genital abnormalities, can be associated with lissencephaly
CDKL5	Cyclin-dependent kinase-like 5	Xp22.13	Early-onset epilepsy, often with IS. Esp if microcephaly, hypotonia, Rett-like features
PNKP	Polynucleotide kinase 3′-phosphatase	19q13.33	OS, WS
SLC25A22	Solute carrier family 25 (mitochondrial carrier, glutamate), member 22	11p15.5	OS, EME, EOEE
STXBP1	Syntaxin-binding protein 1	9q34.11	EOEE, esp if movement disorder and severe DD
Treatable Early-Onset Epilepsies			
ALDH7A1	Aldehyde dehydrogenase 7 family, member A1	5q23.2	Pyridoxine-dependent epilepsy; EOEE, EOEE-SB, or OS
GAMT	Guanidinoacetate methyltransferase	19p13.3	Creatine deficiency, epilepsy
GLDC AMT	Glycine decarboxylase Aminomethyltranserase	9p24.13P21.31	EME, nonketotic hyperglycinemia (NKH)/glycine encephalopathy
PNPO	Pyridoxamine 5′- phosphate oxidase	17q21.32	Pyridoxal-5′-phosphate-dependent epilepsy
SLC2A1	Solute carrier family 2 (facilitated glucose transporter), member 1	1p34.2	Early-onset refractory epilepsy, DD, movement disorder; early-onset absence szs; idiopathic generalized epilepsies
ATP7A	Copper-transporting p-type adenosine triphosphatase	Xq21.1	Menke's syndrome, EOEE

(continued)

TABLE 5.14 Clinically Testable Epilepsy Genes, by Subgroup (Continued)

	Benign Neonatal/Infantile Szs		
KCNQ2	Potassium channel, voltage-gated, KQT-like subfamily, member 2	20q13.33	Benign neonatal szs or EOEE or OS
	GEFS+, Dravet syndrome-like		
GABRG2	Gamma-aminobutyric acid receptor, gamma-2	5q34	GEFs+
PCDH19	Protocadherin 19	Xq22.1	ID and refractory epilepsy in females
SCN1A	Sodium channel, neuronal type i, alpha subunit	2q24.3	GEFS+, Dravet syndrome, MMPEI
SCN1B	Sodium channel, voltage-gated, type i, beta subunit	19q13.11	GEFS+

CAE, childhood absence epilepsy; DD, developmental delay; EME, early myoclonic encephalopathy; EOEE, early-onset epileptic encephalopathy, nonspecific; GEFS+, generalized epilepsy with febrile szs plus; ID, intellectual disability; IS, infantile spasms; JAE, juvenile absence epilepsy; JME, juvenile myoclonic epilepsy; MMPEI, malignant migrating partial epilepsy of infancy; OS, Ohtahara syndrome; West, West syndrome.

Note: There is often phenotypic overlap, and grouping by phenotype is not exclusive. List is not comprehensive and constantly expanding. Yield and clinical utility of testing vary between studies. Not included are syndrome-related genes (e.g., Pitt–Hopkins), or genes associated with structural malformations. In progressive myoclonic epilepsies also consider sialidosis and mitochondrial disorders. Consider other metabolic causes, especially in neonatal/infantile-onset epileptic encephalopathies, most notably EME.

screen broadly for duplications or deletions throughout the genome. Please see other references with regard to specifics of when and how to order genetic testing in epilepsy and consider subspecialty consultation. **Online resources** include (1) www.genetests.org, (2) UCSC genome browser (genome.ucsc.edu), and (3) Online Mendelian Inheritance in Man (OMIM) (www.ncbi.nlm.nih.gov/omim).

PAROXYSMAL NONEPILEPTIC EVENTS

A number of nonepileptic spells are seen in children, and many but not all carry a benign prognosis. Please refer to the beginning of this chapter for **temporary management** of an early unknown diagnosis, and be aware of potential harm of early, wrong diagnosis. These events can be organized by age (Table 5.15) and by predominant feature (Tables 5.16–5.21).

MANAGEMENT OF EPILEPSY

Pharmacological Management

(1) **Temporary management** in early stages of the diagnostic process is discussed in the beginning of this chapter. (2) **To treat or not treat** depends on many factors. Omitting or postponing treatment after a solitary sz or even a single cluster of szs may not worsen the prognosis.[18,19,20] In the absence of a firm diagnosis, this "delayed therapeutic approach" may gain more importance. In case of a transient reversible etiology, treatment of the underlying disturbance may obviate the need for AEDs. (3) **Recurrence rate** after a first unprovoked sz ranges from 30% to 55% over 2 to 5 y.[5] A second sz raises this recurrence risk to 80% to 90%.[21] Clinical factors associated with an increased recurrence risk are remote symptomatic etiology, abnormal neurological examination, occurrence of first sz out of sleep, epileptiform abnormalities on EEG (doubles risk from 30% to 60%).[5] (4) **Choosing a first medication** requires knowledge of electroclinical nature of events (sz type, EEG, age, syndrome) and efficacy and side-effect profile of AEDs (Tables 5.22 and 5.23). Typically start with single drug (monotherapy), and efficacy of medication can be assessed when (high) therapeutic levels are reached. (5) **Compliance** is monitored through history taking, and blood AED levels can be an indication but may not imply regular and correct administration. Consistently subtherapeutic levels raise suspicion for noncompliance. Excessively fast metabolism is rare. In case of poor compliance, increasing the prescribed medication dose may not help. (6) **Blood AED levels** may be helpful in some medications, specifically when noncompliance or toxicity is suspected. However, in most cases dosing according to weight and titration according to side effects are appropriate. AM (not PM) trough level (before taking AED) is most reliable, as there is considerable variation throughout the day. Non-trough levels are of little routine use in most AEDs and only demonstrate the presence of the AED in the serum. Beware of administrative or laboratory errors (e.g., oxcarbazepine vs. carbamazepine). In patients with renal impairment or low albumin levels, dose adjustment and measurement of free (non-protein bound) levels may be needed. (7) **Side effects** should be assessed proactively during each patient encounter, not by awaiting parental report. Long-term monitoring of side effects is warranted in some AEDs, e.g., vitamin D levels and, if indicated, bone mineral density, facial features, kidney stones, menstrual changes, weight, hair growth pattern. (8) **Drug–drug interactions** can be challenging, especially in multiple-drug regimens and during illness (metabolic stress) or changes in dose, diet, weight, or other medications. An enzyme inducer will increase the metabolism of inducible drugs, an enzyme inhibitor will decrease the metabolism

TABLE 5.15 Nonepileptic Paroxysmal Events Grouped by Age (First Seen, or Typical) and Clinical Manifestation

Age	Alterations of Breathing and/or Consciousness or Migraine Spectrum	Motor	Eye Movements	Sleep
0–8 wk	Apnea, ALTE	Jitteriness, hyperekplexia	Benign tonic upgaze	Benign sleep myoclonus
2 m–2 y	Breath-holding spells	Paroxysmal torticollis	Opsoclonus Myoclonus	Head banging
		Sandifer syndrome	Benign paroxysmal vertigo	Rhythmic movements disorder of sleep
		Stereotypies	Benign tonic upgaze	
		Infantile masturbation		
		Shuddering attacks		
2–12 y	Hyperventilation (tetany)	Paroxysmal movement disorders		Parasomnias
	Panic attacks	Kinesiogenic or dystonic choreoathetosis,		Somnambulism
	Syncope	torticollis, ataxia, vertigo		Somniloquy
	Migraine and variants:	Tics		Restless legs and variants
	Abdominal migraine	Dystonic drug reaction		Night terrors
	Cyclic vomiting	Munchausen by proxy		Nightmares
	Migraine with (aura and) focal features	Rage attacks		
	Psychogenic nonepileptic szs	Psychogenic nonepileptic szs		
12–18 y	Syncope	Tremor		Hypnic jerks
	Migraine and variants:	Paroxysmal movement disorders (as above)		Narcolepsy
	Transient global amnesia			
	Psychogenic nonepileptic szs			

ALTE, acute life-threatening event. Note that the age ranges are approximations; overlap occurs.

Loddenkemper T, Wyllie E. Diagnostic issues in children. In: Schachter SC, LaFrance WC, eds. *Gates and Rowan's Nonepileptic Seizures.* Cambridge, UK: Cambridge University Press; 2009:95–114.[78]

TABLE 5.16 Nonepileptic Paroxysmal Events Associated with Sleep

Condition	Age	Hx/Clues	Dx, Rx, Prognosis
Sleep myoclonus (benign, neonatal, infancy)[79]	<1 y and older	Never involves face, does not waken child from sleep, gone with arousal, never during wakefulness, usually within 1st h of sleep or upon falling asleep. Can migrate between limbs, and cluster or vary in intensity. Duration up to >30 min (neonate) **DDx:** (1) isolated or series of hypnagogic (hypnic) jerks occur at all ages, and are gone in deeper stages of sleep; (2) myoclonic szs	May lead to inpatient video-EEG Spontaneous remission, reassurance, good prognosis
Parasomnias including Night terrrors[80]	<6 y	Night terrors (2 h after falling asleep, loud scream, anxious, sit up, diaphoresis and tachycardia, duration 15–60 min, fall asleep again, no memory of event), sleepwalking, violently turning over, sitting up, muttering, moaning, vocalizations, hypnagogic and hypnopompic hallucinations. Also refer to Chapter 20 **DDx:** nocturnal frontal lobe szs: complex, bizarre motor and other behaviors and automatisms. Typically brief, very stereotyped, multiple per night, abrupt onset and termination, posturing or hyperkinetic semiology (e.g., pedaling with legs), no postictal phase, may have daytime szs, challenging electroclinical Dx **Synonyms/related:** arousal disorders, pavor nocturnus, sleepwalking	May lead to inpatient video-EEG Spontaneous remission, reassurance, good prognosis
Head banging[81]	Infants and young children	Sleep-related rhythmic movement disorder of soothing (falling asleep) or parasomnic (sleep) head- or leg-banging and body rocking. More w/ developmental delay, autism, abuse or neglect. Min to h, may continue in sleep. Typically not violent enough to cause injury **DDx**: stereotypies or self-stimulation, attention seeking **Synonyms:** jactatio capitis (nocturna)	Reassurance, remission by age 4 with normal development and no traumatic sequelae

Note: Also see narcolepsy and cataplexy, paroxysmal dyskinesias below.

TABLE 5.17 Nonepileptic Paroxysmal Events Associated with Feeding

Condition	Age	Hx/Clues	Dx, Rx, Prognosis
Reflux (GERD) and Sandifer syndrome[82]	Up to 6 y	**Gastroesophageal reflux disease (GERD):** after feeding (min–1 h), not during. Failure to thrive, coughing, recurrent regurgitation, rumination and spitting up, irritability **Sandifer syndrome:** Body posturing, stiffening, opisthotonus, torticollis—impressive, complex contortions and posturing that relieve GERD-associated discomfort. Positional changes may appear counterintuitive (e.g., head lower than shoulders) **DDx**: common mis-Dx as szs or paroxysmal dystonia in cognitively impaired children with hypotonia	pH-probe (<4), barium swallow study (aspiration), r/o hiatus hernia PPI, H_2 blocker, thickened feeds, head elevation Prognosis ~ GI intervention

TABLE 5.18 Nonepileptic Paroxysmal Events Associated with Syncope and Anoxia

Condition	Age	Hx/Clues	Dx, Rx, Prognosis
Syncope and reflex anoxic szs (categorical diagnosis)		**Definition:** syncope is (1) **very common** and (2) a **generic term** and not final diagnosis Transient loss of consciousness from sudden reduction of cerebral blood flow and/or oxygen saturation leads to cerebral hypoxemia with or without reflex anoxic sz. Signs, symptoms, duration ~ age of child and mechanism **Common features of reflex anoxic sz:** loss of consciousness, atonia, stiffness during fall, tonic stiffening or opisthotonus on floor, flexion of upper limbs, myoclonic (isolated) or clonic (repeated) asynchronous, less course and nonsustained jerks ("fish on the dry"), eye-jerks, eye deviation, head-turning, snorting or snoring, disorientation, agitation, postevent sleep, urinary incontinence, autonomic phenomena (drooling, cyanosis, pallor, flushing) **Classification of syncope**[83] **A. Reflex syncope** (neurally mediated): **most common**, inappropriate neural control over the circulation, e.g., **vasovagal syncope**, hair-grooming, stretch or micturition syncope **B. Cardiac syncope:** insufficient cardiac output Arrhythmia, e.g., paroxysmal SVT and VT, congenital prolonged QT syndrome Structural cardiac disease, e.g., valvular disease, obstructive cardiomyopathy **C. Autonomic Failure:** insufficient vascular tone results in orthostatic hypotension Primary, e.g., multiple system atrophy, pure autonomic failure Secondary, e.g., diabetic and other neuropathies Drugs, e.g., antidepressants, beta-blockers **D. Hypovolemia:** insufficient circulatory volume, e.g., Addison disease, diuretics, hemorrhage	**Diagnostic aids:** EEG: coincidental findings on EEGs can lead to false Dx of epilepsy Tile-test (typically >7 y) Holter monitoring Home video **Controversial:** Ocular compression test w/ EEG and ECG (change of RR interval 0.5 s, asystole >2–6 s): arbitrary, not sensitive/specific risk of ocular injury, prolonged asystole assesses reactivity, not tone

To specific diagnosis

(continued)

TABLE 5.18 Nonepileptic Paroxysmal Events Associated with Syncope and Anoxia (Continued)

Condition	Age	Hx/Clues	Dx, Rx, Prognosis
Reflex syncope and pallid breath-holding spells[84] (PBS)	<6 y	**Most syncopes are reflex syncopes**, with a short-latency episode of reflex asystole. Most common reflex syncopes in infancy and toddlerhood are PBS **PBS:** always some provocation, painful (head bump, fall) or emotional (sudden fright); crying is brief or absent, and there is **no holding of breath**; followed by profound pallor and limpness (lying deathly still with eyes fixed upward), then abrupt stiffening with arched back and fisted hands, ends within 10–30 s, eye opening and responsiveness returns. Dramatic and prolonged events may occur, including incontinence, confusion (see above: common features of anoxic sz) **Synonyms:** reflex syncope with reflex anoxic sz (nonepileptic) convulsive syncope, pallid (infantile) syncope, pallid syncopal attack, reflex anoxic sz, vasovagal or cardiovagal syncope, reflex asystolic syncope (also see below) **DDx:** may mimic GTC and at times may be followed by a brief GTC sz. Do not miss cardiac arrhythmias, especially prolonged QT-syndrome (syncope with startle, during sleep or exercise, positive FHx, sudden deaths)	**Clinical Dx** if provoking stimulus observed and episodes stereotypical, but stimulus may not have been witnessed **Studies:** see above **Rx:** reassurance, avoiding triggers not feasible, avoid CPR (place on side), rarely atropine or scopolamine, or pacemaker **Prognosis:** excellent
Blue breath-holding spells[85] (BBS)	First months of life–5 y	**Definition:** pain, frustration, fear followed by crying (2–3 cries, whining, prolonged gradually worsening cry), next a sudden noiselessness with **holding breath postexpiration**, mouth open, and an "ominous silence" follows during profound cyanotic apnea. Next recovery (labored inspiration, crying) or anoxic sz (see above). Drowsiness, exhaustion lasting mins common, sleepiness more rare **Synonyms:** prolonged expiratory apnea, cyanotic infantile syncope	Dx, Rx, and prognosis: as above Assess and Rx **iron deficiency anemia**

Reflex syncope (includes vasovagal syncope)[86]	Older than PBH spells	**Aka neurally mediated syncope:** stimulus leads to tachycardia and then drop of BP and HR Vasovagal: fear, pain, prolonged standing Situational: micturition, coughing, sneezing, swallowing, defecation Carotid sinus syndrome: rare, provoked in adults or elderly by subtle pressure to carotid body **Cardioinhibitory** (bradycardia predominant); or **vasodepressor** (hypotension predominant) **Circumstances:** cessation of exercise, pain, fear, standing, sight of blood, fasting **Presyncopal features:** dizziness, blurring or graying or blacking out of vision, pupillary changes, voices and sounds sounding distant, rushing sensations, tinnitus, abdominal pain/nausea, vomiting, pallor, feeling cold, diaphoresis, clamminess, weakness, legs buckling) **Postsyncopal recovery:** typically rapid, but pitfall is early standing up (e.g., with help of bystanders) and recurrence or prolongation of symptoms **Features that do *not* argue against syncope:** any of the features from a reflex anoxic sz (see above), incontinence, anterior tongue-bite (rather than lateral), high frequency of events, brief abdominal sensation (usually nausea), duration >1 min, abrupt onset, postevent confusion, motor phenomena (in up to 50% of fainters) **Synonyms:** fainting, neurocardiogenic syncope. With anoxic sz: convulsive syncope	**Good history:** specific situations or (subtle) stimulus, presyncopal symptoms and postevent course are key **Workup, Rx, and prognosis:** as above. Counseling on position changes, fluid intake and increased salt intake if indicated **Rarely:** fludrocortisone, midodrin, compression stockings, anticipatory crossing legs
Cardiac arrhythmias incl. prolonged QT syndrome[86,87]	All ages (usually older)	**Congenital long QT syndrome:** autosomal dominant or autosomal recessive (with sensorineural deafness). Syncope or anoxic szs during exercise (e.g., swimming and diving prompt dive reflex), sleep, sudden auditory stimulus or startle (e.g., alarm clock), emotional stress or shock. Polymorphic ventricular arrhythmia (torsade de pointes) may lead to sudden cardiac death **Other cardiac arrhythmias and congenital cardiac defects:** less of a diagnostic challenge	**FHx is key:** syncope, szs, sudden death, congenital deafness **Routine ECG:** may not rule out, refer to cardiology

TABLE 5.19 Nonepileptic Paroxysmal Events, Movement Predominant

Condition	Age	Hx/Clues	Dx, Rx, Prognosis
Infantile masturbation[88]	1st mo of life–4 y	Stimulation seeking **normal part of sexual development**. At times of stress, excitement, or boredom. Episodes can be interrupted. Typically frequent rhythmic movements (adduction/tightening of legs, pelvic thrusting), grunting or moaning, "trance"-like state or staring, sweating, and facial flushing **Persistent and in public, worsening:** think of familial/emotional stress or abuse **Synonyms:** gratification behavior, ritualistic movements. Some parents may be taken aback by the terminology *infantile masturbation*; gratification behavior may be more helpful for the families due to stigma associated with terminology **DDx:** abdominal discomfort, epilepsy (absence, partial, complex)	**Clinical diagnosis** Home video EEG (rarely needed) **Reassurance**, remission is anticipated at 7–8 y, no sexual deviance associated Careful distraction from behavior without conveying taboo
Shuddering attacks[89]	Infancy to <5 y	Several seconds of **rapid shivering** of head, shoulder and occasionally trunk, "as if cold water is poured down the back," up to 100/day, great intra- and intervariability **Common condition** (7% of nonepileptic paroxysmal events), normal children. Some parents may not bother to report and recognize it as benign	Clinical diagnosis Home video EEG (rarely needed) Reassurance, remission
Hyperekplexia[90]	Birth	Rare AD or AR channelopathy w/ abnormal glycine-R affecting Cl- influx with inhibitory interneuron dysfunction. **(1) Exaggerated startle reflex** to (subtle, any) stimulus that does not extinguish with repetition, with jitteriness and rhythmic repetitive movements, occasional apnea. **(2) Tonic stiffening** on handling (diaper change), generalized hypertonia and hypokinesia, prominent sleep myoclonus, and periodic limb movements. Intellect normal, some mild impairment. Adults milder, startle with unprotected falls **DDx**: startle epilepsy, tonic or GTC szs	**Clinical Dx**, FHx Genetic testing *GLRA1*, others (see ref. 90) EEG: not epileptic Clonazepam 1st choice

Episodic ataxia[91]	Early childhood to later	**Episodic ataxia with loss of balance**, lasting seconds to minutes, may be provoked by startle, emotion, exercise, alcohol. Myokymia ("waves" of muscle contractions) and nystagmus (ictal, interictal) can be seen. Rare, group of monogenic disorders, classically channelopathies (Ca^{++}, K^{+}), but phenotypically and genetically heterogeneous	Acetazolamide 1st choice See Chapter 16
Paroxysmal torticollis[92]	Childhood	**Recurrent episodes of abnormal rotation and tilting of the head (cervical dystonia).** Duration minutes to days, if short may resemble sz. Frequent associations: irritability, vomiting, pallor, ataxia, tortipelvis, and delayed gross and fine motor development, relationship with other periodic movement disorders and later migraine. **DDx**: acute and persistent torticollis—consider posterior fossa lesion, CN palsies	Often refractory including meclizine, chlorpromazine Remission by age 3 y, development may accelerate at that time
Paroxysmal dyskinesias and dystonias[93,94]	All ages	**Episodic dystonia/dyskinesia w/ involuntary movements (choreoathetosis, ballism) without symptoms or neurologic symptoms in between episodes.** Overlap with paroxysmal dyskinesia, episodic ataxia, channelopathies, other paroxysmal d/o. **Kinesiogenic:** brief (sec–5 min), frequent, precipitated by sudden movement, M > F, AD inheritance, sporadic or secondary **Spontaneous:** prolonged (up to 6 h), provoked by coffee, tea, alcohol, fatigue, more resistant to treatment **Exercise-induced dystonia:** mainly affecting feet, continuous exercise (walking/running), different from action-induced dystonia and dopa-responsive dystonia (see chapter on movement d/o) **Secondary paroxysmal dyskinesias:** hypothyroidism, diabetes, multiple sclerosis, stroke, traumatic brain injury, infection **DDx:** tonic spasms (in MS), (pseudo-)szs, psychogenic symptoms, genetic dystonias, childhood Huntington's disease	Genetics: *see full ref*s Kinesiogenic: AEDs (CBZ 1st choice) Spontaneous and exercise induced: often refractory See Chapter 16

(continued)

TABLE 5.19 Nonepileptic Paroxysmal Events, Movement Predominant (Continued)

Condition	Age	Hx/Clues	Dx, Rx, Prognosis
Stereotypies, mannerisms, self-stimulation[95]	All ages	**Abnormal, repetitive, stereotyped movements** in patients occur frequently in neurologically impaired children (e.g., Rett, autism, Angelman): staring, rhythmic movements (flapping, clapping, waving, head shaking or nodding, rocking, slumping), eye movements (incl. sustained deviation), chewing, tongue thrusting, tonic posturing, arching, episodic hypo- or hyperventilation (Rett), tremor ↑ when excited or upset. High comorbidity of tic d/o, OCD and ADHD **DDx:** may be difficult to discern from szs, and may co-occur in same patient	If clinical Dx not possible, inpatient video-EEG needed to avoid unnecessary AED Rx
Tics (review,[96] treatment[97])	All ages	**Stereotyped repetitive involuntary movement or sound, frequently preceded by premonitory sensations or urges.** Vocal, orolingual, labial, guttural, nasal, motor, complex (OCD like). Classically can be briefly suppressed, which mounts into release in burst of "catch up" tics. Coprolalia rare. Contrary to common belief, can be present in sleep. Tourette's syndrome: tics >1 y with breaks <3 mo, onset <18 y, multiple motor and at least one vocal tic (not necessarily concurrent), impairment in social or other areas of functioning. FHx often positive, or positive for associated d/o **DDx:** prominent psychosocial factors and comorbidity of OCD, ADHD, rage, other neuropsychiatric d/o, management of which in children can have priority for ↑ QOL	**Dx:** usually not hard **Medication:** see Behavioral Neurology, Chapter 15 **Education, counseling:** acceptance and positive attitude of family members, peers, teachers, and coaches

TABLE 5.20 Nonepileptic Paroxysmal Events, with Prominent Eye Movements

Condition	Age	Hx/Clues	Dx, Rx, Prognosis
Paroxysmal tonic upgaze (benign, infancy, childhood)[98]	Onset usually <1 y	**Episodes of variably sustained conjugate upward eye deviation with subtle compensatory neck flexion, downbeating saccades in attempted downgaze and normal horizontal eye movements.** Fluctuations (diurnal, relief by sleep, ↑ w/ fever, stress, pain, fatigue), at times associated ataxia. Neurological examination nl. Autosomal-dominant inheritance described but rare **DDx:** paroxysmal tonic upgaze in neurologically abnl children can be szs, movement d/o, structural lesions, (fetal) toxic exposure with cognitive impairment and residual oculomotor d/o	Reassurance, remission, nl outcome Studies (e.g., EEG, imaging studies, CSF NT) normal Neurologically abnormal child (development, exam): expand etiological workup
Spasmus nutans (SN)[99]	6–12 mo, lasts 1–2 y	Benign transient syndrome of **rapid, asymmetric, low-amplitude nystagmus with compensatory head tilting and titubation, torticollis**, and resolution with age, normal neurological outcome. Mimicry frequent, clinically challenging Dx **DDx:** SN-like with CNS abnormalities (e.g. hypothalamic), from sensory deficits (optic pathway tumors, retinopathy), (causes of) infantile or congenital nystagmus	Dx of exclusion Consider nystagmography, ERG, MRI brain, referral to (neuro-)ophthalmologist
Oculogyric crisis[100]	Childhood and up	**Tonic, (near-)painful acute dystonic upward or lateral eye deviation.** Mins (range sec–h). Typically w/ antipsychotics, more with high dose/potency, parenteral administration, family Hx(+). Associated with torti- or retrocollis, opisthotonus, oromandibular dystonia. May be recurrent w/ maintenance or reexposure to the drug. Can occur with PHT (or ophthalmoplegia), CBZ, GBP	Prevention and/or withdrawal of drug Rx: anticholinergics (trihexyphenidyl), antihistamines (diphenhydramine)

TABLE 5.21 Nonepileptic Paroxysmal Events, Miscellaneous

Condition	Age	Hx/Clues	Dx, Rx, Prognosis
Migraine (basilar, with aura)	Childhood	**Visual disturbances, altered body image, ataxia, reduced level of consciousness.** Visual aura: migraine (minutes) white/silver/gold, geometric fortifications, scotoma scintillans, floaters. Epileptic: shorter, definite objects (people), circles, multicolored	See Chapter 14
Benign paroxysmal vertigo[101]	2–4 y, <5 y	**Sudden frightened appearance, pale and poor coordination with fall, without loss of consciousness, often accompanied by vomiting, and if examined, nystagmus.** Older child complains of dizziness (i.e. vertigo). Idiopathic/otologic disorder vs. migraine-equivalent. FHx for migraines, motion sickness often (+). Association with other periodic disorders, e.g., recurrent abdominal pain, cyclic vomiting	Clinical Dx Reassurance, remission by age 5 y, symptomatic Rx for longer episodes
Münchausen syndrome by proxy[102]	All ages	**Münchausen:** perpetrator (parent/caretaker) inflicts or abuses child, common: suffocation or strangulation, poisoning (salt, medications) or overdosing (AEDs, others). Episodes never happen in absence of abusing parent. **Meadow syndrome:** parent falsifies or fabricates the Hx. Sometimes Dx w/ video-EEG. If no intervention, can be lethal	Difficult Dx and Rx, multidisciplinary approach (neurology, psychiatry, social services, law enforcement)[103]

TABLE 5.22 Antiepileptic Drugs in Children

Medication	Dose	Side Effects (SEs)	Labs/Checks	Level
Carbamazepine (CBZ)	Start 5–10 mg/kg/d, inc 5 mg/kg/d q week, goal 15–30 mg/kg/d div b.i.d.	Rash, leucopenia, hepatitis, low Na, ataxia, NDDU[e]	LFTs, CBC, lytes	4–12
Clobazam (CLB)	0.1–0.2 mg/kg/day (5 mg if >12 y), inc by 0.1 mg/kg/day (or 5 mg if >12 y) q week to goal of 0.4–1.0 mg/kg/day div b.i.d. max 40 mg daily	Sedation, behavioral problems	CBC, chem, LFTs	NA
Ethosuximide (ESM)	Start 5 mg/kg/d, inc 5mg/kg/d q week, goal of 15–40mg/kg/day div b.i.d.	NDDU[e]	CBC	40–100
Gabapentin (GBP)	Start 10–20 mg/kg/d, inc q 3 d to goal of 100 mg/kg/d	Mild sedation, unsteadiness, behavior changes	Not very potent	2–18
Lacosamide (LAC)	Start 1 mg/kg/day, inc by 1 mg/kg/day weekly, goal 10 mg/kg/day div b.i.d.	Prolonged PR interval, AV block, headache, GI upset	ECG LFTs, lytes	5–20
Lamotrigine (LTG)	Initial dose and inc 0.6 mg/kg/d (+inducer), 0.3 mg/kg/d (mono or with other AEDs), or 0.15 mg/kg/d (+VPA). Maint 5–15 mg/kg/d (+inducer/mono) or 1–5 mg/kg/d (+VPA) div b.i.d.	NDDU[e], Stevens–Johnson syndrome (mucosal bullae in orifices and genitalia, rarely toxic epidermal necrolysis)	VPA raises levels significantly	2–20

(continued)

TABLE 5.22 Antiepileptic Drugs in Children (Continued)

Medication	Dose	Side Effects (SEs)	Labs/Checks	Level
Levetiracetam (LEV)	Load 20–30 mg/kg/dose Maint 20–100 mg/kg/d div b.i.d. or t.i.d.	Irritability and behavioral dysregulation, rarely somnolence and asthenia in acute phase, may aggrav. depression. Limited evidence for improvement with PO pyridoxine	Risk of SEs highest in patients with preexistent behav dysfct & cogn delay, depression	5–45
Lorazepam (LZP)	0.05–0.1 mg/kg/dose	Sedation, respiratory depression at high doses, lower tone, drooling, tolerance, dependence, withdrawal	sO_2, RR, BP	NA
Oxcarbazepine (OXC)	Start 5–10 mg/kg/day, inc 5 mg/kg/d q week, goal 30 mg/kg/d div b.i.d.	See CBZ—just less. Rash c CBZ: 25% also rash with OXC	See CBZ	12–35
Phenobarbital (PB)	Load 20 mg/kg/dose Maint 5 mg/kg/day div q day or bid Bolus $V_d \times$ (desired – measured), V_d (infant) = 0.9, V_d (adult) = 0.55 Direct postload level: yes	Same as LZP, and decreased intellectual function and behavior, most potent inducer (other AEDs may fail to reach level)	acute: O_2-sats, RR, BP chronic: other AED levels	15–45

Phenytoin (PHT) If V_d is unknown, you can calcuate it: V_d = IVdose/ Δconc.	Load 20 mg/kg/dose Maint 2–8 mg/kg/day div bid or tid Bolus V_d × (desired−measured) in mg/kg [b, c] V_d (infant) = 0.7−0.8, but large variability V_d (child) = 1.0 V_d (adolescent) = 0.7−1.0 V_d (adult) = 0.7 Direct postload level: yes	Rash, acne, coarse face, hirsutism, gingival hypertrophy, cerebellar atrophy, ataxia, slurred speech, low folate, transient dystonia/ophthalmoplegia, osteomalacia	*Not* with bradycardia, 2nd or complete AV block, hypotension, low EF *Load:* cardiac monitor, BP	10–20*a* Not ½, but a steady rate of elimin.
Rufinamide (RFA)	Start 10 mg/kg/day, inc by 10 mg/kg/day (up to every other day), goal 45 mg/kg/day div b.i.d.	QT shortening (check ECG prior), GI upset, headache, behavior changes, worsening szs	VPA inc, enzyme inhibitors dec levels, CBC, ECG	10–25
Topiramate (TPM)	Start 1 mg/kg/d inc 1 mg/kg/d q week, maint 5–9 mg/kg/d, max 30 mg/kg/d div daily or b.i.d.	Weight loss, cognitive slowing, language delay, low CO_2	CO_2 Renal US	2–25

(continued)

TABLE 5.22 Antiepileptic Drugs in Children (Continued)

Medication	Dose	Side Effects (SEs)	Labs/Checks	Level
Valproic acid (VPA) Switch from VPA to VPA ER: increase dose by 10%–20% to achieve bioequivalence	Load 20 mg/kg/dose Start 5–10 mg/kg/d and inc 5 mg/kg/d q week, maint 15–20 mg/kg/day div bid (or tid) $V_d = 0.2$ Direct postload level: no Only level of use is AM trough level, other levels highly variable, so only for presence vs. absence of medication in bloodstream	Stomach upset, weight gain, thin hair or hair loss, PCO/amenorrhea, easy bruising, tremor, encephalopathy w/ or without NH_3 increase, pancreatitis, hepatotoxicity, teratogenicity	CBC LFTs Amy/Lip VPA pushes PHT off albumin [d]	50–100
Vigabatrin (VGB)	Start 30–40 mg/kg/d, inc 10 mg/kg/d q week, goal of 80–100 mg/kg/d div b.i.d.	Mild drowsiness, behavior changes, irreversible peripheral visual field constriction, reversible restricted diffusion BG/thalami/brainstem/dentate on MRI	ERG, routine ophthalmologic exams, follow guidelines from	1.4–14
Zonisamide (ZNS)	Start 2–4 mg/kg/d b.i.d., maint 4–8 mg/kg/d, max 12 mg/kg/d div q day or b.i.d.	Anhidrosis, anorexia, low CO_2	LFTs	15–30

[a] Adjusted level PHT = measured / [(0.2 × albumin) + 0.1]}.
[b] PHT bolus (in mg/kg) = V_d × (desired – measured PHT level), e.g., adult 85 kg level 8, bolus = 0.7 × (18 – 8) = 7 mg/kg = 595 mg.
[c] PHT IV dose = oral dose + 10%. [d] Free fraction of PHT ~ VPA level: Free PHT (%) = 10% (=baseline) + (0.1 × VPA level).
[e] NDDU, nausea, drowsiness, dizziness, unsteadiness (usually dose-related).
Enzyme inducers: CBZ, PHT, PB, PRM, OXC. Enzyme inhibitors: VPA, FBM
Inducible drugs: CBZ, VPA, ESM, FBM, LTG, TPM, TGB, OXC, ZNS, BDZ. Inhibited drugs: LTG, PB, ESM, FBM, VPA

TABLE 5.23 Antiepileptic Drugs in Children Based on Seizure Type and Syndrome

Sz Type or Syndrome	First-Choice AEDs	Second-Choice AEDs	Third-Choice AEDs	Consider
Partial szs with/without secondary generalization	OXC, LEV	LTG, VPA (male), PGB	LAC, TPM, ZNS, PHT	TGB, RFA, PB, PRM, BDZ, AAA
Generalized tonic–clonic	LEV, LTG, VPA (male)	TPM, OXC, PHT	ZNS, PB, PRM	
Childhood absence epilepsy	ESM, VPA (if convulsions)	VPA, LTG		MSM, BDZ, LEV, TPM, ZNS, AAA
Juvenile absence epilepsy	Females: LTG (±ESM) Males: VPA	LTG, ESM (add-on)	MSM, LEV, TPM, ZNS, BDZ, AAA	
Juvenile myoclonic epilepsy	Females: LEV, LTG Males: VPA	LEV, LTG, TPM, CZP (not alone)	ZNS, PB, PRM	
BRECTS	STM, GBP	LEV, OXC, VPA		LTG, TPM, ZNS, PGB, LAC
Infantile spasms	ACTH (cryptogenic), VGB (TS, lesional)	Prednisone, VPA, TPM, ZNS, BDZ, KGD		RFA, pyridoxine, LEV, LTG, FBM
LGS	TPM, LTG	RFA	VPA, KGD, CLB, FBM, ZNS	PB, ESM, MSM, steroids, LEV, pyridoxine
LKS	ACTH or steroids, VPA	LEV, LTG		IVIG
CSWS	BDZ, VPA	STM, LEV, LTG		IVIG
Neonatal szs	PB	PHT		BDZ, TPM, LTG

AAA, acetazolamide; ACTH, adrenocorticotropic hormone; BRECTS, benign Rolandic epilepsy with centrotemporal spikes; BDZ, benzodiazepines; CBZ, carbamazepine; CLB, clobazam; CSWS, continuous spike waves of sleep; CZP, clonazepam; ESM, ethosuximide; FBM, felbamate; GBP, gabapentin; LAC, lacosamide; LEV, levetiracetam; LGS, Lennox–Gastaut syndrome; LKS, Landau–Kleffner syndrome; LTG, lamotrigine; MSM, methsuximide; OXC, oxcarbazepine; PB, phenobarbital; PGB, pregabalin; PHT, phenytoin; PRM, primidone; RFA, rufinamide; STM, sulthiame; TGB, tiagabine; TPM, topiramate; VGB, vigabatrin; VPA, valproate; ZNS, zonisamide. Updated from Hadjiloizou SM, Bourgeois BF. Antiepileptic drug treatment in children. *Expert Rev Neurother.* 2007; 7:179–193.[104] (updated to 2011 with Blaise Bourgeois).
Disclaimer: Treatment decisions and AED choices in practice can be complex and will consider many variables and individual risk factors and presentations. The authors cannot assume responsibility but rather aim to provide guidance.

of inhibited drugs. Consult a pharmacist or refer as needed. (9) **Adolescent females** should be explicitly warned about teratogenic effects of AEDs and educated thoroughly on safe-sex practices and anti-conception methods. Some AEDs may decrease the efficacy of birth-control pills. (10) **Stopping AEDs** is typically done after 2 y of sz freedom, but early discontinuation after 6 to 12 mo is advocated by some[22] for children with favorable risk factors: onset 2 to 12 y, idiopathic, normal development/cognition and neurological examination, prompt initial AED response, infrequent szs, low drug levels at the time of decision, sz-free interval much longer than 2 y, benign epilepsy with centrotemporal spikes (BECTS), childhood absence epilepsy (CAE).[5] Unfavorable risk factors include age at onset ≥12 y, mental retardation and abnormal neurological examination, poor initial AED response, >1 AED at the time of decision to taper AEDs, EEG abnormalities, family history of epilepsy, juvenile myoclonic epilepsy (JME), symptomatic partial szs. An abnormal EEG does not unequivocally predict recurrence of szs in the absence of AEDs, as the spikes can "outlive" the period of active szs (e.g., BECTS). There is insufficient data to recommend slow taper over a more rapid withdrawal,[23] but in practice AEDs are typically tapered over weeks to months. An unsuccessful discontinuation trial in a patient with controlled epilepsy does not lead to intractability in most cases, although counseling on this scenario prior to withdrawal is important.[24] Psychosocial consequences of an unsuccessful trial may be more limited if done during a school break.

Nonpharmacologic Options

In medically refractory patients (≥3 appropriately chosen AEDs at effective dose or level and nonepileptic events are excluded), sz frequency or medication toxicity cannot be acceptable.

(1) Vagus Nerve Stimulator (VNS)[2]: Provides electrical pulses to the left vagus nerve with retrograde transmission to the brain. Unclear antiepileptic mechanism, hypotheses include immediate (de)synchronization of cortical electrical activity and long-term effects on neurotransmitter levels and regional cerebral blood flow. Surgery is done on the left vagus nerve at a cervical level, as it has 80% afferents, less pain fibers, widespread anatomic projections, and less cardiac innervation. Typical setting include 20- to 30-Hz, 250- to 500-ms pulse width stimulus of 0.25 to 3.5 mA, lasting 30 s, q 1.1–5 min. Magnet activation (see below) gives a higher current, has a longer duration & bigger pulse width. The battery life ranges from 5 to 12 y. **Efficacy** >50% sz frequency reduction in ~30% of patients, so many nonresponders. No consistent predictor of efficacy, although trend to better response in generalized szs. Benefits include a lack of CNS adverse effects, no AED interactions, no compliance concerns, potential for increased quality of life (alertness, communication skills, mood, independence, others; in part from decreasing AEDs). Drawbacks include the invasive nature, the cost (debated as other costs can decline), potential for lack of response. **Complications** from surgery include infection (1%–2%), hoarseness/temporary vocal cord paralysis (0.7%), hypesthesia/lower left facial paresis (0.7%), diaphragmatic paralysis (rare), asystole during lead-testing (<0.1%), and surgical mortality in rare cases. Adverse effects during stimulator on-time may decrease over time or change with simulator setting changes. These include voice alteration (58%), cough (38%), ear/throat pain (1%), salivation (1%), headache, dysphagia (rare). No deaths, no idiosyncratic reactions, no increase in sudden unexplained death in epilepsy (SUDEP) have been reported. The VNS is MRI compatible once turned off (call supplier if needed). **Two acute interventions** can be done: (a) Pass magnet over the pulse generator to

start on-demand mode. This can potentially stop or shorten a sz (cluster), decrease sz severity or the duration of the postictal phase. (b) Tape magnet over pulse generator to stop stimulating.

(2) Ketogenic Diet (KGD) [25]**:** For children with medically intractable epilepsy and in specific metabolic diseases, for example, glucose transporter deficiency (GLUT-1) or pyruvate dehydrogenase deficiency (PDH). **Contraindicated** in hyperlipidemia, certain metabolic diseases (e.g., pyruvate carboxylase deficiency, organic acidurias, disorders involving defects in fatty acid transport or β-oxidation), and use of steroids. Unclear, but likely multifactorial antiepileptic mechanism. **Definition:** High-fat, low-carbohydrate diet resulting in ketogenesis, that is, the production of ketones (acetoacetate, beta-OH-butyrate [BOHB]) when free fatty acids are the main energy source. With the KGD 90% of calories come from fat, 10% from protein & carbohydrates, while allowing for sufficient nutrition for growth and development with the help of a specialized nutritionist. Variations include "low glycemic index" diet, modified Atkins, polyunsaturated fatty acids, and others. Ratio of fat: (CHO + protein) = usually 3:1 to 4:1. Urine check: 3–4+ ketones ~60 to 80 mmol/L, corresponds to 30 to 100 mg/dL (2–12 mmol/L) plasma BOHB. Goal BOHB is >40 mg/dL. Complications and management issues are summarized in Tables 5.24 and 5.25.

(3) Epilepsy Surgery[26] **Referral:** Key is evidence for a resectable focal epileptogenic zone, but indications for referral have broadened. Generalized sz semiology, generalized findings on EEG, nonlesional focal or multiregional epilepsy, and even genetic etiology may no longer be contraindications. In patients with catastrophic and multifocal epilepsies, palliative epilepsy surgery may be considered. **Concept:** Resective epilepsy surgery aims to provide a safe, permanent, and curative procedure with minimal impact on healthy, eloquent brain. Seizure freedom is achieved by resection of the *epileptogenic zone* (the area of cortex that is indispensable for the generation of epileptic szs). Unfortunately there is currently no single technique that can provide this information, and therefore an extensive presurgical workup is needed. Other zones overlap and assist with the identification of the epileptogenic zone: The region involved in the EEG onset of szs is called the *ictal onset zone*. Interictal discharges demarcate the *irritative zone*. Seizure symptoms reflect involvement of the eloquent cortex from the *symptomatogenic zone*. Finally, the *functional deficit zone* is the area that displays abnormal function during the interictal period. **Presurgical workup:** Testing includes (video-) EEG, neuropsychological and psychosocial assessments, MRI, and sometimes laboratory tests to rule out (toxic-) metabolic, inflammatory, endocrine, genetic, and degenerative etiology. Optional are magnetoencephalography (MEG), single photon emission computed tomography (SPECT), positron emission tomography (PET), functional MRI, Wada test, and transcranial magnetic stimulation. In the second, invasive phase subdural and depth electrode recordings are often done, and the epileptic cortex can be further delineated from the eloquent cortex by cortical stimulation with functional mapping, evoked potentials, and intraoperative monitoring and stimulation. **Success rates**[27,28]**:** Temporal lobectomy for MTS accounts for 8% to 29% of pediatric epilepsy surgeries, and the rates of sz freedom after surgery are comparable to those in adults (58%–78%). Second to mesial temporal lobe resections are neocortical resections with success rates of 59% to 70% (temporal) and 54% to 66% (extratemporal) resections. Nonlesional etiologies carry a success rate of 45%. Factors predicting favorable outcomes include unilobar temporal resection, single focal lesion on MRI, complete lesional resection and of the active region on EEG/electrocorticography, and absence of preoperative generalized tonic–clonic szs.

TABLE 5.24 Acute Complications and Management of the Ketogenic Diet

Acute	Symptoms	Cause(s)	Rx at Home	Rx in Hospital
Dehydration	Lethargy, decreased urine output, dry mucous membranes, sunken eyes, no tears, tachycardia	Intercurrent (GI) illness. Ketosis inhibits thirst, dehydration increases ketosis; acidosis may induce vomiting	Sugar-free fluids: water, diluted eggnog, formula (RCF: soy protein based plus glucose polymer powder & microlipids; KetoCal: cow's milk protein based, fat source is soy oil), Fruit2O ("smart water"), broth, diet ginger ale	IV fluids (½ NS, other electrolytes as needed, no dextrose)
Hypoglycemia	Lethargy, but often asymptomatic	Medications interfering with carbohydrate metabolism, intercurrent illness (stress, sepsis, infection), caregiver noncompliance	Give 1 tbsp of juice, seek medical attention if needed	Q6h dextrostix **(1)** If <40, and asymptomatic: document w/ lab glucose, go to q2h **(2)** If <25, document, give 30 mL orange juice (OJ), continue q2h until stable >40 **(3)** If symptomatic at any time, document w/ lab, give 30 mL OJ
Vomiting	Vomiting	Excess ketosis or acidosis may induce vomiting	Give 1 tbsp of juice, seek medical attention if needed	Consider IV fluids (see above), antiemetics, supportive therapy
Acidosis	Hyperventilation, vomiting, tachycardia, irritability, facial flushing, lethargy	Excess ketosis, dehydration, intercurrent illness, caregiver noncompliance	To ER unless resolves with hydration	Hospitalization. If HCO_3 <15 mg/dL: supplement w/ Bicitra or Polycitra (2–3 mEq/kg/day div t.i.d. or q.i.d.)
Medications for intercurrent illnesses	E.g., need for antibiotics, steroids	If total adds up to <0.1 g of CHO/day: no need to recalculate. If >0.1, daily dietary total CHO allowance will need adjustment (consult nutritionist). *Note:* Steroids break ketosis (glucocorticoid effects), notify ketogenic diet team		

TABLE 5.25 Chronic and Long-term Complications and Management of the Ketogenic Diet

Chronic	Cause(s)	Management
Poor growth, vitamin and mineral deficiencies, bone demineralization	Increased urinary calcium and phosphate loss, less fluids in diet, so less water-soluble vitamins, dietary deficits	Monitor height, weight, BMI, clinical vigilance for deficiencies, measure Cu, Se, Zn, Ca, Mg, PO_4. Supplement calcium/vit. D. Adjust caloric and protein requirements. Ketogenic nutritionist consultation
Hyperlipidemia, pancreatitis	High fat intake results in linear increase of cholesterol and triglycerides	Long-term effects unknown. Unclear role for lipid-lowering agents. Ketogenic nutritionist consultation
Constipation	Decreased intake of fluids and fiber	Increase fluid intake and fiber intake. Common problem
Urolithiasis	Low urinary pH, decreased urine flow, increased calciuria, use of calcium supplements	Suspect in case of hematuria, crystals, gravel, or stone passes, pain, obstruction. Manage with increased fluid intake, alkalizing agents, lithotripsy, rarely diet discontinuation
Cardiomyopathy	Poorly understood, low HCO_3 and high BOHB, cardiomegaly, prolonged QTc	Rare. Pre-diet ECG. Monitor HCO_3 and BOHB. Avoid selenium deficiency as it can cause cardiomyopathy
Hematologic	Lipid changes in platelet membrane, alterations in platelet proteins can lead to increased bruising or prolonged bleeding	Some patients responsive to DDAVP. Consider presurgical laboratory evaluation for patients on KGD
Immunologic	Ketosis and malnutrition with decreased phagocytosis and killer cell function	Controversial if more infections can be attributed. Has led to discontinuation of diet in some
Miscellaneous	Worsening of GERD, behavioral changes, medication toxicity (topiramate and other carbonic anhydrase inhibitors given increased acidosis but not stones), planning around surgery (CHO-free IV fluids, no drops in glucose, often noted to have pH drop after 3 h of procedure time, manage with 5–20 mEq HCO_3)	

BOHB, beta-hydroxy butyride; CHO, carbohydrate; DDAVP, vasopressin; GERD, gastroesophageal reflux disease; HCO_3 bicarbonate.

Specific Management of Infantile Spasms[29,30]

Goal: Cessation of spasms and normalization of the EEG, or at least resolution of hypsarrhythmia if present. Aggressive treatment is usually associated with improved outcome with respect to development, cognition, and epilepsy. Currently approved first-line treatments for infantile spasms in the United States include ACTH in most cases, and vigabatrin (VGB) as first-line in patients with tuberous sclerosis complex (TSC). There is some evidence that high-dose prednisone may be an alternative to ACTH. (1) **ACTH** is typically given at high dose for 2 weeks, and then tapered gradually. Adverse effects especially with longer treatment duration include immunosuppression, hypertension, cushingoid features, glucosuria, metabolic abnormalities, and rarely hypertropic cardiomyopathy. Monitoring of blood pressure for hypertension and urine for glucose during treatment is important. (2) **Vigabatrin** may be used for a longer period, but is also eventually tapered. This is primarily due to risk of irreversible peripheral visual field defects with prolonged use. Periodic ophthalmologic examinations and serial electroretinograms are required by the FDA. Other adverse effects include sedation, irritability, insomnia, hypotonia, and reversible nonspecific T2 signal changes on MRI in a particular pattern—the latter of unknown clinical significance. (3) **Ketogenic diet** may be used in some refractory cases of infantile spasms. (4) **Other antiepileptic drugs** are also used at times but lack strong evidence of efficacy. (5) **Epilepsy surgery** may be an option for patients with focal lesions and refractory spasms.

Counseling and Education

(1) Psychological effects: Determined by personality, sz type and epilepsy syndrome, effectiveness and side effects of treatment (psychiatric and neurological), comorbidity, relationship with health care professionals, and the attitudes, beliefs, and practices of family, friends, and at school.[29,30] Patients are at increased risk for depression (25%) and anxiety (33%), and may require formal psychological or psychiatric support.[29] Prominent stigmatization still forms a barrier to full participation in society.

(2) Education, behavior, and sleep[29,30]: (1) Cognitive delay (33%) and learning difficulties are common. Regression and unexplained deterioration in school performance should be worked through without delay. Potential contributors include underlying structural lesion (e.g., acquired brain injury, neoplasm), unrecognized and frequent szs (e.g., absence), subclinical (nocturnal) epileptiform activity (see CSWS), cognitive effect from medication, emotional and psychological influences at home or at school, familial traits (e.g., neurofibromatosis), and rarely progressive degenerative disorder (e.g., Lafora disease). (2) Behavioral problems are more prevalent. ADHD occurs in 33%, behavioral dysregulation in 29% in those with uncomplicated epilepsy, up to 58% in case of associated brain injury. Many szs are related to sleep. (3) Sleep disturbance occurs in 33% to 50%. Some szs are provoked by sleep deprivation, others occur more or exclusively during sleep or during the transitions between sleep and wakefulness, and szs may occur in diurnal patterns. Sleep apnea can exacerbate epilepsy, and vice versa. Excessive sleepiness can be associated with medication effects, nocturnal szs, and also with primary sleep disorders (e.g., obstructive sleep apnea syndrome, narcolepsy). Sleep studies can be of benefit in disentangling this relation.

(3) Restrictions, driving, and SUDEP: Restrictions to participate in activities may need to be tailored individually to sz types and frequency.[29] Special precautions and close supervision may be required for bathing, swimming,

open fires and heat sources, heights, heavy machinery and sharp moving objects, horse riding, and cycling. Most children with epilepsy are not photosensitive and need not avoid computers, video games, TV, and stroboscopic lights.[29] Driving is regulated by the state, and most states require 6 months or more of complete sz freedom with or without medication for driving clearance. Some states have mandatory reporting to the Department of Motor Vehicles. See http://www.epilepsyfoundation.org/resources/Driving-Laws-by-State.cfm.

Immunomodulatory Treatments

When an immune-mediated mechanism of epilepsy is suspected or confirmed, treatments including steroids, IVIG, plasma exchange, or a combination of these may be effective.

(1) **Encephalitis related to antibodies to synaptic and neuronal cell surface markers**, including NMDA receptor, AMPA receptor, $GABA_B$ receptor, LGI1, and Caspr2.[31] Second-line immunotherapy for refractory patients include rituximab or cyclophosphamide. In some cases a longer taper of steroids or regular scheduled doses of IVIG may be helpful. If there is a chronic immune-mediated mechanism such as identified antibody with high risk for relapse, chronic immunomodulatory treatment may be indicated with agents such as myocophenolate mofetil or azathioprine. (2) **Rasmussen encephalitis:** immunomodulatory treatments, including IVIG and tacrolimus, may slow atrophy and functional decline, but data are limited. Their efficacy for related epilepsy is less clear,[32] and delay of hemispherectomy may negatively affect outcome.

STATUS EPILEPTICUS

Definition

Prolonged, self-sustaining sz or recurrent szs without return to baseline.[33] Early definitions of SE required a duration $\geq$30 min, but currently more practical approach of considering and treating as SE at $\geq$5 min. This is based on evidence that most szs last $<$5 min and medication delay leads to more prolonged szs.[33–35]

Clinical Presentation, Pathophysiology

(1) SE can be generalized or focal, and convulsive or nonconvulsive.[35] The initial 5 min are referred to as the *prodromal stage*. Subsequent stages of SE are the *early phase* (5–30 min), *established SE* (30 min), and *refractory SE* if persistent despite treatment with adequate doses of 2 to 3 anticonvulsant medications.[34] (2) **EEG** is not needed for acute, early management of convulsive SE, but is useful to identify subtle or nonconvulsive SE, monitor response to treatment, identify a possible sz focus, suggest an etiology, or differentiate from nonepileptic events.[35] **Nonconvulsive SE may follow convulsive SE requiring EEG**. EEG pattern can aid in prognosis in certain situations such as hypoxic ischemic encephalopathy and anoxic brain injury. (3) **Systemic changes** during SE include tachycardia, increased blood pressure, and increased cerebral perfusion in early stages,[34,35] which correlate with increased brain glucose and oxygen use. In later stages, there may be hypotension and/or respiratory compromise (hypoxia, hypercapnia, and aspiration pneumonia). Autonomic complications may include hyperthermia and impaired cerebral autoregulation. Prolonged SE can lead to hyperthermia and rhabdomyolysis, and more rarely to cardiac arrhythmia, stress cardiomyopathy, neurogenic pulmonary edema, renal failure, and bone fractures. From a neurologic

standpoint, cerebral edema, CSF pleocytosis, and excitotoxic neuronal damage may develop especially if SE is prolonged.

Etiology

The most frequent causes of SE in children include acute meningoencephalitis, hypoxia, and metabolic derangements.[36] In children, about 50% of SE occurs in the setting of infection with fever. Other causes include low AED levels and remote or acute pathologies, including cerebrovascular disease.[35] Note that ~50% of patients with SE have a history of epilepsy. About 10% to 15% of children with epilepsy will have an episode of SE, and SE is most associated with focal epilepsies.[35,37] **Etiology and age** are the most important factors affecting outcome and prognosis of both convulsive and nonconvulsive SE. Mortality rates of convulsive SE in children are estimated to be 3% to 9%.[33,36,37] **Longer duration** of SE is associated with higher rates of mortality and morbidity. Rates of cognitive or developmental changes after SE are not well defined, but one study showed lack of cognitive or motor handicaps in a large cohort of children with febrile SE.[38]

Management

Initial management focuses on airway, breathing, and circulation. Several medication treatment protocols for convulsive SE exist, and one recent protocol is provided (Table 5.26).[33] The general principle is a stepwise approach starting with benzodiazepines, then to second-line agents, including most commonly fosphenytoin and phenobarbital. IV phenytoin (not used much in United States) given through peripheral intravenous access can lead to **purple glove syndrome** (local tissue necrosis) in case of extravasation into the surrounding tissue. For refractory SE, anesthetic medications may be required. Consider the need to establish an airway early if proceeding beyond a second AED. Patients with nonconvulsive SE also have higher death rates, prompting an aggressive, proactive treatment approach. However, the choice and specifics of each immediate intervention should be the result of ongoing multidisciplinary discussion about risks and benefits.

TABLE 5.26 Treatment Algorithm for Status Epilepticus

Treatment for Status Epilepticus	AED Treatment
1st-line	Lorazepam 0.05–0.1 mg/kg IV (max 5 mg over 1–4 min) If no IV: diazepam 0.2–0.5 mg/kg/dose PR (max 20 mg/dose)
2nd-line	Fosphenytoin 20 mg PE/kg IV (If no fosphenytoin: phenytoin 20 mg/kg IV)
3rd-line	Phenobarbital 20 mg/kg IV (or levetiracetam, valproic acid, other)
4th-line	Midazolam 0.1–0.3 mg/kg or pentobarbital 3–15 mg/kg bolus, followed by continuous infusion to maintain burst suppression.

The 1st step should always be to take care of airway, breathing, and circulation (ABCs). Additional systemic management during treatment should consider potential correction of hypoxia, hemodynamics, hyperthermia, hypoglycemia, and hyponatremia. Diagnostic laboratory tests, ECG, and imaging may be obtained simultaneously. If <2 y consider pyridoxine 100 mg IV. If status epilepticus becomes refractory (at the latest, after failure of the second medication), continuous EEG monitoring should be initiated.

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ONLINE RESOURCES

www.epilepsy.com – Highly informative site for patients and professionals.

www.epilepsyfoundation.org – Similar high quality site for patients and professionals

www.seizuretracker.org – Log and track seizure activity, appointments, and medication through a simple calendar interface from computer or mobile phone.

www.aesnet.org – American Epilepsy Society, mainly for professionals.

www.childneurologysociety.org – For health care providers, contains all practice parameters.

www.acns.org – American Clinical Neurophysiology Society. LTM and EEG guidelines.

www.genetests.org – Epilepsy gene testing (clinical availability).

www.ncbi.nhm.nih.gov/omim – Online Mendelian Inheritance in Man (OMIM).

6 Neuromuscular Disorders

Jahannaz Dastgir and Basil T. Darras

Neuromuscular disorders may present as a variety of symptoms and consult requests to the pediatric neurologist. Consults may be in reference to vague concerns regarding "floppy" infants or children with "developmental delays". They may also be called regarding more specific complaints such as localized weakness, fatiguability, abnormal gait, myalgias or ptosis. An accurate history and a detailed exam guide testing, for example, serum/urine labs, imaging (MRI/US), electrophysiology, or biopsy (muscle/skin). Figure 6.1 illustrates the diagnostic approach to the infant with hypotonia. Differential diagnosis can be guided by the anatomy of the motor unit (Fig. 6.2).

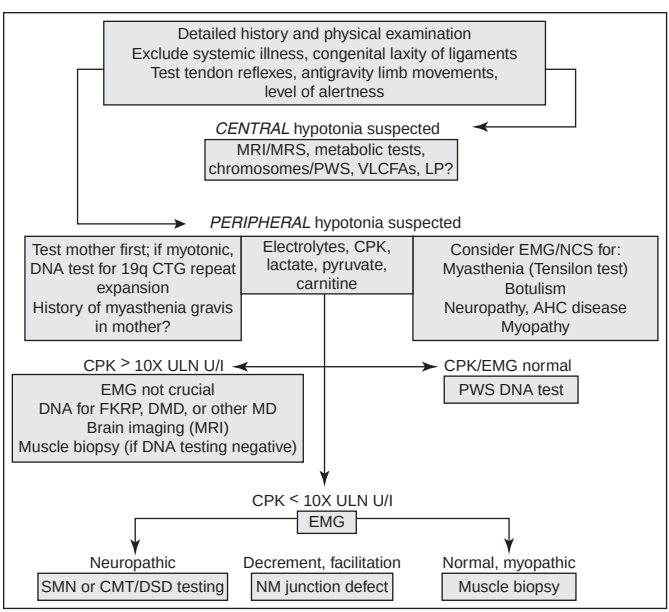


FIGURE 6.1 Approach to Hypotonia. MRI, magnetic resonance imaging; MRS, magnetic resonance spectroscopy; PWS, prader willi syndrome; VLCFA, very long chain fatty acids; LP, lumbar puncture; AHC, anterior horn cell; CPK, creatine phosphokinase; CMT, Charcot Marie Tooth; DMD, Duchenne Muscular Dystrophy; DSD, Dejerine Sottas Disease; EMG, electromyography; NCS, nerve conduction studies; NM, Neuromuscular (From Perlman J, ed. *Neonatology: Questions and Controversies*. London, UK: Elsevier; 2012, with permission.)

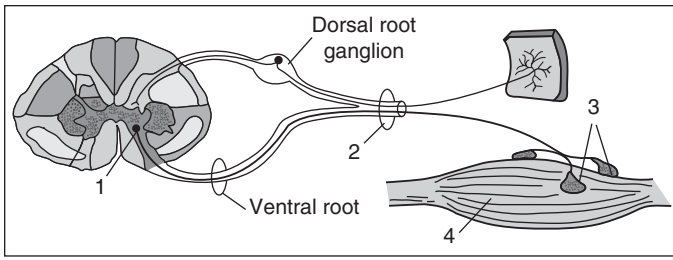


FIGURE 6.2 The Four Anatomic Stations Underlying Lower Motor Neuron Weakness. 1, anterior horn cell; 2, peripheral nerve; 3, neuromuscular junction; 4, muscle fiber (From http://www.neuroanatomy.wisc.edu/SClinic/Weakness/Weakness.htm.)

DISORDERS OF THE MOTOR NEURON

Spinal Muscular Atrophy (SMA)[1]

DEFINITION: Heterogenous group of disorders (Table 6.1) with progressive degeneration of spinal cord anterior horn cells ± motor nuclei in the brainstem (extraocular and sacral motor nerves and cardiac and smooth muscles are selectively spared).

TABLE 6.1 Classification of Spinal Muscular Atrophies (SMA)

SMA1/Werdnig–Hoffmann Disease (onset: <6 mo, never sit)

Genetics: AR homozygous SMN1 deletion (95%); <1–2 SMN2 copies

Exam: severe weakness of the limbs and intercostal muscles; paucity of spontaneous movement at the shoulder and hip girdle; some antigravity movements in the hands and feet. Atrophy of the tongue may be associated with fasciculations. DTRs are absent. Never sit. Normal intellect

Prognosis: >90% mortality; few survive to 2nd decade

SMA2 (onset: 6–18 mo, sit, but never walk)

Genetics: AR homozygous SMN1 deletion with usually 3 SMN2 copies

Exam: Lower extremities are more involved than upper extremities; associated with a tremor affecting the upper extremities (polyminimyoclonus); tongue may have fasciculations. DTRs are absent. Sit, but never walk. Normal intellect

Prognosis: variable, most survive to 2nd/3rd decade

SMA3/Kugelberg–Welander (onset >18 mo [type 3A, <3 y; type 3B, >3 y], able to walk)

Genetics: AR homozygous SMN1 deletion with 3–4 SMN2 copies

Exam: proximal symmetric weakness; muscle weakness may not manifest until adult life. Limb and tongue fasciculation. Able to walk. Type 3A: 20% walking at 40 y; type 3B: 60% walking at 40 y. Normal intellect

Prognosis: will survive into adult life

SMA4/Adult form (onset: after 20 y, walk with waddling gait)

Genetics: 30% AD; AR may be SMN-related, X-linked

Exam: proximal muscles are predominantly involved; impaired joint mobility, waddling gait, lumbar lordosis, and protuberant abdomen. ± DTRs, limb and tongue fasciculations, and tremor

Prognosis: age of symptom onset correlates with cessation of ambulation

EPIDEMIOLOGY: Incidence 1/6,000 to 10,000 live births. 2nd most common hereditary neuromuscular disease after Duchenne muscular dystrophy (DMD) and the 2nd most common AR disease in children after cystic fibrosis.

GENETICS: Due to deletions in "survival of motor neuron" (*SMN*) gene, of which there are 2 types: *SMN1* and *SMN2*. Homozygous deletions (95%) of *SMN1* lead to more severe forms that may vary in presentation depending on the number of *SMN2* genes that are present (the more copies of *SMN2*, the less severe the manifestation of the disease).

CLINICAL PRESENTATION: Widespread muscular denervation and atrophy, with marked reduction of muscle power and spontaneous movement, in a symmetric and proximal > distal distribution. Diaphragm involvement depends upon type of SMA. No cognitive impairment.

DIAGNOSIS: Genetic testing, EMG (spontaneous muscle activity, fibrillation potentials, and residual motor unit potentials that are increased in amplitude and duration), muscle biopsy (not common practice at present; demonstrates small and large group atrophy); CK may range from normal to 5× ULN.

TREATMENT: Symptomatic, aimed at maintaining joint mobility and avoiding contractures. Monitor and support other potential complications, including dysphagia, scoliosis, restrictive lung disease, and poor nutrition.

Other Spinal Muscular Atrophies

(1) Juvenile Segmental SMA (Hirayama)

GENETICS: Primarily a sporadic disorder; may be related to positional cervical cord compression.

CLINICAL: Variable; tends to have asymmetric weakness and atrophy of the unilateral or bilateral hand and forearm muscles. May involve upper-limb amyotrophy ± bulbar amyotrophy, with pyramidal signs and a slowly progressive course.

PROGNOSIS: Progression for 2 to 6 y, then plateau.

(2) Scapuloperoneal Neuropathy

GENETICS: *TRPV4* gene on chromosome 12q24.11 (AD)

CLINICAL PRESENTATION: Progressive weakness in the scapuloperoneal and distal muscles; may also be associated with laryngeal palsy.

PROGNOSIS: Progressive; disease is more severe in succeeding generations (anticipation).

(3) Childhood Bulbar SMA (Fazio–Londe and Brown–Vialetto–Van Laere)

GENETICS: *C20orf54* gene on chromosome 20p13 (AR).

CLINICAL PRESENTATION: Bulbar palsy; Brown–Vialetto–Van Laere also associated with sensorineural deafness. Fazio–Londe may have prominent facial weakness and ophthalmoplegia.

PROGNOSIS: Onset in 1st 2 decades with variable rate of progression.

Acquired Motor Neuron Disease

(1) Acute Poliomyelitis

DEFINITION: Highly contagious via oral–oral and fecal–oral routes. In endemic areas, wild polioviruses can infect virtually the entire human population.

INCIDENCE: The most common cause of acquired anterior horn cell disease. Eradicated in the United States, but prevalent in developing countries. Poliolike diseases due to coxsackie and other echoviruses have also been described.

CLINICAL PRESENTATION: Ranges from asymptomatic to minor illness (1–5 d post exposure; fever, malaise, sore throat, GI symptom) to major illness (4–10 d post exposure; aseptic meningitis, fever, pain). Paralytic disease will manifest in 50% of those with major illness 2 to 5 d after illness. Exam shows localized fasciculations, intense myalgia, hyperesthesia; may be focal or asymmetric; legs > arms > bulbar symptoms. May also have acute dysautonomia.

DIAGNOSIS: CSF pleocytosis and IgM poliovirus specific; stool positive 90% by 20 d; EMG/NCS: selective loss of motor neurons/axons at 7 to 10 d.

TREATMENT: Some cases only involve temporary paralysis and recover. Others may be permanent and supportive measures are necessary.

(2) West Nile Encephalomyelitis

DEFINITION: Tick-borne flavivirus that primarily causes a meningoencephalitis but may also lead to a poliolike disease.

CLINICAL PRESENTATION: Fever, meningeal signs, and CSF pleocytosis that may be followed by a focal asymmetrical flaccid paralysis over the next few days.

DIAGNOSIS: CSF pleocytosis and positive for West Nile virus IgM; EMG/NCS: selective loss of motor neurons/axons at 7 to 10 d; MRI with T2 hyperintensities in the anterior horn cells.

TREATMENT: Supportive. Antiretroviral treatment is under development.

DISORDERS OF THE PERIPHERAL NERVE

Hereditary Motor and Sensory Neuropathies (HMSN)[2]

HMSNs account for ~40% of childhood chronic neuropathies. They involve degeneration of myelin sheaths and disorder of axons and lead to a distal paralytic amyotrophy involving the lower > upper limbs that is also associated with areflexia. In this disease group the neuropathy is *primary* as opposed to only *part of* the disorder.[3]

(1) Charcot–Marie–Tooth Disease (CMT)[4]

EPIDEMIOLOGY: Most common inherited neurologic condition, affecting ~1 in 2,500 people.

GENETICS: >40 genes are known to cause CMT; the majority are AD; X-linked and AR inheritances have also been described. An exhaustive list can be found at www.genetests.org.

CLINICAL PRESENTATION: Variable in age of onset (typically 1st–2nd decade) and speed of progression. Classic phenotype involves steppage gait, pes cavus, sensory loss in a stocking/glove distribution, inverted champagne bottle legs, and atrophy in the hands (all typically symmetric). Patients have decreased or absent deep tendon reflexes, impaired proprioception, and may or may not complain of neuropathic pain. May also be a/w other features distinctive to genetic phenotype: optic atrophy (CMT2A); vocal cord and respiratory involvement (CMT2C, 4A), predominant hand weakness (CMT2D), facial/bulbar symptoms (CMT4B1), scoliosis (CMT4C), sensory ataxia (CMT4F), upper-motor-neuron-like changes (CMT4J).

DIAGNOSIS: Nerve conduction studies allow for classification into demyelinating, axonal, or intermediate groups.

(2) HMSNs Associated With Metabolic and Degenerative CNS Disorders

Abetalipoproteinemia, adrenomyeloneuropathy, amyloidosis, ataxia–telangiectasia, carbohydrate-deficient glygoprotein syndrome, cerebrotendinous xanthomatosis, Cockayne syndrome, Chédiak–Higashi disease, Fabry disease, Farber lipogranulomatosis, GM2 gangliosidosis, Krabbe disease, metachromatic leukodystrophy, mitochondrial disease (Leigh, NARP, MNGIE), neuroaxonal dystrophies, Niemann–Pick disease, porphyria, Refsum disease, Tangier disease, tyrosinemia, vitamins E and B_{12} deficiency.

(3) Hereditary Sensory and Autonomic Neuropathies (HSAN)[5]

DEFINITION: Hereditary group of disorders involving the peripheral nervous system that involve progressive degeneration of the sensory and autonomic neurons. Categorized as types I to V on the basis of age at onset, mode of inheritance, and predominant clinical feature.

GENETICS: 12 genes have been discovered to date (www.genetests.org). Patients with AD forms (HSAN I) typically show juvenile-adult onset of disease; AR forms (HSAN II–V and HSAN w/ spastic paraplegia) show an earlier onset (e.g., congenital or in childhood).

CLINICAL PRESENTATION: Loss of sensations of pain and temperature are the most common symptoms and frequently lead to sensory loss and chronic ulcerations in the feet and hands of the patient. These lesions can lead to extensive soft tissue infections or osteomyelitis and subsequently amputation of the affected limb.

DIAGNOSIS: EMG/NCS show axonal damage to sensory neurons, but demyelination might additionally be present.

Immune-Mediated/Inflammatory Neuropathies

(1) Acute Inflammatory Demyelinating Polyneuropathy (AIDP), or Guillain–Barré Syndrome (GBS)[6, 7]

DEFINITION: Autoimmune neuromuscular disorder with loss of immunologic tolerance and autoreactive T lymphocytes, with antibodies and complement damage to myelinated peripheral nerves.

INCIDENCE: 0.6 to 4 cases per 100,000; men > women; incidence increases with age. Uncommon in the 1st few years of life, but rare neonatal cases have been reported.

CLINICAL PRESENTATION: 2/3 of cases with an antecedent vaccination or infection within 6 wk prior to symptoms onset (e.g., EBV, *Mycoplasma pneumoniae*, *Campylobacter jejuni*, and CMV). Progressive, symmetrical muscle weakness and diminished or absent deep tendon reflexes. Around 50% to 80% (particularly younger children) complain of pain in the back, buttock, or limb and refuse to walk. Symptoms tend to ascend from lower to upper limbs (but not in all cases); weakness of facial muscles in 50%; weakness peaks by 2 to 4 wk post symptoms onset and is followed by progressive recovery. Monitor for respiratory failure (~17%) and dysautonomia (cardiac arrhythmia, hypertension, hypotension, ileus, urinary retention, and difficulty with thermoregulation, in 20%–40%). Miller Fisher variant (much more rare) is also associated with the triad of external ophthalmoplegia (may be asymmetric), ataxia, and areflexia, but also ptosis, mydriasis, facial and oropharyngeal weakness, myalgias, and paresthesias.

DIAGNOSTIC WORKUP: (1) CSF: elevated protein in ~80% (may be normal in 1st wk of illness), and absence of pleocytosis is known as albuminocytologic dissociation. (2) EMG/NCS: normal or decreased motor amplitudes and slowing of conduction velocities (changes may be absent when studying patients early in the disease course). (3) MRI of the brain (with gadolinium) may show cranial nerve enhancement, and of spine may show spinal root enhancement. (4) Antibodies: Miller Fischer variant is often associated with IgG reactivity to GQ1b or GT1b gangliosides.

MANAGEMENT: Close monitoring of respiratory function via serial pulmonary function tests (vital capacity) and bedside negative inspiratory flow and of cardiac function via electrocardiography and monitor. Intravenous immunoglobulin (IVIG) or plasmapheresis within the 1st 4 wk of symptom onset. Oral corticosteroids alone tend to be ineffective, but there are some reports of combination therapy with IV corticosteroids and IVIG accelerating recovery. Physical therapy is essential in the rehabilitation process.

PROGNOSIS: The disease reaches a nadir at 2 to 4 wk, with most patients recovering, but 10% to 20% are left with motor deficits of variable severity and a small fraction of patients die from complications. Adverse prognostic indicators include need for artificial ventilation throughout the course of illness, rapid onset of disease, established history of infection with *C. jejuni* or cytomegalovirus, and evidence of axonal loss on neurophysiologic testing.

(2) Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)[6]

DEFINITION: Distinguished from GBS by the chronic nature of the disease.

CLINICAL PRESENTATION: Progressive or relapsing sensorimotor polyneuropathy disorder polyradiculopathy for at least 2 mo. The majority exhibit an insidious onset.

DIAGNOSIS: Diffuse nerve root thickening and gadolinium enhancement on spine MRI (may also be seen in CMT patients); elevated protein in CSF (may also be seen in CMT patients), and EMG/NCS showing normal or decreased motor amplitudes, slowing of conduction velocities, and occasionally conduction block.

TREATMENT: IVIG, plasmapheresis, corticosteroids, azathioprine (steroid sparing), and physical therapy.

(3) Acute Motor Axonal Neuropathies

DEFINTION: Acute motor axonal neuropathy (AMAN) and acute motor–sensory axonal neuropathy (AMSAN) are neuropathies thought to be related to disruption of node of Ranvier function as brought about by antibodies to GM1 and GD1a.

INCIDENCE: Most commonly found in Japan, China, Mexico, and 3rd world countries; children > adults; no gender predilection, presence of seasonal peaks.

CLINICAL PRESENTATION: Prodrome includes gastrointestinal diarrhea (*C. jejuni* in most), an upper respiratory infection (e.g., *H. influenza* infection), or immunization. AMAN: ascending, symmetric paralysis of the extremities, loss of deep tendon reflexes, and variable involvement of bulbar, respiratory, ocular, and facial muscles. No complaints of paresthesias. AMSAN: will also include sensory symptoms.

DIAGNOSTIC WORKUP: (1) CSF: (AMAN) increased protein; (2) EMG/NCS: (AMAN) normal sensory testing, abnormal motor testing (seen in

first 2 wk); (AMSAN) mildly reduced nerve conduction velocities combined with a marked reduction in motor and sensory action potential amplitudes; (3) serum: (AMAN) IgG reactivity to GM1, GD1a, and GD1b positive, GQ1b negative.

TREATMENT: IVIG, plasmapheresis; corticosteroids are not recommended. AMAN has a shorter course than does GBS.

Vasculitic Neuropathies

To be considered in patients with vasculitides such as SLE, RA, and PAN.

Neuropathies Related to Infection

1. **Leprosy:** *Myobacterium leprae*; HLA-linked genes control susceptibility; predilection for superficial nerves (may see nerve enlargement), skin, anterior third of eye, upper respiratory tract, and testes. May start as a purely sensory polyneuritis predominantly affecting the cooler areas of the body and eventually leading to paralysis. Skin biopsies and serum testing aid in the diagnosis. Treatment as per current WHO recommendations.[8]
2. **Lyme:** With acute, disseminated disease, patients may develop neurologic manifestations, which can include a distal sensorimotor neuropathy or carpal tunnel syndrome. EMG/NCS shows axonal loss. Nerve biopsy shows perivascular inflammation. CSF shows mononuclear pleocytosis and moderately elevated protein. Serum ELISA is done with Western blot confirmation. With neurologic symptoms, patients should receive IV ceftriaxone therapy for 2 to 4 wk as per current recommendations.[9]
3. **HIV:** Sensory > motor neuropathy; increased frequency with higher viral load. Symptoms include pain and dysesthesias. Mainly in the feet. EMG/NCS shows distal axonal loss with or without demyelination. Many also lead to dysautonomia, multiple mononeuropathy, mononeuritis multiplex. CSF shows pleocystosis, low glucose, elevated protein.

Toxic Neuropathies

Can occur with amiodarone, amitryptyline, amphotericin, arsenic, carbon monoxide, chlorambucil, ciguatera cisplatin, cyanate, diphtheria, ethambutol, ethionamide, hydroxyquinolines, isoniazid, lead, lithium, mercury, metronidazole, *n*-hexane nitrofurantoin, organophosphate organic chemicals, phenytoin, thalidomide, thallium, triorthocresylphosphate, vincristine.

Localized Peripheral Nerve Disorders

Brachial Plexus Palsy

DEFINITION: May be obstetrical (caused by forces-generated labor stretching the brachial plexus beyond its resistance; most common), familial congenital, or due to intrauterine maladaption or maternal uterine malformation, congenital varicella syndrome, osteomyelitis involving the proximal head of the humerus or cervical vertebral bodies, exostosis of the 1st rib, and tumors or hemangiomas in the region of the brachial plexus.

INCIDENCE: 0.5 to 1.9/1,000 live births

CLINICAL PRESENTATION: Erb palsy is the most common manifestation (related to disruption of the upper brachial plexus at C5 and 6 nerve roots) and involves an asymmetric Moro reflex, weakness of abduction

and external rotation at the shoulder, elbow flexion, supination at the wrist, and extension at the fingers (aka "waiter's tip"). **Klumpke palsy** is less common (related to disruption at the C7, C8, and T1 nerve roots) and involves weakness of the intrinsic muscles of the hand and flexors of the wrist and fingers (aka "claw hand"). A supinated forearm with absent grasp reflex may be noted on exam. Involvement of the 1st thoracic root can result in an ipsilateral Horner syndrome. The phrenic nerve (arising from C3, C4, and C5) may also be affected and lead to ipsilateral diaphragmatic paralysis.

DIAGNOSIS: Observation of arm weakness distribution. X-ray of chest, clavicle, humerus. MRI of brachial plexus. EMG to evaluate for signs of denervation.

TREATMENT: Surgical intervention may be needed. Aggressive physical therapy and splinting. Majority of patients will recover spontaneously (66%). Moderate weakness remains in 9% and severe weakness in 14%.

DISORDERS OF THE NEUROMUSCULAR JUNCTION

Myasthenia Gravis

(1) Juvenile Myasthenia Gravis[10]

DEFINITION: Autoimmune disease in which antibodies are directed at the postsynaptic membrane of the neuromuscular junction, leading to various degrees of muscle weakness and fatiguability.

INCIDENCE: More common in Asian populations, where up to 50% of all cases of myasthenia gravis peak at 5 to 10 y of age. Caucasian patients are more likely to present in adulthood; prepubertal onset in only $<$10%. Equally present in male and female patients. May be associated with other conditions such as rheumatoid arthritis, juvenile dermatomyositis, thyroid disease, or malignancy.

CLINICAL PRESENTATION: Symptoms may be insidious or start rapidly after an acute febrile illness. Most commonly present with ocular symptoms of unilateral or asymmetric ophthalmoplegia, strabismus, and lid twitch with sustained upgaze. Generalized weakness, painless fatiguability of bulbar and limb musculature, dysphonia, and dysphagia may also be noted. Weakness tends to be fluctuated, being more pronounced as the day goes on and improving with rest. Occasionally, impairment of the respiratory muscles will necessitate ventilatory support, and such a state is referred to as "myasthenic crisis." More severe disease in muscle-specific kinase (MuSK)–positive patients.

DIAGNOSIS: (1) **Tensilon test** (IV infusion of edrophonium will prevent the breakdown of acetylcholine and increase its concentration at the neuromuscular junction) with observation for transient improvement in weakness, ptosis, or dysphonia (with testing, monitor for cholinergic effects such as bradycardia, nausea, and excess salivation). (2) **NCS & EMG:** Repetitive stimulation will show decrement by $>$10%. Single-fiber EMG may also be performed. (3) **Serum antibodies** may be found to nicotinic AChR (binding, blocking, or modulating; less common in prepubertal patients), MuSK (0%–49%, female predominance), and leucine-rich protein 4 (LRP4). (4) **MRI:** Although thymoma is rare, the thymus should also be imaged once the diagnosis is made.

TREATMENT: (1) **acetylcholinesterase inhibitors** (first line) to provide symptomatic relief (e.g., pyridostigmine, but take caution in MuSK-positive children due to risk of acetylcholine hypersensitivity); (2) **thymectomy**

to remove thymic germinal centers and disrupt antibody diversification (although not recommended in MuSK-positive disease); (3) **Immunosuppressive therapies**—(1) corticosteroids (monitor adverse effects such as growth failure, susceptibility to severe infection, and delay in receiving live vaccinations), (2) azathioprine (a purine analog that suppresses B- & T-cell proliferation, but may take months to see effects), (3) mycophenolate mofetil (blocks purine synthesis by selectively inhibiting proliferation of activated T & B lymphocytes; may not see effects until 1 y after start), (4) plasma exchange / IVIG (improvement of symptoms is usually temporary, 4–10 wk).

PROGNOSIS: Children tend to exhibit higher rates of remission (spontaneous and post therapy).

(2) Transient Neonatal Myasthenia

DEFINITION: Presents in 1 in 5 infants born to mothers suffering from active acquired myasthenia gravis; related to the transfer of maternal AChR antibodies across the placenta, leading to defects of neuromuscular transmission in the neonate.

CLINICAL PRESENTATION: Onset in the 1st 24 h of life. The baby is usually normal at birth and subsequently develops hypotonia, weak cry, poor suck, reduced movements, ptosis, facial weakness, and occasional respiratory failure.

DIAGNOSIS: Clinical diagnosis. Not all mothers have detectable AChR antibodies that may or may not be detected in the infant.

TREATMENT: Short-term treatment with anticholinesterase inhibitors is usually sufficient. Even if untreated, the illness usually lasts <5 wk; IVIG is ineffective.

(3) Congenital Myasthenia Gravis[11]

DEFINITION: Heterogeneous genetic disorders of neuromuscular transmission; often misdiagnosed as congenital muscular dystrophy.

GENETICS: All but slow-channel syndrome (AD) are AR. Slow-channel syndrome (*CHRNA1*, *CHRNB1*, *CHRND*, *CHRNE*), fast-channel syndrome (*CHRNA1*, *CHRND*, *CHRNE*), acetylcholine receptor deficiency (*CHRNE*), rapsyn deficiency (*RAPSN*), choline acetyltransferase deficiency (*CHAT*), end-plate acetylcholinesterase deficiency (*COLQ*), MuSK deficiency (MUSK), familial limb-girdle myasthenia with tubular aggregates (*GFPT1*), agrin deficiency (*AGRN*), β2-lamin deficiency (*LAMB2*), type Ia1 (*unk* gene), sodium-channel myasthenia (*SCN4A*), Escobar syndrome (*CHRNG*), plectin defect (*PLEC1*).

CLINICAL PRESENTATION: Onset of symptoms tends to be at birth; may present with bulbar and respiratory difficulties, $\pm$ hypotonia, generalized weakness, arthrogryposis, and delayed motor development; all are symptoms not specific to congenital myasthenic syndromes. Fatiguability, ptosis, and ophthalmoplegia may also develop.

DIAGNOSIS: EMG/NCS shows decremental response with repetitive nerve stimulation; muscle biopsy shows nonspecific myopathic changes; DNA analysis.

TREATMENT: May respond or worsen with exposure to pyridostigmine; albuterol, ephedrine, and 3,4-diaminopyridine have been tried.

(4) Lambert–Eaton Myasthenic Syndrome

DEFINITION: A rare autoimmune disorder of the neuromuscular junction that can be associated with a variety of neoplasms. 5% of all cases are in childhood, and such cases tend not to be associated with neoplasms.

CLINICAL PRESENTATION: Unlike myasthenia gravis, weakness (mainly in limb-girdle distribution) is worse upon awakening and lessens later in the day. Cranial nerve and respiratory involvement are less common than in myasthenia gravis. Deep tendon reflexes are reduced or absent but may appear with repeated tendon percussion.

DIAGNOSIS: Tensilon test—edrophonium may produce mild improvement in strength, but this does not differentiate Lambert–Eaton from myasthenia gravis. **Serum:** Antibodies to voltage-gated calcium channels may be found. **EMG/NCS:** Increment after rapid (50 Hz) nerve stimulation, sustained muscle contraction (~10 s), or cooling.

TREATMENT: Clinical improvement has been noted with the use of 3,4-diaminopyridine, plasma exchange, IVIG, prednisone, or pyridostigmine.

(5) Botulism[12]

DEFINITION: Caused by the ingestion of spores (infants; most in Utah, Pennsylvania, and California) or preformed botulinum toxin (canned foods, honey), which then binds to presynaptic nerve terminals and inhibits the release of acetylcholine. There are ~110 cases per year; 72% are infantile.

CLINICAL PRESENTATION: Descending paralysis that begins with the cranial nerves (ptosis, ophthalmoplegia, mydriasis, poor suck and feeding, reduced gag, weak cry) and extends toward the extremities (symmetric; proximal > distal; hypotonia). Deep tendon reflexes tend to be reduced. Symptoms begin with constipation and cranial nerve palsies and then progress to generalized weakness, sometimes leading to respiratory failure.

DIAGNOSIS: EMG/NCS: Rapid repetitive nerve stimulation shows an increment in 50% to 60% of patients. Motor action potentials are small; sensory potentials are normal; EMG shows denervation, fibrillations, and positive sharp waves. Stool culture and analysis for toxin.

TREATMENT: Administer botulinum immunoglobulin (BIG-IV) promptly if diagnosis is suspected. Otherwise supportive care (nutrition, fluid, ventilation) with close monitoring for respiratory failure.

DISORDERS OF MUSCLE

Congenital Myopathies[13] (Table 6.2)

(1) Myotubular/Centronuclear Myopathy

GENETICS: Majority are X-linked recessive; 90% with mutations in the myotubularin gene (*MTM1*) on chromosome Xp28; AD forms manifest later in life and are milder (dynamin 2; *DNM2* mutations); sometimes in infancy or childhood.

DIAGNOSIS: CK may be normal; DNA testing; biopsy demonstrates numerous centrally located nuclei in the muscle fibers that appear similar to the myotube (immature stages of muscle fiber). Perinuclear halos often surround these nuclei. Type I fiber predominance.

CLINICAL PRESENTATION: The most severe of all congenital myopathies. This is a slowly progressive weakness of the limb girdles and neck muscle with acute fluctuations coinciding with respiratory illnesses. Ptosis and

TABLE 6.2 Congenital Myopathies

Disease	Genes	Inheritance	Protein	Onset	Weakness	Cardiac	Respiratory	Facial	Oculomotor	Prognosis
Myotubular/centronuclear myopathy										
Severe	*MTM1*	XL	Myotubularin	Prenatal–congenital	+++	−	++	+++	+++	Death during infancy, some survive to adulthood
Classic	*?*		?	Late infancy–early childhood	+	−	++	++	++	Ambulation until adolescence
Adult	*DNM2* *BIN1* *RYR1*	AD AR AD/AR	Dynamin 2 Amphiphysin Ryanodine receptor	Infancy, childhood, 2nd–3rd decade	+	−	−	+	+/−	Slowly progressive
Nemaline myopathy										
Severe congenital	*ACTA1* *NEB* *TPM3* *TNNT1*	AD/AR AR AD AR	α-actin Nebulin Tropomyosin 3 Troponin T type 1	Birth	+++	−	++	+++	−	Death in neonatal period
Typical congenital	*ACTA1* *NEB* *TPM3* *TPM2* *CFL2*	AD/AR AR AD AD AR	α-actin Nebulin Tropomyosin 3 Tropomyosin 2 Cofilin 2	1st year	++	+/-	+	+++	−	Many survive to adulthood

Mild, childhood	*ACTA1* *NEB* *TPM3* *KBTB13*	AD AR AD AD	α-actin Nebulin Tropomyosin 3 BTB/Kelch protein family	Prepubertal	+	−	−	−	−	Many survive to adulthood
Adult	*ACTA1* *NEB*		α-actin Nebulin	3rd–6th decade	+	+	+/−	++	−	Adulthood
Central core, classical	RYR1	AD/AR	Ryanodine receptor	Infancy–early childhood	+	R	−	+	−	Adulthood?
Multiminicore disease	*SEPN1* *RYR1*	AR Sporadic	Selenoprotein N1	Infancy–early childhood	++	R	++	++	R	Variable
Congenital myopathy & fatal cardiomyopathy	*TTN*	AD	Titin	Infancy–childhood		+++	?	−	−	?
Congenital fiber-type disproportion	*ACTA1* *SEPN1* *TPM3* *RYR1*	AD AR AD AR	α-actin Selenoprotein N1 α-tropomyosin Ryanodine receptor	1st year	+ to +++	R	+ to +++ (30%)	+	+/−	Variable

AD, autosomal dominant; AR, autosomal recessive; +++, severe; ++, moderate; +, mild; ±, mild or absent; −, not reported so far; P, ptosis; R, rare.

Courtesy Dr. Peter Kang, Neuromuscular Program, Boston Children's Hospital, and adapted from Perlman J, ed. *Neonatology: Questions and Controversies*. London, UK: Elsevier; 2012, with permission.

weakness of the extraocular movements appear to be characteristic for most cases. Facial weakness and dysarthria may also develop.

TREATMENT: Supportive. Respiratory failure typically leads to death within the 1st y of life. Mothers who are obligate carriers show mild muscle weakness with secondary kyphoscoliosis and have minor changes in their muscle biopsy. Genetic counseling.

(2) Nemaline Myopathy

GENETICS: Six genes have been associated with this condition (AD/AR) with variable penetrance and each coding for thin filament-associated proteins.

TYPES: (1) Severe Congenital: Almost always fatal and manifesting as hypotonia, weakness, and respiratory impairment. May be associated with contractures and congenital fractures. Fetal akinesia sequence has been reported and associated with intrauterine onset. (2) Milder Congenital: Able to breathe and move at birth, but during early childhood, they may develop proximal weakness, especially in neck flexors. It is also associated with facial, bulbar, and respiratory weakness. Contractures tend to develop early. (3) Mild Childhood: No facial weakness. A dysmorphic appearance and deformities of the palate, spine, and feet have been observed. (4) Adult Onset: Benign course or at times progresses rapidly. May also be associated with a cardiomyopathy. This form is sporadic and not related to either of the two genetic forms found in children.

DIAGNOSIS: Muscle biopsy/pathology demonstrates aggregates of thread-like, intracytoplasmic rods in most muscle fibers. There is also evidence of congenital muscle fiber-type disproportion, particularly in infants.

CLINICAL PRESENTATION: Severe myopathy manifesting with no spontaneous movements or respirations at birth. Highly arched palate, cardiomyopathy, and ophthalmoplegia can occur in all forms.

TREATMENT: L-tyrosine has been reported to improve certain clinical aspects of patients with this condition. Tyrosine treatment appears to diminish drooling and increase appetite and physical activity level.

(3) Central Core Disease

GENETICS: AD > AR; chrom 19q12-p13.1; linked to the ryanodine receptor (*RYR1*). Mutations in this gene may also lead to malignant hyperthermia.

DIAGNOSIS: CK is normal; DNA analysis; biopsy demonstrates type I fiber predominance and round, delineated areas, within these fibers, that are devoid of oxidative enzyme activity.

CLINICAL PRESENTATION: Predominantly appears in infancy or early childhood with a mild and static/slowly progressive muscle weakness (including facial) that is proximal/generalized, developmental delay (many are eventually able to walk), hypotonia, muscle contractures around the knees and hips with various skeletal defects, including congenital dislocation of the hips and patella, kyphoscoliosis, and pes cavus. High incidence of cardiac abnormalities, and virtually all subjects are susceptible to malignant hyperthermia.

TREATMENT: Supportive. Also make sure that patients have malignant hyperthermia precautions applied in themselves and affected family members.

(4) Multiminicore Disease

GENETICS: AR, mutations in the selenoprotein-N gene (*SEPN1*) and the ryanodine receptor (*RYR1*) gene, may also be sporadic.

TYPES: (1) **Classic:** severe neonatal hypotonia, predominant axial muscle weakness especially in neck flexors, delayed motor development, severe scoliosis, and significant respiratory involvement. May also have limb joint hyperlaxity and myopia. (2) **Ophthalmoplegic form:** consists of typical findings plus variable ophthalmoplegia and often severe facial weakness.

DIAGNOSIS: CK is normal; DNA analysis; distinctive MRI findings in muscle and is confirmed by muscle biopsy showing multiple cores within myofibers with defects in histochemical enzymatic activities in the cores. EMG is myopathic.

CLINICAL PRESENTATION: Onset at birth to 18 mo with a benign, nonprogressive, generalized hypotonia. Varying degrees of scoliosis. A large proportion also develops a rigid spine. May also be associated with compromise of the accessory respiratory muscles, hypertrophic cardiomyopathy, endocrinopathies, severe MR.

TREATMENT: Supportive and preventative with monitoring for scoliosis, careful monitoring of respiratory function and secondary cardiac impairment.

(5) Congenital Fiber-Type Disproportion

GENETICS: May be associated with mutations in one of the following genes tropomyosin 3 [*TPM3*], α-actin [*ACTA1*], selenoprotein N1 [*SEPN1*], ryanodine receptor [*RYR1*].

DIAGNOSIS: CK normal, DNA testing, EMG with minimal nonspecific myopathic features, muscle biopsy (characteristic disproportion in the ratio of types I [80% or more] and II myofibers; type I fibers are uniformly smaller than normal from birth, whereas type II are of normal diameter or mildly hypertrophic to compensate; no myofiber degeneration/regeneration).

CLINICAL PRESENTATION: Proximal and limb girdle static weakness in association with myopathic facies, dolichocephaly, and highly arched palate. Occasional scoliosis. FTT is also common. May be seen as a syndrome or component of another disease (Krabbe, nemaline rod disease, congenital myotonic dystrophy, multiple sulfatase deficiency, congenital hypothyroidism, fetal alcohol syndrome, rigid spine syndrome, minicore myopathy, oculocerebrorenal disease of Lowe).

TREATMENT: Supportive. 25% have a severe course, with death usually due to respiratory failure in childhood.

Muscular Dystrophies[14–16]

A. Congenital Muscular Dystrophies[17]

Genetically and clinically heterogenous group of muscle disorders presenting with muscle weakness at birth or in 1st y of life (Table 6.3). Typical presentation as a "floppy infant" with poor muscle tone and limited spontaneous movement, later delay or arrest of motor development and rigid joints and spine. Over time weakness can worsen, remain unchanged, or improve; however, eventually most patients will progress with more weakness, contractures, (kypho-)scoliotic deformities, and respiratory compromise. Some have severe CNS involvement. Life span is shortened.

TABLE 6.3 Congenital Muscular Dystrophies

Name	Gene	Protein	Subtype Name or Other Phenotype	Inheritance	Clinical Features	CNS Involvement
Defects of Structural Protein						
Laminin α-2 deficiency (MDC1A)	*LAMA2*	Laminin-α2	Merosin-deficient CMD, MDC1A	AR	Sitting and standing with support as maximal motor ability if complete deficiency, neuropathy, epilepsy in about 30%, possible subclinical cardiomyopathy, generally normal mental development	White matter T2 signal abnormalities, 5% with occipital pachy- or agyria, rare ponto-cerebellar atrophy
Collagen VI-deficient CMD	*COL6A1* COL6A2 COL6A3	Collagen VI Collagen VI Collagen VI	Ullrich CMD (UCMD) / Bethlem myopathy	AD AR	Ullrich (UCMD) on severe end and Bethlem on mild end of spectrum, others of intermediate severity. Muscle disorder (variable motor abilities, precludes ambulation in severe cases), and connective tissue disorder (distal joint hyperextensibility, proximal contractures, soft palmar skin)	No

Defects of Glycosylation						
Dystroglycanopathy	*POMT1*	Protein-O-mannosyltransferase 1	WWS LGMD2K	AR	Walker–Warburg syndrome (WWS) is severe, lethal within first years of life due to severe CNS involvement	WWS: lissencephaly type II, pachygyria, hydrocephalus, encephalocoele, hypoplastic brainstem, cerebellar abnormalities, eye malformations
	POMT2	Protein-O-mannosyltransferase 2	WWS, LGMD2N	AR	Muscle–eye–brain (MEB) disease is associated with severe weakness and mental retardation, and dysmorphism (macrocrania, prominent forehead, flat midface). Ambulation typically not achieved, severe worsening spasticity. Ocular involvement (severe myopia, retinal hypoplasia)	MEB: Lissencephaly type II, pachygyria, brainstem and cerebellar abnormalities, eye malformations
	FKTN	Fukutin	WWS, MEB-like CMD FCMD LGMD2M	AR		FCMD: lissencephaly type II, pachygyria, hypoplastic brainstem, cerebellar abnormalities
	FKRP	Fukutin-related protein	WWS, MEB-like CMD, MDC1C LGMD2I	AR	Fukuyama CMD (FCMD) is frequent in the Japanese population. Never walk, mental retardation, epilepsy is common. Overlaps with MEB	MDC1C: wide range from normal to severe malformations
	LARGE	Large	WWS, MDC1D	AR	MDC1C (Fukutin-related proteinopathy) may present like MDC1A but wide spectrum of severity from LGMD to severe CMD and WWS MDC1D (LARGE-related proteinopathy) is extremely rare. CMD with profound mental retardation, reminiscent of WWS and MEB spectrum	MDC1D: white matter T2 signal abnormalities, hypoplastic brainstem, mild pachygyria
	POMGNT1	O-linked mannose β1,2-*N*-acetylglucosaminyltransferase	MEB, LGMD	AR	For the limb-girdle muscular dystrophies (LGMD), see Table 6.4	

(continued)

TABLE 6.3 Congenital Muscular Dystrophies (Continued)

Name	Gene	Protein	Subtype Name or Other Phenotype	Inheritance	Clinical Features	CNS Involvement
Defects of Proteins of the Endoplasmic Reticulum						
SEPN1-related myopathy	*SEPN1*	Selenoprotein N	Rigid spine syndrome (RSMD1)	AR	Delayed ambulation, predominantly axial weakness with early development of rigidity of the spine, restrictive respiratory syndrome	No
Defects of Nuclear Envelope Proteins						
LMNA-related CMD (L-CMD)	*LMNA*	Lamin A/C	Dropped-head syndrome	AR	Severe early-onset is associated with absence of motor development, later onset in first years of life with dropped-head syndrome. Selective axial weakness and wasting of the cervicoaxial muscles. Limb involvement predominantly proximal in arms and distal in legs. Talipes and a rigid spine with thoracic lordosis develop early. Later proximal contractures typically in legs, with sparing of elbows. Respirator dependency common. Cardiac arrhythmias may occur	No

Data derived from Genetest.org (Sparks S, Quijano-Roy S, Harper A, et al. Congenital Muscular Dystrophy Overview. Jan. 22, 2001 [updated May 24, 2012]. In: Pagon RA, Bird TD, Dolan CR, et al., eds. *GeneReviews*™ [Internet]. Seattle, WA: University of Washington; 1993. Available from: http://www.ncbi.nlm.nih.gov/books/NBK1291) and from Schessl J, Zou Y, Bönnemann CG. Congenital muscular dystrophies and the extracellular matrix. *Semin Pediatr Neurol*. 2006;13:80–89.

B. Dystrophinopathies

(1) Duchenne Muscular Dystrophy (DMD)

GENETICS: Xp21.2; X-linked recessive disorder. Most patients have deletions of the dystrophin gene. Presents in 1 in 3,300 male births; females may exhibit skewed X-inactivation (exhibiting some symptoms as well).

DIAGNOSIS: CK is 10 to 30K × normal; genetic testing (dystrophin immunohistochemistry is rarely done); muscle biopsy (rarely necessary due to the availability of genetic testing) demonstrates fiber size variation. Over time degeneration of muscle exceeds regeneration as muscle gets replaced with fat and connective tissue; neither heart nor smooth muscle is spared, and there is myocardial degeneration with fatty infiltration and fibrosis of myocardial fibers. Can see contiguous gene syndromes secondary to chromosomal deletion, including retinitis pigmentosa, McLeod neuroacanthocytosis, glycerol kinase deficiency, adrenal hypoplasia. These deletions can be delineated by chromosomal microarray.

CLINICAL PRESENTATION: Onset usually 2 to 5 y of age. Symmetric muscle involvement manifesting as difficulty in performing activities that involve the pelvic muscles (climbing, arising from the floor); may have anterior hip rotation with increased lumbar lordosis and a waddling gait. Patellar DTRs are often diminished early in the course. Pseudohypertrophy is noted (calves > deltoids/infraspinati). Contractures are common in the hamstrings and Achilles tendons.

MANAGEMENT: Corticosteroids will stabilize/improve strength of children with DMD, and they are the only demonstrated treatment for this disease. Annual spirometry and good pulmonary hygiene in addition to the pneumococcal and annual flu vaccine. Avoidance of high-resistance exercise. Avoidance of anticholinergic drugs and ganglionic blocking agents due to risk of malignant hyperthermia. Gene replacement, myoblast transplantation, or replacement of dystrophin by other dystrophin-related proteins are under investigation.

PROGNOSIS: May be modified with aggressive pharmacologic and rehabilitation treatments. Ambulation ceases at 12 to 13 y if untreated but 3 to 5 y later if corticosteroids are used. Death is common in adolescence and may be due to further complications from cardiac (cardiomyopathy, persistent tachycardia, electrocardiographic abnormalities), smooth muscle degeneration (gastric hypomotility, abdominal pain/distension, diarrhea/constipation, malabsorption), kyphoscoliosis, respiratory disease (secondary to weakness of the intercostals and diaphragmatic muscles and impaired mucociliary clearance leading to increased risk for pneumonia), sleep-disordered breathing, dysthymia, and some cognitive impairment (verbal > nonverbal).

(2) Becker Muscular Dystrophy (BMD)

GENETICS: X-linked recessive with mutation at Xp21.2

DIAGNOSIS: Labs—CK is 2,000 to 20,000; DNA testing; muscle biopsy pathology is dystrophic.

CLINICAL PRESENTATION: Onset in childhood (usually after 8 y), but may be asymptomatic for decades. Pseudohypertrophy (less than DMD), proximal hip weakness resulting in a Gower sign; may have calf pain/muscle cramps after exercise. Ankle reflexes are often lost. Pes cavus in 60%. Intelligence is usually normal.

TREATMENT: Use of prednisone for more severely affected patient. Rarely wheelchair-bound before 16 y of age; most survive into adulthood.

C. Other Muscular Dystrophies

(1) Emery–Dreiffus Muscular Dystrophy (EDMD)

GENETICS: X-linked recessive (mostly), Xq28 for protein emerin, AD (1q12 coding lamin A/C); or AR (1q11-q23 coding for lamin A/C) transmission is also recognized; asymptomatic female carriers may have arrhythmias.

DIAGNOSIS: Labs—CK, moderately elevated. Emerin, lamin A/C gene mutation analysis.

CLINICAL PRESENTATION: Symptom onset at 5 to 15 y of age with weakness, diffuse/maximal in the proximal muscles of the upper extremities; early contractures (most prominent at the elbows; these remain disproportionate to the degree of weakness and may be the major factor in functional impairment), muscle wasting and weakness (mild and slowly progressive) in a humeroperoneal distribution, and cardiac (cardiomyopathy; severe and potentially fatal cardiac arrhythmias). Considerable phenotypic variability exists regarding age at onset and rate of progression.

TREATMENT: Close cardiac follow-up because complications are common in both patients and some carriers. Contracture management.

(2) Fascioscapulohumeral Muscular Dystrophy (FSHD)

GENETICS: AD, 4q35 contraction of *D4Z4* repeat; affects 1 in 20,000 (men > women). Inappropriate expression of the double homeobox-containing gene (*DUX4*) in muscle cells.

DIAGNOSIS: Serum CK normal or slightly elevated. DNA testing (1–10 *D4Z4* repeats; normal is 11–150 repeats).

CLINICAL PRESENTATION: Symptoms tend to present by 14 y in 50% and later in the rest with asymmetric, slowly progressive weakness of the facial muscles (transverse smile), fixators of the scapula (winging), and dorsiflexors of the ankle. Severity is highly variable. Supporting diagnosis include asymmetry of motor deficits, sparing of the deltoid/neck flexor/and calf muscles as well as ocular and bulbar musculature; involvement of the wrist extensors and abdominal muscles. Sensorineural hearing loss (esp in children <10 yo) involving high frequencies and retinal vasculopathy (Coats disease). Congenital form (very rare) may be associated with MR and epilepsy. No cardiac involvement or contractures.

TREATMENT: No definitive treatment. Corticosteroids are not effective, but albuterol may induce some improvement. Orthopedic scapular fixation may be beneficial. Remain functionally independent throughout life. 20% will eventually require a wheelchair. Normal life expectancy.

(3) Limb-Girdle Muscular Dystrophies (LGMD)[18]

LGMDs typically have involvement of skeletal muscle only, and present with weakness and wasting of musculature of arms and legs, proximal greater than distal (Table 6.4). Muscle degeneration and regeneration are seen on muscle biopsy. Bulbar musculature is typically spared but not in all genetic subtypes. There is wide phenotypic variability in age of onset, speed of progression, and distribution of the weakness and wasting.

TABLE 6.4 Limb-Girdle Muscular Dystrophies (LGMD)

LGMD Form	Inheritance	Genetics	CK	Clinical Presentation
LGMD1A	AD	5q31; myotilin	N to +	Some with dysarthria; otherwise distal or proximal weakness, cardiac and respiratory complications may be more common with non-myotilin myofibrillar myopathies
LGMD1B	AD	1q11-21; lamin A/C	N to +	Presence in patient or family of rigid spine and contractures; high risk of arrhythmia with requirement for implantable defibrillator, cardiomyopathy, and respiratory failure
LGMD1C	AD	3p25; calveolin 3	+ to ++	Rippling muscle disease; percussion-induced repetitive contractions
LGMD2A	AR	15q15.1; calpain 3	++	Scapular winging, early contractures, and preserved respiratory function
LGMD2B	AR	2p13; dysferlin	+++	Typical onset age, 17–25 y; difficulty with standing on toes; often misdiagnosed as inflammatory muscle disease that is unresponsive to steroids
LGMD2C-F	AR	13q12, 17q21, 4q12, 5q33 (γ, α, β, δ sarcoglycan, respectively)	++ to +++	Scapular winging more prominent than in dystrophinopathy. Hypertrophy of calves and other muscles. Cardiomyopathy and respiratory impairment may be complications
LGMD2I	AR	19q; FKRP	++ to +++	Hypertrophy of calves and other muscles

AD, autosomal dominant; AR, autosomal recessive; CK, creatine kinase; FKRP, fukutin-related protein; N, normal; +, moderate elevation; ++, very high; +++, extremely high.

Adapted from Bushby K. Diagnosis and management of the limb-girdle muscular dystrophies. *Pract Neurol.* 2009;9:314–323, with permission.

(4) Myotonic Dystrophy

An AD disorder characterized by myotonia (failure of voluntary muscles to relax after contraction ceases and by a slow, tonic response to mechanical and electric stimulation; lessened by repetitive movements and aggravated by exposure to cold), muscle atrophy in a characteristic distribution (masseter and temporal muscles; inability to relax the smile and pelvic girdle), cognitive impairment, ECG abnormalities (e.g., prolonged PR interval

> arrhythmias such as atrial flutter in ~86%), posterior cortical cataracts, endocrine abnormalities (frontal baldness, loss of body hair, testicular atrophy; some develop an unusual insulin-resistant form of DM that usually occurs before adolescence), and excessive daytime sleepiness. Both types DM1 and DM2 usually appear in late adolescence or early adult life, but DM1 may also manifest as juvenile or congenital forms (20% of all cases of myotonic dystrophy).

Myotonic Dystrophy (DM1)

GENETICS: CTG trinucleotide expansion (19q13.3) in a serine/threonine protein kinase (*DMPK*) gene. Earlier onset and increasing severity of clinical manifestation in successive generations (genetic anticipation).

DIAGNOSIS: Currently based on genetic testing. Muscle biopsy (characteristic, but not diagnostic) demonstrating excessive numbers of fibers with internal nuclei and selective type I fiber atrophy (a feature shared with Emery–Dreiffus dystrophy). There is also a preferential loss of larger myelinated fibers. CK usually normal. EMG/NCS: trains of high-frequency discharges arising from single fibers or groups of muscle fibers in response to electrode insertion or movement. Amplified, their sounds are like that of a dive-bomber; brain MRI shows ventricular enlargement and, in some instances, hypoplasia of the corpus callosum and abnormal myelination.

CLINICAL PRESENTATION: Usually appear in late adolescence or early in adult life. Congenitally affected children will display weak suck, delayed speech, retarded motor development, generalized hypotonia; facial diplegia in 87% and intellectual disability in 68%; mothers have polyhydramnios; may have arthrogryposis at birth. Clinical myotonia is absent before 1 y.

PROGNOSIS: Clinical course demonstrates gradual debilitation with respiratory insufficiency, dysphagia, aspiration, and poor GI motility. Cardiac

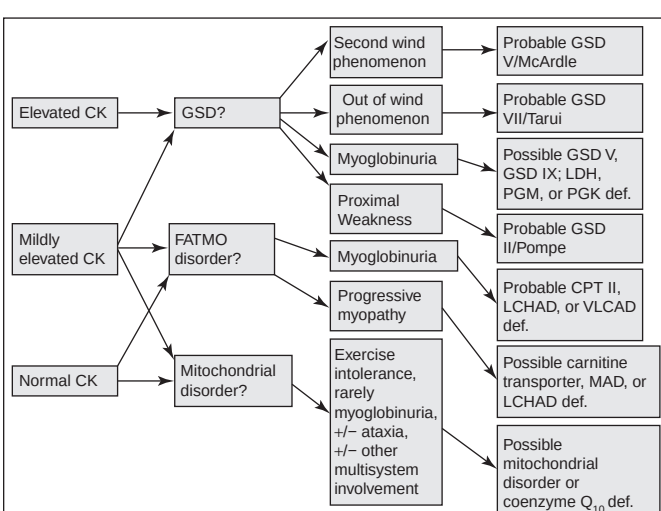


FIGURE 6.3 Algorithm for Elevated CK and Suspected Metabolic Myopathy. (From Smith EC, et al. Metabolic myopathies: clinical features and diagnostic approach. *Rheum Dis Clin N Am.* 2011;37(2):201–217, with permission.)

TABLE 6.5 Metabolic Myopathies: An Overview

Disorder	Presentation	Provocation	Screening Laboratory Testing	Confirmatory Testing	Treatment	Differential Diagnosis	Inheritance
McArdle disease (GSD V)	Acute rhabdomyolysis, second wind phenomenon	Vigorous exercise	Abnormal ischemic forearm test, ± elevated CK, elevated muscle glycogen content	Myophosphorylase gene mutation, phosphorylase activity	Oral sucrose before exercise	PK deficiency	AR
Carnitine palmitoyl transferase II (CPT II) deficiency	Delayed rhabdomyolysis	Fasting, prolonged exercise	Abnormal acylcarnitine profile when stressed, normal CK	*CPT II* gene mutation, CPT activity in fibroblasts or muscle	Carbohydrate ± MCT oil before exercise, avoidance of fasting	Disorders of β-oxidation of long-chain fatty acids	AR
Phosphofructokinase (PFK) deficiency (GSD VII/Tarui)	Exercise intolerance, muscle pain	Stress, illness, exercise	± Elevated CK, ± elevated muscle glycogen content	*PFK* gene mutation, PFK activity in muscle	High protein diet, aerobic conditioning	Mitochondrial disorders	AR

(continued)

TABLE 6.5 Metabolic Myopathies: An Overview (Continued)

Disorder	Presentation	Provocation	Screening Laboratory Testing	Confirmatory Testing	Treatment	Differential Diagnosis	Inheritance
Phosphorylase *b* kinase (PK) deficiency (GSD IXd)[16]	Acute rhabdomyolysis	Vigorous exercise	± Elevated CK, elevated muscle glycogen content	*PK* gene mutation, PK activity in muscle	High protein diet	McArdle disease	AR or X-linked recessive
Mitochondrial disorders (mitochondrial oxidative phosphorylation defects)	Exercise intolerance	Stress, illness, exercise	Abnormal urine organic acids, normal or slightly elevated CK. Serum lactate, pyruvate	Electron transport chain (ETC) testing in muscle, coenzyme Q_{10} in muscle	Coenzyme Q_{10}/ creatine monohydrate/ α-lipoic acid supplementation	PFK deficiency	AR or maternal inheritance (mitochondrial DNA mutations)
Acid maltase deficiency (GSD II)/ Pompe disease	Proximal weakness	Not applicable	Elevated urinary glucose tetrasaccharide, baseline elevated CK, elevated muscle glycogen content	Acid α-glucosidase (*GAA*) gene mutations, GAA activity in blood, fibroblasts, muscle. Genetic testing	Enzyme replacement with recombinant human GAA	Limb-girdle muscular dystrophies	AR

MCT, medium-chain triglyceride; MERRF, myoclonic epilepsy and ragged-red fibers.

From Smith EC, et al. Metabolic myopathies: clinical features and diagnostic approach. *Rheum Dis Clin N Am*. 2011;37(2):201–217, with permission.

involvement presents in the form of conduction defects and ultimately congestive heart failure or sudden death secondary to arrhythmias.

Proximal Myotonic Myopathy (DM2)

GENETICS: Associated with unstable CCTG repeat expansion (3q21.3); prevalent in northern European families. Anticipation, but relationship between repeat length and disease severity is not clear.

DIAGNOSIS: CK is usually normal; muscle biopsy demonstrates preferential type II fiber atrophy in contrast to the type I atrophy seen in DM1 subjects. EMG/NCS: trains of high-frequency discharges arising from single fibers or groups of muscle fibers in response to electrode insertion or movement. Amplified, their sounds are like that of a dive-bomber.

CLINICAL PRESENTATION: Symptoms may start in the 1st decade. Weakness is proximal (legs > arms) and distal (finger flexion). Associated with electrographic myotonia, cataracts, diabetes, cardiac conduction defects. DM2 initial symptoms often involve proximal lower extremity musculature, whereas DM1 is more associated with severe distal muscle atrophy and symptomatic finger flexor weakness. *Muscle pain/cramping may be a prominent feature.*

TREATMENT: Supportive; may have cardiac conduction abnormalities, cataracts, insulin resistance, and sleep disorders.

Metabolic Myopathies[19]

Disorders of glycogen or lipid metabolism or mitochondrial functions that may involve muscle, either as the sole or predominant participant or as part of a multisystem syndrome. The myopathy may be permanent with progressive weakness, or intermittent with episodes of myalgia, rhabdomyolysis, and myoglobinuria often triggered by exercise or other factors. Figure 6.3 shows the algorithm that should be pursued when a child has an elevated CK and metabolic myopathy is suspected. Metabolic myopathies are summarized in Table 6.5.

Myotonia Congenita[20]

GENETICS: Sequence analysis of *CLCN1*, encoding a chloride channel, detects > 95% of mutations causing both the AR and AD forms.

CLINICAL PRESENTATION: Muscle stiffness and hypertrophy, with variable age of onset (AD typically earlier, AR typically more severe). All striated muscle groups, including the extrinsic eye muscles, the facial muscles, and the tongue, may be involved. Men are more severely affected than women. Stiffness is relieved by repeated contractions of the muscle (the "warm-up" phenomenon). AR form can be associated with worsening but limited distal weakness and attacks of transient weakness induced by movement after rest.

DIAGNOSIS: Clinical diagnosis: Myotonia beginning in early childhood, relief of stiffness by "warm-up," myotonic contraction on percussion of muscles. Supportive data from EMG with myotonic bursts, elevated serum CK, and family history.

MANAGEMENT: Supportive. Mexiletine, tocainide, procainamide, quinine, or phenytoin may decrease muscle stiffness.

GENETIC COUNSELING: Given increased risk for adverse anesthesia-related events, testing of young family members is appropriate. Avoid depolarizing muscle relaxants, adrenaline, β-adrenergic agonists, propranolol, and colchicine.

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ONLINE RESOURCES

http://neuromuscular.wustl.edu/ – Outstanding site for education and reference

http://health.nih.gov/topic/neuromusculardisorders – For families and patients, limited topics

http://genetests.org –Extensive disease coverage and genetic information, diagnostic testing algorithms for multiple disease

http://library.med.utah.edu/pedineurologicexam/html/home_exam.html – For health care professionals on the neurological examination and developmental assessment of the pediatric patient

http://musclegenetable.fr/ – A genetic database for neuromuscular diseases

7 Metabolic Disorders

Patricia L. Musolino and Katherine B. Sims

INHERITED METABOLIC DISEASES WITH NEUROLOGICAL INVOLVEMENT

This section is designed to allow the reader to quickly screen through the main metabolic disorders w/ neurological si/sx *presenting during infancy or childhood.* The first subsection presents diagnostic algorithms. The subsequent subsection presents more detailed information about specific disorders. A current expert review for each disease is referenced from the NCBI/NIH GeneReviews chapter where their up-to-date contact information is also available. Detailed instructions on diagnostic testing can be found through www.genereviews.org (see Tables 7.1 to 7.3, Figures 7.1 to 7.3, and Table 7.4).

TABLE 7.1 Most Common Presentations of Neurologic Metabolic Diseases by Age

Age	Neonatal 1–28 d	Late Infancy 1–12 mo	Childhood	Adolescence/ Adulthood
Neuro si/sx	lethargy, diff feeding, hypotonia, irritability, seizures	lethargy or coma w/ nonfocal neuro exam a/w fasting	psych d/o, ataxia, movement d/o, recurrent episodes of coma, paraplegia, seizures, visual d/o	movement d/o, psych d/o, ataxia, peripheral neuropathy, seizures, recurrent episodes of confusion
Other si/sx	Vomiting, abnl respiration, metab acidosis, urine maple syrup smell (MSUD), sweaty foot odor (isovaleric acidemia, glutaric aciduria type II)	recurrent vomiting, liver dysfunction, metabolic acidosis	vomiting, bone deformities, coarse facies, hepatosplenomegaly	recurrent rhabdomyolysis, myoglobinuria, cardiomyopathy

(continued)

TABLE 7.1 Most Common Presentations of Neurologic Metabolic Diseases by Age (Continued)

Age	Neonatal 1–28 d	Late Infancy 1–12 mo	Childhood	Adolescence/ Adulthood
DDx	UCD, OTC, amino-acidopathies, MSUD, organic acidurias, fatty acid oxidation defects, medium chain ACoA dehydrogenase deficiency (MCAD)	*same as for neonatal* +: peroxisomal and lysosomal disease, Niemann–Pick, I-cell disease, MPS VII, alpha-1-antitrypsin, hemochromatosis	lysosomal d/o: Gaucher III, NCLs, Niemann-Pick, RCD	*Movement d/o*: metal metab d/o, RCD, neurotransmitter disorders, intermediary metab d/o *Peripheral Neuropathy*: porphyrias, Refsum, PDH, CTX, Wilson, Fabry, ALD, RCD. *Spastic paraparesis*: UCD, homocysteine remethylation defects, biotinidase def, PKU, NKH, DRD, cerebral folate def, CTX, ALD, lysosomal, Sjögren–Larsson *Recurrent confusion*: UCD, porphyria, homocysteine remethylation disorders, CTX *Chronic psych sx*: homocystinuria, Wilson disease, lysosomal d/o, NCLs, NKH, MPS III

Adapted from Paritosh P. *Pocket Pediatrics*. Philadelphia, PA: Lippincott Williams & Wilkins; 2009.

TABLE 7.2 Basic Initial Workup for Suspected Metabolic Disorder

Test/Study	Abnormalities of Interest
Urine: collect each fresh sample separately in clean container and stored at 4°C (short term). Freeze at –20°C. Compare samples collected before and after Rx.	Smell (special odor), look (special color) Acetone Reducing substances Keto acids (DNPH) pH Sulfitest Sulfite oxidase Electrolytes (Na^+, K^+, phos) Uric acid (search for hyperuricuria) Organic acids (quantitative)

TABLE 7.2 Basic Initial Workup for Suspected Metabolic Disorder (Continued)

Test/Study	Abnormalities of Interest
Blood: 5 mL plasma (heparinized) at –20°C and10 mL whole blood in EDTA (for molecular DNA studies) and blood on filter paper("Guthrie test")	Blood cell count Electrolytes (look for anion gap, glucose, calcium) Blood gas (pH, pCO_2, $HCO3^-$, pO_2) Uric acid Prothrombin time Transaminases (and other liver tests) Plasma ammonia (on ice) Lactic acid (on ice; STAT processing) Pyruvic acid (requires special de-proteinization tube) 3-OH-butyrate, acetoacetate (ketones) Free fatty acids Serum amino acids (quantitative)
CSF: neurotransmitters (collected in specific tubes & transported in dry ice); collect 2 mL STAT (on ice) for chemistries & lactic acid	Opening and closing pressures Cell count, protein, glucose (obtain simultaneous serum glucose) Lactic acid (on ice) Pyruvate Ammonia Amino acids Neurotransmitters, neopterins, biopterins, MTHF
ECHO/EKG	Cardiomyopathy in storage diseases
CXR/KUB	Organomegaly Nephrocalcinosis

Adapted from Saudubray JM, Charpentier C. Chapter 66. In: Scriver CR, et al. (eds). *The Metabolic and Molecular Bases of Inherited Diseases*. 8th ed. New York, NY: McGraw-Hill; 2000, with permission.

TABLE 7.3 Advanced Workup for Suspected Metabolic Disorder

Study	Abnormalities of Interest
MRI/MRS brain	T1, T2 abnormalities; lactate, NAA, creatine peak analysis
Skin biopsy (fibroblast culture)	Enzyme analysis in cultured fibroblasts (FAO, PDH/PC) Staining for lipids, glycogen, cholesterol, fatty acids NP-C (cholesterol esterification, filipin staining) DNA analysis EM for storage inclusions (lysosomal, mitochondrial)
Muscle biopsy	Light & electron microscopy, immunohistochemistry, trichrome for ragged red fibers (RRF, mitochondrial diseases), lipid storage Different patterns of myotubular organization in myopathies
Liver, muscle biopsy (fresh & frozen at –70)	Electron transport chain (ETC activity), coenzymeQ10, acylcarnitines & carnitines (free, total, esterified) Staining for accumulation of lipids, glycogen, cholesterol, fatty acids; immunohistochemistry
EMG/SSEP	Lower motor neuron disease pattern Neuropathies Myopathies
Brain US (neonates)	White matter changes Ventriculomegaly Intraventricular hemorrhage (IVH) Neonatal strokes

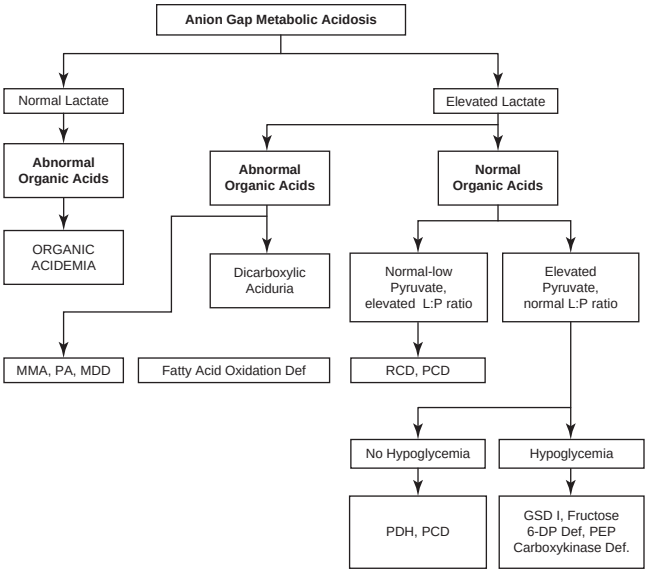


FIGURE 7.1 Metabolic Emergencies: Anion Gap Metabolic Acidosis. Adapted from Saudubray JM, Charpentier C. In: Scriver CR, et al. (eds). *The Metabolic and Molecular Bases of Inherited Diseases*. 8th ed. New York, NY: McGraw-Hill; 2000 and Fenichel GM. *Clinical Pediatric Neurology*. 6th ed. Philadelphia, PA: Saunders, Elsevier; 2009.

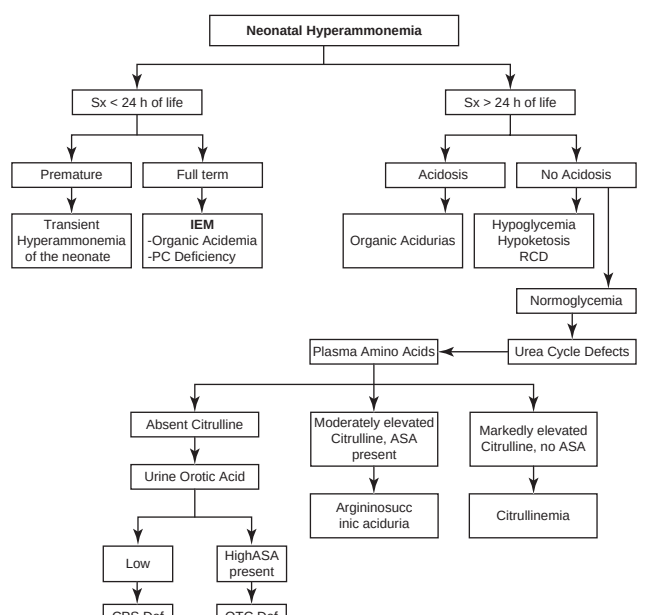


FIGURE 7.2 Metabolic Emergencies: Neonatal Hyperammonemia. Adapted from Saudubray JM, Charpentier C. In: Scriver CR, et al. (eds). *The Metabolic and Molecular Bases of Inherited Diseases*. 8th ed. New York, NY: McGraw-Hill; 2000 and Fenichel GM. *Clinical Pediatric Neurology*. 6th ed. Philadephia, PA: Saunders, Elsevier; 2009.

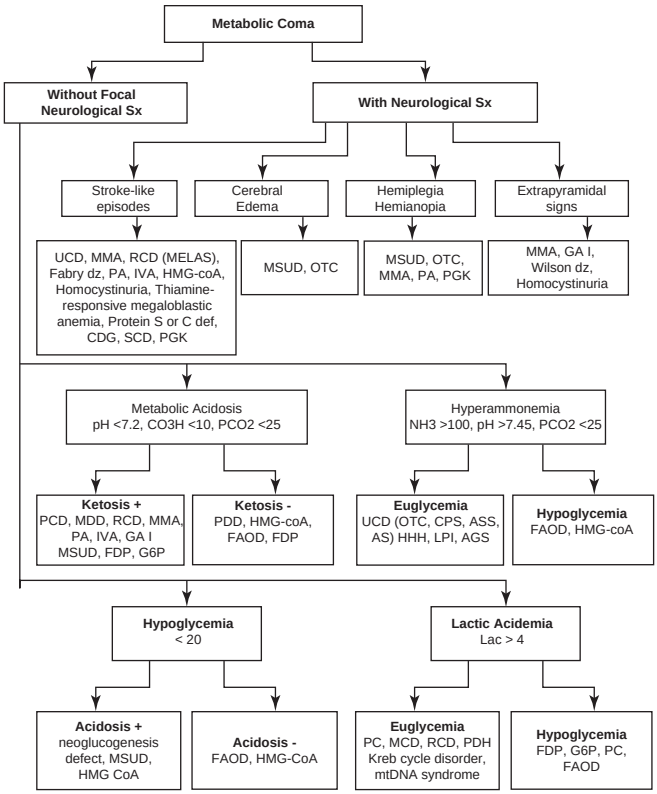


FIGURE 7.3 Metabolic Emergencies: Metabolic Coma. Adapted from Saudubray JM, Charpentier C. In: Scriver CR, et al. (eds). *The Metabolic and Molecular Bases of Inherited Diseases*. 8th ed. New York, NY: McGraw-Hill; 2000 and Fenichel GM. *Clinical Pediatric Neurology*. 6th ed. Philadelphia, PA: Saunders, Elsevier; 2009.

TABLE 7.4 Differential Diagnosis of Lactic Acidosis

Erroneous elevation	Poor collection technique (use of a tourniquet, slow blood flow), poor sample handling (not on ice or processing delay), physiologic, anaerobic exercise
Systemic diseases	Hypoxia, hypotension, shock, sepsis, renal failure, cardiac failure/cardiomyopathy, short bowel syndrome (D-lactate)
Cerebral diseases (can cause ↑ CSF lactate levels)	Prolonged seizures, meningitis/encephalitis, cerebral ischemia, malignancy, other metabolic disorders
Metabolic diseases	Amino acid disorders, organic acidurias, urea cycle defects, pyruvate metabolism disorders, Krebs cycle defects, mitochondrial OXPHOS disorders, fatty acid oxidation disorders, disorders of liver glycogen metabolism, disorders of liver gluconeogenesis, biotinidase deficiency
Other	Thiamine deficiency Toxin exposure (carbon monoxide, methanol)

Management of Metabolic Emergencies

When suspected metabolic disorder or unknown source of metabolic acidosis, hyperammonemia, or coma, ***Start Rx Before*** confirmation of diagnosis.

1. STOP protein, fat, galactose, & fructose
2. Consult metabolic specialist
3. Remove metabolites
   - Hyperammonemia: immediate hemodialysis (HD) for coma, ventilator dependency, or signs of cerebral edema
   - Acidosis: give bicarbonate w/ frequent ABGs, severely acidotic → HD
   - Organic acidemia: Vitamin B_{12} (1 mg) IM for B_{12} responsive form of methylmalonic acidemia. Biotin (10 mg) PO or NGT

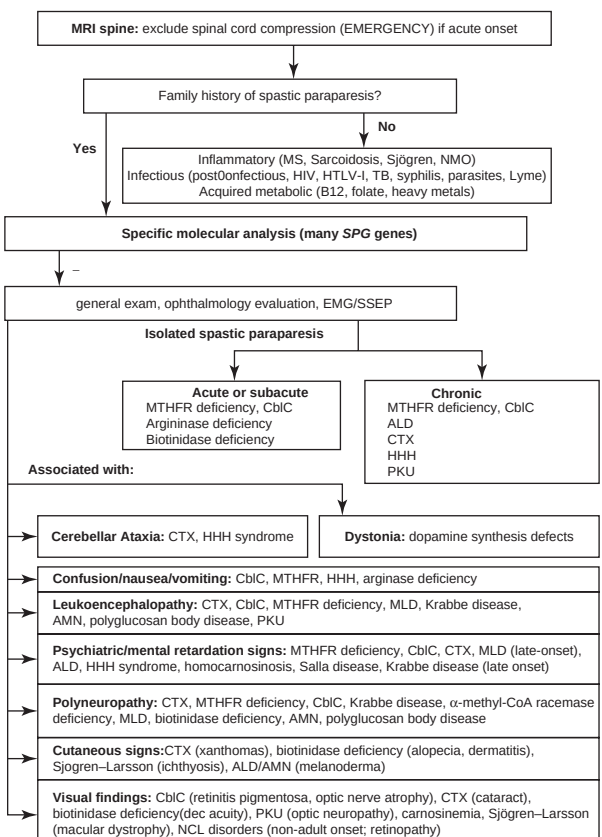


FIGURE 7.4 Progressive Spastic Paraparesis Associated with Metabolic Disorders. Adapted from Sedel F, Fontaine B, Saudubray JM, et al. Hereditary spastic paraparesis in adults associated with inborn errors of metabolism: a diagnostic approach. *J Inherit Metab Dis.* 2007;30(6):855–864, with permission.

for biotin-responsive carboxylase deficiency. May need HD or peritoneal dialysis if coma
- Urea cycle defect: 6 cc/kg of 10% arginine HCL IV over 90 min

4. Prevent catabolism
   - IV glucose (calories needed to keep euglycemia) D10 150 cc/kg/d w/ electrolytes
   - STOP protein (after 24–48 h restart essential amino acids), IV lipids should be given for urea cycle defects

Diagnostic Algorithms by Main Presenting Symptoms

Progressive Spastic Paraplegia

See Figure 7.4.

Ataxia

See Figures 7.5 and 7.6.

Epilepsies Associated with Metabolic Diseases

See Figure 7.7 and Table 7.5.

Movement Disorders and Extrapyramidal Signs

See Figures 7.8 and 7.9.

Peripheral Neuropathy Secondary to Inborn Error of Metabolism

See Figure 7.10.

Ocular Findings in Inborn Errors of Metabolism

See Table 7.6.

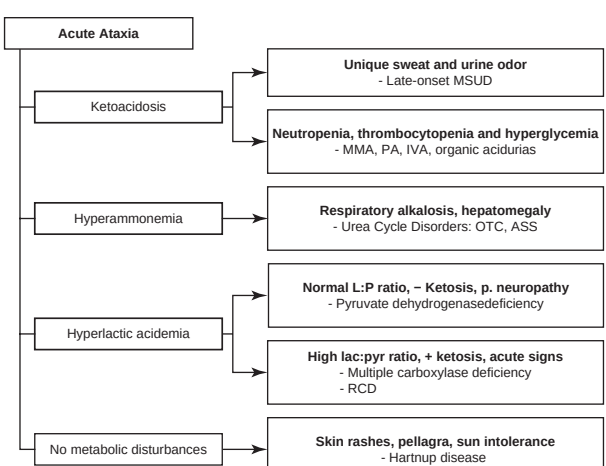


FIGURE 7.5 Acute Ataxia Associated with Metabolic Disorders. Adapted from Saudubray JM, Charpentier C. In: Scriver CR, et al. (eds). *The Metabolic and Molecular Bases of Inherited Diseases.* 8th ed. New York, NY: McGraw-Hill; 2000, with permission.

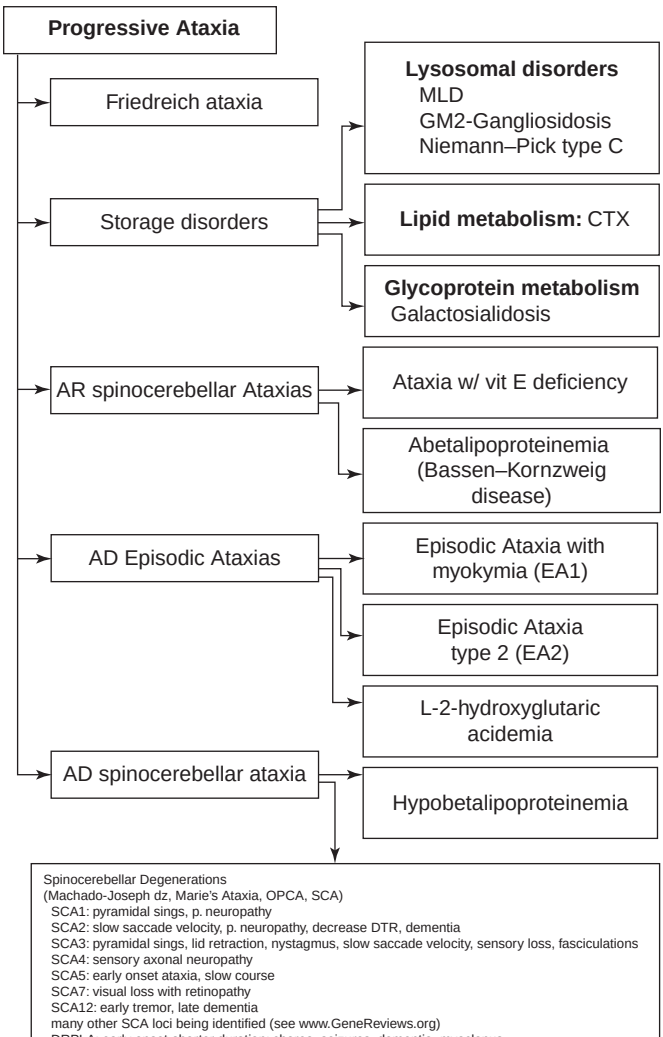


FIGURE 7.6 Progressive Ataxia Associated with Metabolic Disorders. Adapted from Saudubray JM, Charpentier C. In: Scriver CR, et al. (eds). *The Metabolic and Molecular Bases of Inherited Diseases*. 8th ed. New York, NY: McGraw-Hill; 2000, with permission.

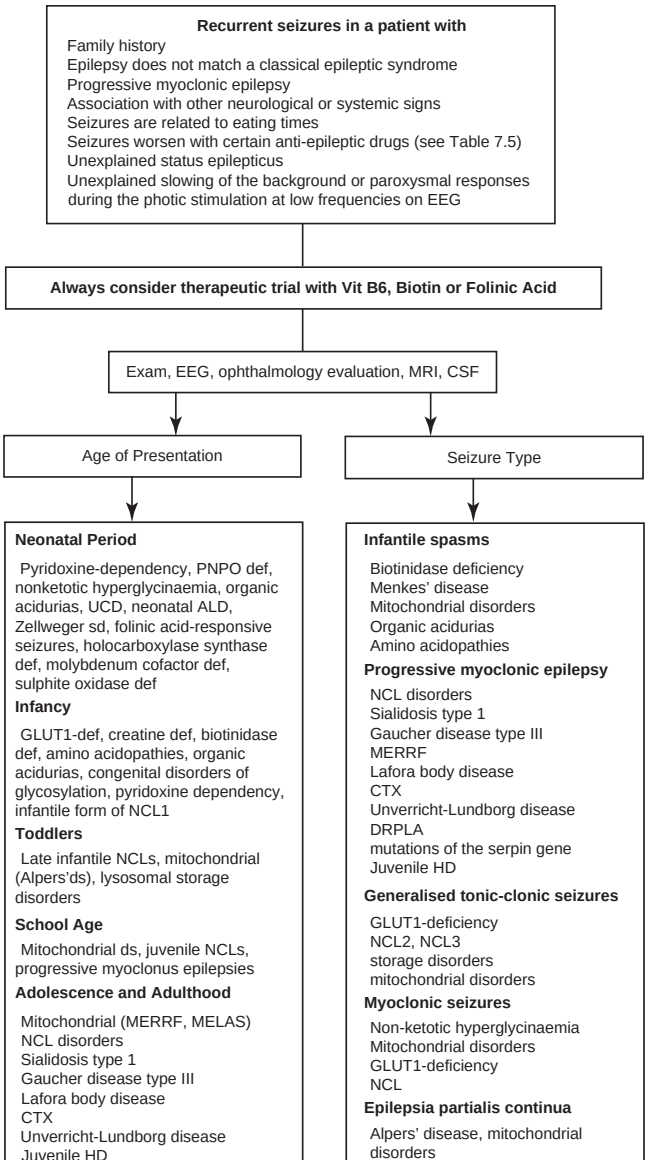


FIGURE 7.7 Epilepsies Associated with Metabolic Disorders. Adapted from Sedel F, Fontaine B, Saudubray JM, et al. Hereditary spastic paraparesis in adults associated with inborn errors of metabolism: a diagnostic approach. *J Inherit Metab Dis.* 2007;30(6):855–864[50] and Wolf NC. Epilepsy in inborn errors of metabolism. *Epileptic Disord.* 2005; 7 (2): 67–81, with permission.[51]

TABLE 7.5 Anticonvulsants to be Avoided in Metabolic Disorders

Disease	Drugs that may Exacerbate Epilepsy or Metabolic Attacks
PME	Phenytoin, carbamazepine, gabapentin, vigabatrin, tiagabine, lamotrigine
GLUT-1 deficiency	Diazepam, phenobarbital, oxcarbamazepine
Porphyrias	Valproate, lamotrigine, oxcarbamazepine, carbamazepine, phenytoin, topiramate
Urea cycle defects	Valproate
Mitochondrial disorders	Valproate

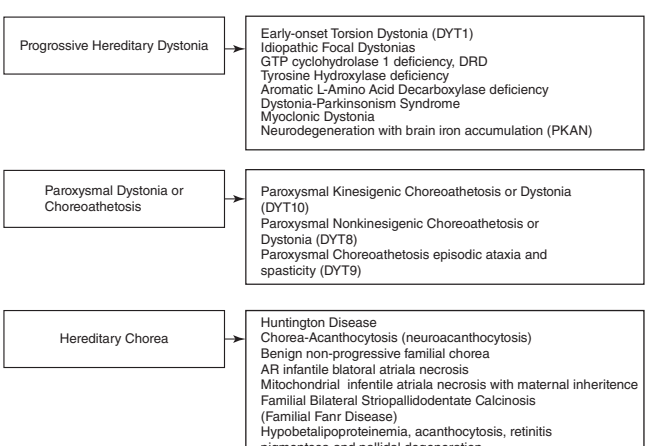


FIGURE 7.8 Movement Abnormalities Associated with Metabolic Disorders.

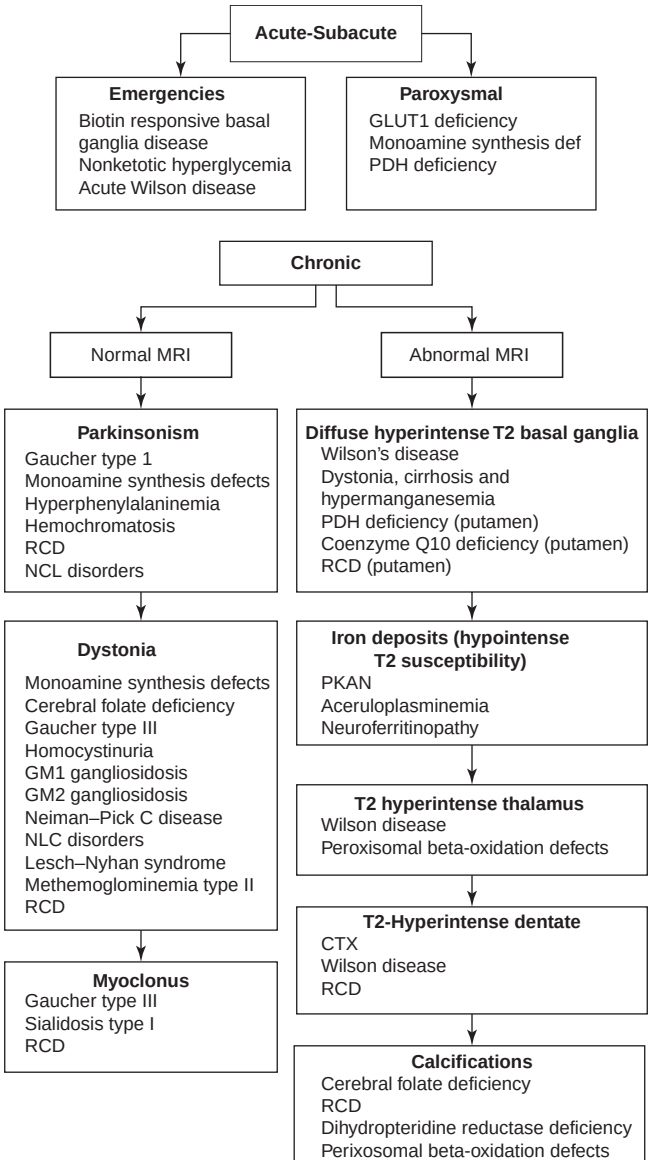


FIGURE 7.9 Movement Disorders Associated with Metabolic Disorders, Characterized by Onset and MRI Findings. Adapted from Sedel F, Saudubray JM, Roze E, et al. Movement disorders and inborn errors of metabolism in adults: a diagnostic approach. *J Inherit Metab Dis.* 2008;31(3):308–318, with permission.[50]

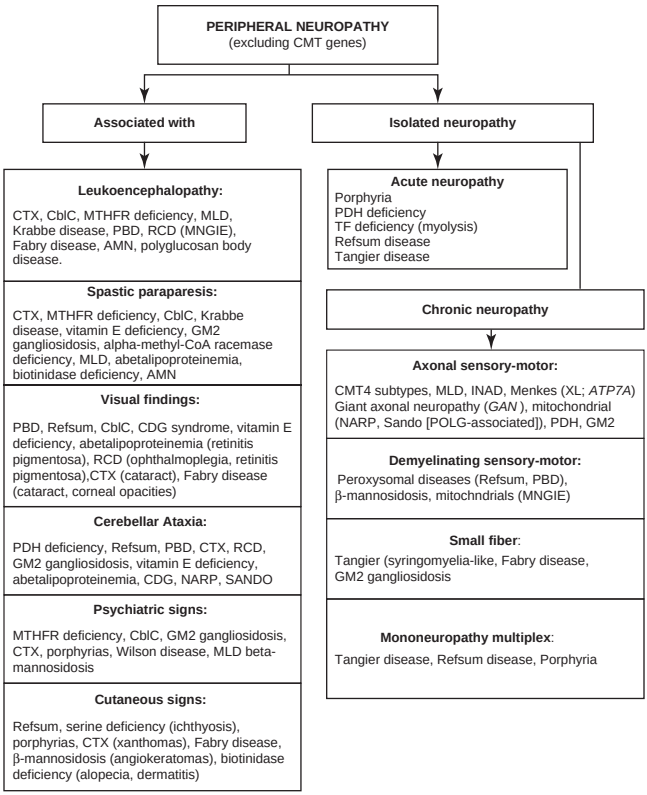


FIGURE 7.10 Peripheral Neuropathies Associated with Metabolic Disorders. Adapted from Sedel F, Baumann N, Turpin JC, et al. Psychiatric manifestations revealing inborn errors of metabolism in adolescents and adults. *J Inherit Metab Dis.* 2007;30(5):631–641, with permission.

TABLE 7.6 Ocular Findings Associated with Metabolic Disorders

	Disorder
Optic glioma	NF type I
Retinitis pigmentosa	Peroxisomal disorders
	Sjögren–Larsson syndrome (ichthyosis, spastic paraplegia, MR)
	NCL disorders
	Refsum disease
	Kearns–Sayre syndrome
	Pantothenate kinase deficiency/infantile neuroaxonal dystrophy
	Bardet–Biedl syndrome (obesity, polydactyly, MR)
	Usher type II (deafness, severe MR)
	Joubert (MR, vermis atrophy, hyperventilation episodes)
	NARP
	MILS
	Abetalipoproteinemia
	Congenital defects of glycosylation
	RCD
	LCHAD
	Mucopolysaccharidoses type I, II, III, IV

TABLE 7.6 Ocular Findings Associated with Metabolic Disorders (Continued)

	Disorder
Macular degeneration (cherry-red spots)	MLD
	Niemann–Pick disease
	Wolman disease
	Galactosialidosis
	GM1 gangliosidosis
	GM2 gangliosidosis
Optic atrophy or central blindness	ALD
	MLD
	Krabbe disease
	Zellweger spectrum
	Refsum disease
	MELAS
	LHON
	Canavan disease
	3-methylglutaconic aciduria
	NCL disorders
	Homocystinuria
Lens dislocation	Sulfite oxidase deficiency
	Molybdenum cofactor deficiency
	Homocystinuria
	Marfan syndrome
	Ehlers–Danlos syndrome
Neonatal cataracts	Galactosemia
	Galactokinase deficiency
	Tyrosinemia type II
	Peroxisomal disorders
	Glucose-6-phosphate dehydrogenase deficiency
	Sorbitol dehydrogenase deficiency
	Lowe syndrome
	Cockayne syndrome
	Congenital infection (syphilis, rubella, mumps)
Infantile cataracts	RCD
	Sialidosis
	α-mannosidosis
	Mevalonic aciduria

Adapted from Saudubray JM, Charpentier C. In: Scriver CR, et al. (eds). *The Metabolic and Molecular Bases of Inherited Diseases*. 8th ed. New York, NY: McGraw-Hill; 2000, with permission.

DISEASES AFFECTING METABOLIC PATHWAYS

Metal Metabolic Disorders

Wilson Disease[1]

Familial hepatolenticular degeneration

Defect: Defect in copper-transporting ATPase 2, (*ATP7B*).

FHx: AR, Mediterranean descent

Presentation: Classically p/w movement d/o (tremors, poor coordination, loss fine-motor, choreathetosis) + hepatic failure. Hepatic failure predominates in children w/ onset at <10 y. If onset in 2nd decade, one neurologic

si/sx such as gait or speech disturbance, unchanged for years & then development of movement d/o (e.g., dysarthria, dystonia, dysdiadochokinesia, facio-linguo-pharyngeal rigidity, & gait difficulties). Other sx: rest & action tremor (rubral tremor) ± chorea & parkinsonism. Psychiatric si/sx precedes movement d/o in 20% of cases.

Other si/sx: Hepatic failure/cirrhosis, corneal Kayser–Fleischer ring (seen in 100% cases w/ CNS involvement) & azure lunulae of the fingernails. Fanconi syndrome.

Prognosis: Variable. Can have normal life span if therapy instituted early.

Dx: ***Imaging:*** MRI: cerebral atrophy, T2 hypointensity of the globus pallidus, & T2 hyperintensity of caudate, putamen, thalamus, dentate nucleus, & pons. ***Labs:*** Low serum copper & ceruloplasmin. Elevated LFTs, increased urinary copper. ***Liver biopsy:*** Elevated copper in liver w/ assay of copper content by spectrometry (copper content > 250 mcg dry weight of liver). ***Definitive dx*:** Neuro-ophthalmologic slit-lamp exam showing corneal Kayser–Fleischer rings, mutational analysis (*ATP7B).* Screen siblings.

Rx: Lifelong; copper-chelating agents: D-penicillamine, trientine, tetrathiomolybdate; zinc, antioxidants, restriction of foods very high in copper. Liver transplant controversial.

Aceruloplasminemia[2]

Defect: Mutation of the ceruloplasmin gene (*CP*) on chromosome 3q25. Accumulation of iron in liver, pancreas, brain, & retina.

FHx: AR

Presentation: Very rare, p/w progressive neurodegeneration resulting in dystonia or chorea, dementia, retinal degeneration, & cerebellar ataxia.

Other si/sx: Microcytic anemia, diabetes.

Dx: ***Imaging:*** MRI: iron accumulation (T2 hypointensity) in the putamen, caudate, thalamus, dentate nuclei. ***Labs:*** Undetectable serum ceruloplasmin, ↓ iron, ↓ copper, ↑ ferritin, microcytic anemia. LFTs normal. ***Biopsy:*** liver iron deposits in hepatocytes & RE system. ***Definitive dx:*** DNA mutation analysis (*CP*).

Rx: Iron chelators (e.g., desferrioxamine, FFP), antioxidants. Avoid iron supplements.

Hemochromatosis[3]

Prevalence: High carrier rate (1:250), but very low incidence (phenotypic) in children.

Defect: Classic type I: *C282Y* gene. Class II juvenile: AR hemojuvelin gene (*HFE2*) and hepcidin antimicrobial peptide (*HAMP*). Class III: AR transferrin receptor-2 (*TFR2*). Class IV: AD ferroportin (*FPN1*).

FHx: All AR except Class IV, which is AD.

Presentation: More common in adults, but can be seen as early as 2 y (in children: cardiomyopathy & gonadal failure). Neurologic signs include: parkinsonism, cerebellar ataxia, dementia, myoclonus, action tremor, cervical dystonia.

Other si/sx: Cirrhosis & primary hepatocellular carcinoma, arthritis, DM, bronze skin pigmentation.

Prognosis: Depends on progression of disease before therapy. Children often die of cardiac cause.

Dx: ***Imaging:*** Normal MRI (may have brain atrophy). ***Labs:*** High serum iron, transferrin saturation, & ferritin. ***Biopsy:*** Hepatic iron is the most sensitive index of preclinical disease. Confirmed by hepatic iron index score >1.9 or hepatic iron >80 μmol/g dry weight of liver or grade 3 or 4 on Perls stain. ***Definitive dx:*** Liver biopsy & genetic testing.

Rx: Phlebotomy for ferritin >300 mcg/L in men; ferritin > 200 mcg/L in women, regardless of the presence or absence of symptoms.

Neurodegeneration with Brain Iron Accumulation (NBIA)[4]

Infantile Neuronal Dystrophy (INAD; Seitelberger disease)

FHx: AR; *PLA2G6* mutations.

Presentation: Progressive degeneration of CNS and PNS. Infantile hypotonia followed by spasticity, opisthotonic posturing, optic atrophy. Death usually by 5 y.

Pathology: Axonal spheroids on skin or nerve biopsy.

Dx: MRI: diffuse cerebellar hyperintensity and atrophy ± iron in basal ganglia. EMG: anterior horn cell dysfunction, denervation. NCV, normal; ERG, normal.

Rx: Symptomatic

Pantothenate Kinase–Associated Neurodegeneration (PKAN)

Defect: Pantothenate kinase deficiency, *PANK2* mutations.

FHx: AR

Presentation: Onset 7 to 10 y w/ dystonia, dysphagia, parkinsonism, choreathetosis, and retinitis pigmentosa. Cognitive and psychiatric disorders, along w/ spasticity follow.

Prognosis: Spastic quadriplegia and death within 5 to 10 y.

Dx: ***Imaging:*** T2 hyperintensity w/ surrounding hypointensity in medial globus pallidius ("eye of the tiger sign"). ***Definitive dx:*** *PANK2* mutation analysis.

Rx: Symptomatic, deep brain stimulation for dystonia.

Menkes: Trichopolydystrophy[5]

Defect: Defect in the intestinal transport of copper, *ATP7A* gene mutation.

FHx: X-linked recessive.

Presentation: Symptoms result from secondary deficiency of copper-dependent enzymes (cytochrome-c-oxidase, dopamine-beta-hydroxylase, lysyl oxidase, etc.). Most marked are neurodegenerative changes and connective tissue abnormalities. Infants are usually hypotonic, progressing to spastic quadriparesis. Autonomic dysfunction, temperature instability, and hypoglycemia are seen in neonates.

Other si/sx: Sparse, poorly pigmented, pili torti (kinky hair), osteogenesis imperfecta, high arched palate, micrognathia, fullness of the cheeks, occipital horns.

Prognosis: Progressive encephalopathy leaves patients vegetative by 1 y, death usually by 1.5 to 2 y, no therapy. Cases surviving up to 20 y have been described.

Dx: ***Labs:*** Low plasma ceruloplasmin; copper microscopic examination of the hair (pili torti seen in carriers). ***Biopsy:*** Skin for enzyme assay in cultured fibroblasts. ***Definitive dx:*** *ATP7A* mutation analysis. Prenatal testing.

Rx: subcutaneous injections of copper histidine or copper chloride before 10 d of age normalizes developmental outcome.

Peroxisomal Disorders[6]

Refsum Disease (Phytanic Acid Oxidase Deficiency)

Defect: Defect of phytanoyl-CoA hydroxylase (*PAHX* or *PHYH* gene).

FHx: AR, more common in Scandinavian, British, German, & French.

Presentation: Insidious onset in 1st through 3rd decade w/ night blindness (retinitis pigmentosa), recurrent or chronic polyneuropathy (often symmetric, distal, vibration > pain & temp), palpable nerves, cerebellar ataxia, dysmetria, dysarthria. When presenting in infants, severe hypotonia w/ absent DTRs seen. Symptoms made worse by fasting. Other si/sx: sensorineural hearing loss, cardiomyopathy, ichthyosis, pes cavus.

Prognosis: Variable, progressive w/ periods of stability & exacerbations. Death may occur from sudden cardiac event.

Dx: ***Imaging:*** MRI: symmetrical T2 hyperintensity involving the corticospinal tracts, cerebellar dentate nuclei, & corpus callosum (only seen on infantile form). ***Labs:*** ↑ plasma branched-chain FAs (mostly phytanic acid), ↑ CSF protein (1–7 g/L). ***Biopsy:*** Skin for enzyme assay in cultured fibroblasts. ***Definitive dx:*** *PAHX* or *PHYH* mutation analysis.

Rx: Dietary modification to avoid phytanic acid ± plasmapheresis.

X-linked Adrenoleukodsytrophy (XALD), see Chapter 9.

Zellweger Spectrum disorders, see Chapter 9.

Lysosomal Disorders

GM1 Gangliosidosis[7] (type I: infantile, type II: late infantile/juvenile, & type III: adult)

Defect: Beta-galactosidase deficiency, *GLB1* gene mutation.

FHx: AR.

Presentation: Type I (infantile onset): difficulty feeding/failure to thrive, hypotonia. Type II (late infantile/juvenile): initially ataxia, strabismus, & dysarthria, followed by seizures, mental regression, & spasticity.

Other si/sx: Type 1: hepatosplenomegaly, deafness, mental retardation, kyphoscoliosis, vertebral & hip dysplasia (resembling Hurler disease, but w/o corneal opacities & w/ macular cherry-red spots [50%]), renal disease, dilated and/or hypertrophic cardiomyopathy.

Type II: no visceromegaly & only mild skeletal abnormalities.

Prognosis: Death typically occurs within 1 y in the infantile form. Later onset associated with survival into 1st or 2nd decade.

Dx: ***Imaging:*** T2 hyperintensity of posterior putamen. ***Labs:*** Low beta-galactosidase activity in leukocytes. ***Biopsy:*** Liver, heart, kidney, fibroblast show accumulation of gangliosides. ***Definitive dx:*** Beta-galactosidase activity in leukocytes & *GLB1* molecular testing.

Rx: Symptomatic or Miglustat (inhibitor of glucosylceramide synthase)

GM2 Gangliosidosis, type I[β]: Tay–Sachs Disease (infantile, juvenile/chronic adult forms)

Defect: Hexosaminidase A deficiency; *HEXA* mutations.

FHx: AR, Ashkenazi Jews with high carrier rate.

Presentation: Infantile form (most common): persistent startle reaction to sound, developmental regression, followed by paralysis, dementia, & blindness. Juvenile onset (late-onset form; onset late childhood to adulthood): childhood clumsiness or incoordination, can see psychiatric presentation; associated findings include: proximal muscle weakness (typically LE first), ataxia, dysarthria, & tremor, abnormal saccades. LMN disease.

Other si/sx: Classic macular cherry-red spot. No organomegaly (distinct from GM1). Chronic adult: progressive dystonia, spinocerebellar degeneration, motor neuron disease with muscle weakness and fasciculations, and/or psychosis.

Prognosis: For infantile form severe retardation & spasticity by 1 y, death by 2 to 5 y. Variable for juvenile/adult form.

Dx: ***Imaging:*** MRI marked cerebellar atrophy. ***Labs:*** Elevated CPK, foamy leukocytes, deficient enzyme activity in leukocytes. ***Biopsy:*** Liver or rectal, accumulation of globosides and GM2 gangliosides. ***EMG:*** Fasciculations. ***Definitive dx:*** Absent to near-absent hexosaminidase A enzymatic activity in the serum or leukocytes in the presence of normal or elevated activity of the beta-hexosaminidase B isoenzyme. Molecular genetic testing (*HEXA).* Prenatal testing amniocentesis (*N*-acetylglucosaminyl oligosaccharides; *HEXA* mutational analysis).

Rx: For up-to-date trials, search ClinicalTrials.gov.

GM2 Ganglisidosis, Type II: Sandhoff Disease

Defect: Hexosaminidase B enzyme deficiency; *HEXB* mutations.

FHx: AR

Presentation: Infantile onset is very similar to Tay–Sachs, weakness in the first 6 mo of life, startle reaction, early blindness, progressive mental and motor deterioration, doll-like face, cherry-red spots, and macrocephaly. Later onset p/w learning difficulties, emotional labiality, intermittent psychosis, or confusional state. Muscle atrophy, fasciculations, supranuclear gaze palsy, hyperreflexia, & extensor plantar responses (less dystonia & extrapyramidal signs in children).

Other si/sx: Macular cherry-red spot, moderate hepatosplenomegaly.

Prognosis: Death usually occurs by age 3 y.

Dx: ***Imaging:*** Cerebellar & cortical atrophy are common. ***Labs:*** Enzymatic activity in dried blood on filter paper or in leukocytes. ***Biopsy:*** Liver or rectal, accumulation of globosides & GM2 gangliosides. Foamy histiocytes in bone marrow. Skin for fibroblast culture. ***Definitive dx:*** Low activity of beta-hexosaminidase subunit B activity (serum, leukocytes, & cultures fibroblasts). *HEXB* mutation analysis. Prenatal testing amniocentesis (*N*-acetylglucosaminyl oligosaccharides; *HEXB* mutational analysis).

DDx: Clinically indistinguishable from Tay–Sachs (suspect in non-Jews).

Rx: Supportive. Outdated trials/gene therapy. Search ClinicalTrials.gov.

Niemann–Pick disease[10] (Type A: neonatal & Type C: juvenile)

Defect: Sphingomyelinase deficiency. Type A: *SMPD1* gene; [Type B: non-neurological]; Type C: *NPC1* or *NPC2* gene.

FHx: AR. Ashkenazi Jews affected more often in type A.

Presentation: Type A: neonatal w/ an acute onset of feeding difficulty/failure to thrive & hepatomegaly followed by psychomotor regression, hypotonia, & blindness. Type C: Early onset: neonatal hypotonia, developmental delay, clumsiness, learning difficulties, ataxia, dysphagia, vertical gaze palsy. Juvenile onset: 2 to 8 yo w/ a slower onset of cerebellar ataxia, seizures, & supranuclear ophthalmoplegia w/ paralysis of vertical gaze & spasticity followed by progressive mental regression.

Other si/sx: Type A: cherry-red macula in 50%, jaundice, splenomegaly as disease progresses. Type C: macular cherry-red spot (early form mostly), moderate hepatosplenomegaly.

Prognosis: Type A: death by 1 y. Type C: early onset death by 3 to 5 y. Juvenile form death by 15 y.

Dx: ***Labs:*** NP-A with decreased sphingomyelinase enzyme activity. NP-C with decreased low cholesterol esterification and abnormal filipin staining (fibroblasts). ***Biopsy:*** Not mandatory for disease. Foamy & sea blue histiocytes in bone marrow. ***Definitive dx:*** Decreased sphingomyelinase activity in leukocytes & cultured fibroblasts. Mutation analysis of *SMD1* gene. **Rx:** Supportive. Hematopoietic cell transplantation for NPD type A can prevent somatic symptoms but has not reversed the neurological phenotype. A Phase I enzyme replacement therapy trial in adults with NPD-B is underway and expected to be completed soon. Search ClinicalTrials.gov.

Sialidosis Type I[11]

Defect: Deficiency of alpha-neuraminidase, *NEU1* gene mutation.

FHx: AR.

Presentation: Hydrops fetalis in severe forms, action & stimulus-sensitive myoclonus, tonic–clonic seizures, & cerebellar ataxia.

Other si/sx: Macular cherry-red spot, punctuate lenticular opacities.

Dx: ***Imaging:*** Cerebral & cerebellar atrophy. ***Labs:*** Urine—abnormal excretion of sialio-oligosaccharides, low enzyme activity in leukocytes & fibroblasts. ***Biopsy:*** Skin for enzyme assay in cultured fibroblasts. ***Definitive dx:*** Enzyme analysis of cultured fibroblast or *NEU1* mutational analysis.

Rx: Supportive.

Gaucher disease[12] (type I: non-neuropathic, type II: infantile neuronopathic form, type III: variable onset, somatic and neurologic features)

Defect: Beta-glucosidase (glucocerebrosidase) deficiency, *GBA* mutations.

FHx: AR, Ashkenazi Jews.

Presentation: *Type I:* bone disease (osteopenia, focal lytic or sclerotic lesions, and osteonecrosis), hepatosplenomegaly, anemia and thrombocytopenia, lung disease, NO CNS symptoms except for increased risk of late-onset parkinsonism. *Type II*: normal at birth, then rapid developmental regression, cranial neuropathy, & hypotonia developing into spasticity presenting before 6 mo. Opisthotonos, dysphagia, and stridor seen within a few months of age. ± seizures. *Type III:* childhood to adulthood onset w/ slower progression of myoclonic & tonic–clonic seizures, cranial neuropathy, progressing to spasticity, ataxia, ophthalmoplegia and dementia.

Other si/sx: *Type II:* splenomegaly > hepatomegaly, growth arrest, ichthyosiform-collodion skin. *Type III:* marked hepatosplenomegaly.

Prognosis: *Type I:* normal life span, increased risk of PD over normal population. *Type II:* death within 1 to 2 y, hydrops in aggressive form. *Type III:* variable. Some survive into adulthood.

Dx: ***Labs:*** Thrombocytopenia, anemia, leukopenia. Low enzyme activity in leukocytes & fibroblasts. ***Biopsy:*** Skin for enzyme assay in cultured fibroblasts. Bone marrow: lipid-engorged macrophages ("Gaucher cells"). ***Definitive dx:*** Enzyme analysis of leukocytes or cultured fibroblasts (1%–15% of normal). Prenatal testing of cultured chorionic villi. *GBA* mutational analysis.

Rx: Chronic neurologic involvement (type III GD) can benefit from BMT. Enzyme replacement therapy (imiglucerase or velaglucerase alfa) & substrate reduction therapy (Miglustat: inhibitor of glucosylceramide synthase) are successful in treatment of non-neurological symptoms.

Fabry Disease[13]

Defect: Alpha-galactosidase A deficiency with accumulation of glycosphingolipids, primarily globotriaosylceramide (Gb3). *GLA* mutations. Some mutations are inducible and candidates for chaperone (small molecule) therapy agents.

FHx: X-linked (but women are also affected, not simple carriers). Incidence: 1:4,000.

Presentation: Painful crises in the extremities (acroparesthesias) and abdomen (autonomic dysfunction), hypohydrosis (heat intolerance, recurrent fever). Proteinuric renal failure, hypertrophic cardiomyopathy, early-onset stroke, hearing loss, depression are common in classic males and often in females. **Other si/sx:** Diarrhea, angiokeratoma (periumbilical, bathing suit distribution), cornea verticillata (on slit-lamp exam), tinnitus.

Prognosis: Survive into advanced age, but often die of stroke, renal, or cardiac complications.

Dx: ***Imaging:*** MRI: T1-hyperintense pulvinar (thalamus). T2-hyperintense periventricular white matter changes. CTA: vertebrobasilar dolichoectasia. Stroke (mostly ischemic but also hemorrhagic). ***ECHO:*** LVH (hypertrophic cardiomyopathy), diastolic dysfunction. ***Labs:*** Increased plasma globotriaosylceramide (Gb3). Urinary trihexoside assay & microalbuminuria. ***Biopsy:*** Skin for enzyme assay in cultured fibroblasts. ***Definitive dx:*** Alpha-galactosidase enzyme assay and molecular *GLA* screening. Females (heterozygotes) may have normal enzyme activity, DNA mutation identification may be required to make diagnosis. Not yet included in newborn screening. Prenatal diagnosis from amniocentesis by DNA testing.

Rx: Enzyme replacement therapy (ERT) has been shown to stabilize cardiomyopathy and renal function, if started early enough to prevent secondary fibrotic changes. Experimental ex vivo hematopoietic stem/progenitor cell gene therapy. Diphenylhydantoin, carbamazepine, or gabapentin to reduce pain (acroparesthesias); ACE inhibitors to reduce proteinuria; chronic hemodialysis, and/or renal transplantation for ESRD.

Farber Lipogranulomatosis[14, 15]

Defect: Acid ceramidase deficiency, *ASAH1* mutations.

FHx: AR

Presentation: Mental retardation late in the course.

Other si/sx: Subcutaneous nodules, arthritis, & laryngeal involvement, hepatosplenomegaly, macular cherry-red spot.

Prognosis: Death by 2 y from lung disease

Dx: ***Labs:*** Urine: elevated ceramide. ***Biopsy:*** Skin for enzyme assay in cultured fibroblasts. ***Definitive dx:*** Low enzyme activity in peripheral leukocytes or cultured fibroblast. *ASAH1* mutation analysis.

Rx: Symptomatic.

Mucopolysaccharidoses (Only Those with Neurological Features)

Hurler Syndrome (MPS I)[16]

Defect: Accumulation of glycosaminoglycan due to deficiency of alpha-L-iduronidase, *IDUA* gene mutation.

FHx: AR.

Presentation: Normal at birth, starting at age ~2 y developmental regression (cognitive & motor). Hydrocephalus from leptomeningeal thickening may occur. Mild forms present in later 1st decade w/ relatively normal intellect & life span.

Other si/sx: Coarse facies (noted early), corneal clouding (constant feature), hearing loss, hernias, dysostosis multiplex w/ growth arrest at age 3 y (dwarfism), cardiomyopathy (stiff walls, AR), CAD, & hepatosplenomegaly.

Prognosis: Death usually occurs by age 10 y without treatment.

Dx: ***Imaging:*** MRI: T1-hypo & T2-hyperintense cystic perivascular lesions (accumulation of glycosaminoglycan within the foam cells in the Virchow–Robin space). Long bones X-rays w/ dysostosis multiplex. ***Labs:*** High urinary excretion of glycosaminoglycans. ***Biopsy:*** Skin for enzyme assay in cultured fibroblasts. ***Definitive dx:*** Low enzyme activity in peripheral leukocytes or cultured fibroblast. *IDUA* mutations. Prenatal diagnosis from amniocentesis.

Rx: Bone marrow transplant halts disease progression. Enzyme replacement therapy. Gene therapy w/ transduced autologous bone marrow cells w/ retroviral vector carrying gene.

Hunter Syndrome[17] *(MPSIIA & MPSIIB)*

Defect: Accumulation of chondroitin sulfate B & heparan sulfate due to iduronate sulfatase deficiency, *IDS* mutations.

FHx: X-linked w/ mosaicism in different cell lines.

Presentation: Similar to Hurler syndrome. MPSIIA: Severe form w/ progressive mental retardation. MPSIIB: Mild form w/ cognitive decline.

Other si/sx: Similar to Hurler syndrome but no corneal clouding.

Prognosis: MPSIIA: death before age 15 y. MPSIIB: gradual decline w/survival into early adulthood.

Dx: ***Imaging:*** MRI: T1-hypo- & T2-hyperintense cystic perivascular lesions (accumulations of foam cells in the Virchow–Robin space). ***Labs:*** Large amounts of urinary chondroitin sulfate B & heparan sulfate. ***Biopsy:*** Skin for enzyme assay in cultured fibroblasts. ***Definitive dx:*** Low enzyme activity in peripheral leukocytes or cultured fibroblast. *IDS* mutation analysis. Prenatal diagnosis from amniocentesis.

Rx: Enzyme replacement therapy & possible bone marrow transplant in early stages may slow disease progression.

Sanfilippo Disease (MPS III)[18]

Defect: 4 types. IIIA: *N*-sulfoglucosamine sulfohydrolase deficiency (*SGSH*). IIIB *N*-alpha-acetylglucosaminidase deficiency (*NAGLU*). IIIC: heparin acetyl-CoA:alpha-glucosaminide *N*-acetyltransferase, (*HGSNAT*). IIID: *N*-acetylglucosamine-6-sulfatase (*GNS*).

FHx: AR.

Presentation: Onset between 2 and 5 y w/ psychomotor retardation, sleep disorders, and hyperactivity followed by dementia.

Other si/sx: Moderately severe claw hand & visceromegaly, little or no corneal clouding or skeletal dysostosis compared w/ other MPS disorders.

Prognosis: Severe mental retardation (IQ $<$ 50) and death by teenage years.

Dx: ***Imaging:*** MRI: T1-hypo- & T2-hyperintense cystic perivascular lesions (accumulations of within the foam cells in the Virchow–Robin space). X-rays: persistent biconvexity of the vertebral bodies & very thick calvarium. ***Labs:*** Large amounts of urinary heparan sulfate w/ absent dermatan sulfate. ***Biopsy:*** Skin for enzyme assay in cultured fibroblasts. ***Definitive dx:*** Low enzyme activity in cultured fibroblast. Genetic mutation analysis (*SGSH, NAGLU, HGSNAT, GNS*). Prenatally: amniocentesis.

Rx: Symptomatic. VP-shunt for nonresponsive severe behavioral symptoms. Experimental bone marrow transplant.

Sly (MPS VII)[19]

Defect: Beta-glucuronidase deficiency, *GUSB* gene.

FHx: AR.

Presentation: Variable onset, usually between age 1 and 3 y w/ mental regression, but can present in young adulthood or at birth. Spastic tetraplegia w/ hyperactive DTR & Babinski reflex from cervical spinal cord lesions are common.

Other si/sx: Hepatomegaly, skeletal anomalies, coarse facies, corneal clouding (Hurler-like).

Prognosis: Variable, hydrops fetalis to survival into adulthood, but w/ significant mental disability.

Dx: ***Imaging:*** Cervical MRI & CT scans showed a dense pseudoarthrosis w/ odontoid dysplasia, a hypoplastic atlantal arch. ***Labs:*** Increased urinary excretion of glycosaminoglycans (dermatan, chondroitin, & heparan sulfate). ***Biopsy:*** Skin for enzyme assay in cultured fibroblasts. ***Definitive dx:*** Low enzyme activity in cultured fibroblast. *GUSB* gene mutations. Prenatal dx from amniocentesis.

Rx: Experimental allogeneic bone marrow transplant improves extra CNS symptoms

Disorders of Intermediary Metabolism: Organic Acidemias

Propionic Acidemia[20] *(infantile form & adult form)*

Defect: Propionyl-CoA carboxylase deficiency, *PCCA* and *PCCB* genes.

FHx: AR.

Presentation: *Infantile form:* normal at birth, hypotonia, difficulty feeding, dehydration, recurrent episodes of metabolic acidosis–coma w/ ketosis, massive ICH, chorea in those that survive, basal ganglia necrosis. *Adult form:* chorea, dementia, mental retardation, acute episodes of confusion–coma w/ ketosis.

Other si/sx: Ketotic hyperglycinemia w/ hyperammonemia, acute episodes of nausea and bleeding diathesis, hepatomegaly in 28% of infantile form.

FHx: AR.

Dx: ***Imaging:*** Some have T2-hyperintense symmetric involvement of the basal ganglia (globus pallidus), widening of cerebrospinal fluid spaces, some delay in myelination in infantile form. ***Labs:*** Urine organic acids: increased 3-hydroxy propionate, propionylglycine, methylcitrate, tiglylglycine. Plasma: Increased propionylcarnitine, elevated acetylcarnitine:carnitine ratio. Low enzyme activity in leukocytes & fibroblasts. ***Biopsy:*** Skin for enzyme assay in cultured fibroblasts. ***Definitive dx:*** Newborn screening, enzyme analysis of cultured fibroblast. *PCCA* and *PCCB* mutation analysis.

Rx: Diet low in branched-chain amino acids. Metabolic crisis: IVF, bicarbonate, glucose, dialysis, ammonia scavengers (sodium benzoate, sodium phenylacetate).

Glutaric Aciduria Type I (infantile form[21] & adult onset[22])

Defect: Glutaryl-CoA dehydrogenase deficiency, *GCDH* gene.

FHx: AR.

Presentation: *Infantile form:* macrocephaly, orofacial dyskinesias, headache, supranuclear ophthalmoparesis and epilepsy. Choreathetosis and dystonia if basal ganglia necrosis occurs. *Adult onset:* macrocephaly, orofacial dyskinesias, headache, dementia, seizures, dystonia, ataxia, and supranuclear ophthalmoparesis.

Other si/sx: Retinal hemorrhages.

Prognosis: Variable, severe disability common and correlates w/ acute onset & mortality. Many patients die in childhood, but some survive into early adulthood.

Dx: ***Imaging:*** Temporal pole atrophy, bilateral basal ganglia involvement w/ T2-hyerintense lenticular nucleus (necrosis—"bat wing") ± subdural hematomas (infantile). ***Labs:*** Urine: high 3-hydroxyglutaric acid, 3-hydroxyglutaric acid and gluconate. ***Biopsy:*** Skin for enzyme assay in cultured fibroblasts. ***Definitive dx:*** Newborn screening, enzyme analysis of cultured fibroblast, *GCDH* mutation analysis.

Rx: L-carnitine and riboflavin (B2), diet restricted in lysine, trihexyphenidyl for focal dystonia.

Glutaric Aciduria Type II[23] (variable onset)

Defect: Multiple acyl-coA dehydrogenase deficiency producing ETC riboflavin complex deficiency. Caused by mutations in at least three different genes: *ETFA* (GAIIA), *ETFB* (GAIIB), and *ETFDH* (GAIIC).

FHx: AR.

Presentation: Suspect in any child w/ lipid-storage myopathy. Onset varies, presents as episodic vomiting, recurrent episodes of muscle weakness and hypoglycemic coma w/ febrile illnesses. Progressive spastic ataxia.

Other si/sx: Recurrent episodes of severe hypoglycemia, fatty infiltration of the liver, muscle, and heart. Congenital bilateral polycystic kidneys. Atrophic thymus.

Prognosis: Good if dietary modifications made early.

Dx: ***Imaging:*** Leukodystrophy w/ bilateral temporal lobe atrophy. ***Labs:*** Elevated urinary glutaric, lactic, ethylmalonic, butyric, isobutyric, 2-methyl-butyric, & isovaleric acids. ***Biopsy:*** Skin for enzyme assay in cultured fibroblasts, postmortem fatty acid composition analysis. ***Definitive dx:*** Newborn screening, enzyme analysis of cultured fibroblast, genetic analysis (*ETFA, ETFB, ETFDH*).

Rx: Riboflavin (B_2), tryptophan; low-fat diet reduced the episodes of muscle weakness.

Methylmalonic Acidemia[24]

Defect: Heterogeneous disorder of cobalamin (cbl; vitamin B_{12}) metabolism due to deficiency of methylmalonyl-CoA mutase (*MUT*), defects in transport or synthesis of its cofactor, adenosyl-cobalamin (cblA, cblB, cblD) or deficiency of methylmalonyl-CoA epimerase (*MCEE*).

FHx: AR.

Presentation: Episodic vomiting, lethargy, encephalopathy, & recurrent strokes.

Other si/sx: Chronic metabolic acidosis, chronic renal failure.

Prognosis: Depends on mutation. cblA defect has good prognosis w/ survival into adulthood

Dx: ***Imaging:*** Leukomalacia, sequelae of prior strokes or acute stroke, pronounced calcified atherosclerosis of intra- and extracranial vessels. ***Labs:*** Elevated urinary methylmalonic acid and methylcitrate w/ or w/o elevated urine and plasma homocysteine; decreased plasma methionine. ***Biopsy:*** Skin for enzyme assay in cultured fibroblasts. ***Definitive dx*:** Mutation analysis and enzymatic assay of cultured fibroblasts.

Rx: *In vivo* responsiveness to vitamin B_{12} (cobalamin) should be determined in all affected individuals. Acute: restore volume and acid–base status, reduce protein intake, increase glucose to arrest catabolism. Chronic management: high-calorie diet low in propiogenic amino acid precursors; B_{12} injections, carnitine supplementation.

Isovaleric Acidemia[25]

Defect: Isovaleryl-CoA dehydrogenase deficiency; *IVD* mutations.

FHx: AR.

Presentation: *Acute neonatal form:* massive metabolic acidosis, vomiting, lethargy, and death. *Chronic form:* attacks of severe ketoacidosis w/ retarded psychomotor development.

Other si/sx: A peculiar odor resembling sweaty feet, aversion to dietary protein, pernicious vomiting.

Prognosis: Variable depending on age of onset, severity of enzyme deficiency, and delay to treatment. Ranges from infantile death to little disability and survival into late adulthood.

Dx: ***Labs:*** Increased urinary isovaleryl-lysine. ***Biopsy:*** Skin for enzyme assay in cultured fibroblasts. ***Definitive dx****: IVD* mutational analysis & enzymatic assay of cultured fibroblasts. Newborn screening.

Rx: Restriction of leucine intake, oral glycine, and L-carnitine supplementation can be useful in management.

Biotinidase Deficiency[26] (Late-onset Biotin-Responsive Multiple Carboxylase Deficiency)

Defect: Biotinidase deficiency, deficient biotin absorption; *BTD* mutations.

FHx: AR.

Presentation: Onset several days to 3 mo after birth w/ seizures & hypotonia, followed by ataxia and mental retardation.

Other si/sx: Dermatitis, alopecia, recurrent infections, SNHL hearing loss.

Prognosis: Coma then death, but depends on initiation of treatment and compliance.

Dx: ***Labs:*** Elevated 3-hydroxyisovaleric acid and 3-hydroxypropionic acid. Ketoacidosis and hyperammonemia. ***Definitive dx:*** Serum biotinidase activity $<10\%$.

Rx: Early biotin replacement reverses most symptoms & may prevent mental retardation.

Disorders of Intermediary Metabolism: Aminoacidopathies and Neurotransmitter Disorders

Homocystinuria[27]

Defect: Cystathionine beta-synthase deficiency; *CBS* gene mutations.

FHx: AR.

Presentation: Variable onset w/ mental retardation, psychiatric disorders, epilepsy, strokes, venous sinus thrombosis and characteristic accompanying physical features.

Other si/sx: Lens dislocation $\pm$ pupillary block, glaucoma, Marfan-like appearance, hypopigmentation, thromboembolic events, acute pancreatitis.

Prognosis: Depends on delay to treatment. Patients often disabled or die from recurrent thromboembolism.

Dx: ***Imaging:*** Leukomalacia sequelae of prior strokes, pronounced calcified atherosclerosis of intra- and extracranial vessels. ***Labs:*** Hyperhomocysteinemia >100 mmol/L, hypermethioninemia. Elevated urinary homocysteine and methionine. Total urinary homocysteine, after methionine loading, is the most sensitive screening test. ***Definitive dx:*** Neonatal screening, *CBS* mutational analysis.

Rx: Vitamin B_6, protein-restricted diet, vitamin C, ameliorates endothelial dysfunction.

Glycine Encephalopathy[28] (Nonketotic Hyperglycinemia [NKH])

Defect: Mitochondrial glycine cleavage system. 70% to 75% *GLDC* (glycine dehydrogenase; 9p24.1); ~20% *AMT* (aminomethyltransferase; 3p21.31); $<1\%$ (*GCSH* (glycine dehydrogenase) mutations.

FHx: AR.

Presentation: Majority present in neonatal period (85% severe, 15% mild forms). *Acute signs:* paroxysmal movement disorders, intractable seizures, encephalopathy, supranuclear gaze palsy. *Chronic signs:* seizures, mental retardation, dementia, cerebellar ataxia, motor neuropathy, optic atrophy.

Prognosis: Infantile death common. Those who survive typically have severe mental retardation.

Dx: ***Labs:*** Elevated plasma, urine, and CSF glycine. Elevated CSF/plasma glycine ratio (>0.08 μmol/L). ***Biopsy:*** Liver for glycine cleavage enzyme analysis. *EEG:* burst-suppression pattern evolving into multifocal spikes and then hypsarrhythmia by 3 mo. ***Definitive dx:*** Liver biopsy and comprehensive mutation analysis (*GLDC, AMT, GCSH*).

Rx: Sodium benzoate, dextromethorphan, ketamine. AEDs (except valproate, which increases CSF glycine). L-carnitine supplementation.

Phenylketonuria and Hyperphenylalaninemia[29]

Defect: Deficiency of phenylalanine hydroxylase, *PAH gene.*

FHx: AR.

Presentation: Normal at birth w/ hyperphenylalaninemia 48 to 72 h after feeding starts, developmental delay, 25% seizures. Children w/ MR, aggressiveness, and hyperactivity.

Other si/sx: Musty odor of the urine, blond hair, pale skin, blue eyes due to lack of pigment, eczema.

Prognosis: Depends on severity of disease and delay to treatment.

Dx: ***Imaging:*** Progressive calcifications of the basal ganglia. ***Labs:*** Elevated plasma phenylalanine and tyrosine (if >15 g/dL in urine—green after ferric chloride solution is added). ***Definitive dx*:** NBS, enzymatic analysis, prenatal DNA analysis of chorionic villi biopsy or amniocentesis.

Rx: Phenylalanine-restricted diet if plasma phenylalanine >20 mg/dL w/ goal of 4 to 6 mg/dL to prevent cognitive decline. Tetrahydrobiopterin for those patients w/ BH_4 deficiency.

Maple Syrup Urine Disease[30] *(MSUD)*

Defect: Deficiency of branched-chain alpha-keto acid dehydrogenase complex proteins. 45% *BCKDHA* (MSUD type 1A; 19q13.2); 35% *BCKDHB* (MSUD type 1B; 6q14.1); 20% *DBT* (MSUD type 2; 1p21.2) mutations.

FHx: AR.

Presentation: Normal at birth; from 5 mo to 2 y, stress (infection, surgery, high-protein diet) triggers attacks of ataxia, irritability, and progressive lethargy. May lead to severe metabolic acidosis. Survivors have near-normal psychomotor development.

Other si/sx: Maple syrup odor of urine during attacks.

Prognosis: Variable. In mild cases, only moderate retardation results. In severe, infantile death occurs.

Dx: ***Labs:*** Elevated plasma and urine branched-chain amino acids (leucine, isoleucine, valine; allo-isoleucine) and ketonuria, only during attacks. ***Biopsy:*** Skin for enzyme assay in cultured fibroblasts. ***Definitive dx:*** Enzyme assay in cultured fibroblasts, lymphoblasts.

Rx: Attacks: reverse ketoacidosis (peritoneal dialysis use in life-threatening acidosis). Protein-restricted diet. Thiamine (1 g qd) during attacks, followed by 100 mg/d.

GTPHC 1 Deficiency[31] *(Segawa Disease)*

Defect: GTP-cyclohydrolase 1 deficiency, *GCH1* gene mutations.

FHx: AD.

Presentation: Variable onset w/ dystonia, parkinsonism, pseudospastic paraparesis (dystonia) w/ diurnal fluctuations, mental retardation, and depression.

Other si/sx: Sleep disturbances/hypersomnolence and hyperphagia.

Prognosis: Variable. Characterized by its dramatic responsiveness to L-dopa.

Dx: ***Labs:*** CSF-low or normal biopterins, neopterins, HVA (homovanillic acid), & 5-HIAA (5-hydroxyindoleacetic acid). Abnormal phenylalanine-loading test. ***Definitive dx:*** GTPCH1 gene mutations.

Rx: L-dopa, anticholinergic drugs, dopamine agonists.

Tyrosine Hydroxylase Deficiency[32]

Defect: Tyrosine hydroxylase deficiency; mutations in *TH* gene.

FHx: AR.

Presentation: Dystonia, parkinsonism, pseudospastic paraparesis, pyramidal signs, mental retardation, and progressive encephalopathy.

Prognosis: Encephalopathy is not L-dopa responsive and often progresses to coma and death.

Dx: ***Labs:*** CSF-low HVA w/ normal biopterins, neopterins, & 5-HIAA. ***Definitive dx:*** Genetic testing (*TH*) & TH enzyme activity analysis.

Rx: L-dopa (for dystonia & parkinsonism), anticholinergic drugs, dopamine agonists.

Glucose Transporter Type-1 Deficiency Syndrome[33] *(GLUT1-DS)*

Defect: GLUT1 transporter deficiency; *SLC2A1* (solute carrier family 2, facilitated glucose transporter member 1) mutations. Includes Dystonia 18 and Dystonia 9.

FHx: AD and sporadic.

Presentation: Classic: onset in first few months of life w/ epilepsy resistant to AEDs (atypical childhood absence/myoclonic epilepsy), followed by developmental delay, acquired microcephaly. Other clinical features (along continuum): intermittent ataxia, choreathetosis, dystonia, and alternating hemiplegia. Symptoms are triggered by fasting. Milder phenotypes exist.

Prognosis: Variable depending on severity of disease phenotype.

Dx: ***Labs:*** Hypoglycorrhachia—CSF/BL glucose ratio <0.4 (normal > 0.6). EEG: 2.5- to 4-Hz spike-wave improving w/ food. ***Definitive dx:*** *SLC2A1* mutation analysis.

Rx: Ketogenic diet, avoid fasting.

Biotin-Responsive Basal Ganglia Disease[34]

Defect: Defect in the transporter of biotin across the BBB; *SLC19A3* gene mutations.

FHx: AR.

Presentation: Onset in childhood w/ acute signs of encephalopathy, coma, epilepsy, rigidity, and sometimes chronic dystonia.

Prognosis: Very good w/ patients returning to baseline within days of treatment.

Dx: ***Imaging:*** Bilateral head of caudate & putamen T2 hyperintensity. ***Definitive dx****: SLC19A3* mutation analysis.

Rx: Biotin 5 to 10 mg/kg/d.

Cerebral Folate Deficiency[35]

Defect: Unknown, possible autoantibodies against folate receptors, possibly congenital.

FHx: Sporadic cases only.

Presentation: Normal development until 4 mo, then delayed head growth, followed by hypotonia, dyskinesias, cerebellar ataxia, deafness, spinal amyotrophy, and eventually, spasticity.

Prognosis: Severe disability w/ spastic tetraplegia.

Dx: ***Imaging:*** Progressive basal ganglia and other subcortical calcifications. ***Labs:*** CSF: Low 5-methyltetrahydrofolate, normal folate in blood. ***Definitive dx****:* Low 5-methyltetrahydrofolate in CSF that normalizes w/ folinic acid supplementation.

Rx: Folinic acid (enters CSF).

Biopterin Disorders[36]

Suspect in patient with movement disorder, psychomotor regression, and persistent elevated phenylalanine, despite low-phenylalanine diet ("atypical PKU").

Sepiapterin Reductase Deficiency[37]

Defect: Sepiapterin reductase deficiency, component of tetrahydrobiopterin (BH_4) synthetic pathway, severe dopamine and serotonin deficiencies; *SPR* gene mutations.

FHx: AR.

Presentation: Progressive psychomotor retardation, dopa-responsive dystonia (diurnal fluctuations), hypersomnolence.

Dx: ***Labs:*** CSF- elevated biopterins (biopterin, dihydropterin), low HVA, low 5-HIAA, without hyperphenylalanemia. ***Definitive dx****: SPR* mutational analysis.

Rx: Low-phenylalanine diet. L-dopa, 5-hydroxytrytophan (5-HTP)

Tetrahydrobiopterin (BH_4) Synthase Deficiency[38]

Defect: Deficient BH_4 as cofactor for multiple enzymes: phenylalanine hydroxylase (PAH), tyrosine hydroxylase (TH), tryptophan hydroxylase (TPH1), hyperphenylalanemia. Most common form is $HPABH_4A$—6-pyruvoyltetrehydrobioterin synthase (PTS) deficiency, *PTS* gene mutations; others include: $HPABH_4B$—GTP-cyclohydrolase deficiency, *GCH1* gene mutations; $HPABH_4C$—dihydropteridine reductase (DHPR) deficiency, *QDPR* gene mutations; $HPABH_4D$—pterin-4-alpha-carbinolamine dehydratase (PCBD) deficiency, *PCBD* gene mutations.

FHx: AR.

Presentation: Dystonia (generalized or paroxysmal; diurnal fluctuation), psychomotor retardation, extrapyramidal signs.

Other si/sx: Axial hypotonia, truncal instability, chorea, oculogyric crises.

Prognosis: Depends on delay to treatment. Progressive psychomotor deterioration and swallowing difficulties can lead to death.

Dx: ***Imaging:*** Spongy vacuolation of brainstem, diffuse demyelination, progressive basal ganglia, and other subcortical calcifications. ***Labs:*** Hyperphenylalaninemia, CSF: low biopterin, 5-HIAA and HVA, elevated neopterins. Urine: low pterins. ***Definitive dx*:** Phenylalanine-loading studies and assay of GTP-cyclohydrolase I activity in the liver.

Rx: Low-phenylalanine diet, BH_4, L-dopa, 5-HTP.

Dihydropteridine Reductase Deficiency[39] (DHPR)

Defect: Dihydropteridine reductase deficiency (DHPR, enzyme in the salvage pathway for BH_4), *QDPR* gene mutations.

FHx: AR

Presentation: Fluctuating and progressive encephalopathy with mental retardation; epilepsy; and extrapyramidal (dystonia), pyramidal, and cerebellar signs.

Dx: ***Imaging:*** Spongy vacuolation of brainstem, diffuse demyelination, progressive basal ganglia, and other subcortical calcifications (if folate not replaced). ***Labs:*** Hyperphenylalaninemia; CSF—elevated biopterins, low HVA, low 5-HIAA. ***Definitive dx:*** *QDPR* gene mutations, prenatal diagnosis.

Rx: Low-phenylalanine diet; L-dopa, 5-HTP.

Disorders of Amino Acid Transport

Hartnup Disease[40]

Defect: Failed amino acid transport in kidney and intestine, *SLC6A19* gene. Same incidence as PKU, but rarely seen in the U.S. due to high-protein diet.

FHx: AR.

Presentation: Normal at birth, then intermittent episodes of cerebellar ataxia w/ nystagmus, emotional instability to AMS triggered by stress.

Other si/sx: Pellagra-like light-sensitive rash, liver cirrhosis, aminoaciduria.

Prognosis: Good with treatment. Patients often have average life expectancy.

Dx: ***Labs:*** Monoamino-monocarboxylic aciduria and defects in the intestinal absorption of monoamino-monocarboxylic acids, as determined by oral loading. ***Definitive dx*:** *SLC6A19* mutation analysis.

Rx: Daily oral nicotinamide (50–300 mg/d) may reverse skin and neurological complications, high-protein diet.

Lowe Disease[41] (oculocerebrorenal syndrome)

Defect: Amino acid transporter deficiency (inositol polyphosphate 5-phosphatase), expressed in the eye, kidney, and brain, *OCRL* gene mutations.

FHx: X-linked recessive (females may be affected if skewed X inactivation).

Presentation: Hypotonia w/ hyporeflexia & bilateral cataract in newborns, followed by Fanconi-like renal disease (proteinuria, generalized aminoaciduria, carnitine wasting, phosphaturia) and mental retardation. Behavioral disorder (tantrums, stubbornness, stereotypies) in milder forms that survive to adulthood.

Other si/sx: Hydrophthalmia, vitamin D–resistant rickets, aminoaciduria;

Prognosis: Most infants die, most who survive are moderately/severely mentally retarded, some with near-normal IQ.

Rx: ***Imaging:*** MRI diffuse T2 hyperintensity in white matter. ***Labs:*** Renal tubular acidosis. ***Definitive dx:*** Clinical triad. Mutation analysis is limited to families in which the *OCRL* mutation is known.

Rx: Alkalinization therapy, potassium, phosphate, calcium, and L-carnitine supplementation.

Urea Cycle Disorders[42]

Hyperammonemia resulting from multiple defects of enzymes and cofactors involved in urea synthesis: most common inborn error of metabolism, 1:8,000.

Defect: 5 catalytic enzymes: Carbamoyl phosphate synthase I deficiency (*CPS1*), ornithine transcarboxylase deficiency (*OTC*), arginase deficiency (*ARG*), argininosuccinic acid lyase (*ASL*), argininosuccinic acid synthetase (ASS1); cofactor: *N*-acetylglutamic synthase deficiency (*NAGS*).

FHx: All AR, except OTC (X-linked).

Presentation: *Newborns:* progressive lethargy, vomiting (plasma $NH_3 > 200$ μg/dL), and hypotonia starting on 1st day of life (even before protein feeding); leading to coma ($NH_3 > 300$ μg/dL) and seizures ($NH_3 > 500$ μg/dL). *Infants/children*: FTT, feeding problems, vomiting, lethargy, ataxia, and seizures. *Adults*: chronic psychiatric symptoms, altered mental status, lethargy, psychosis.

Prognosis: Variable depending on onset.

Dx: ***Imaging:*** Ultrasound, CT, or MRI with cerebral edema. ***Labs:*** Hyperammonemia >150 μg/dL + no acidosis + normal anion gap + normal glucose. Elevated plasma amino acids. ***Biopsy:*** Liver for enzyme assay. **Definitive dx**: Enzymatic assay of cultured hepatocytes, NBS (MS/MS); genetic analysis (multigene panels).

Rx: Limit nitrogen intake to 1.2 to 2 g/kg/d of essential amino acids. Sodium benzoate and phenylacetic acid (alternative NH_3 pathway), reduce catabolism with calories from carbohydrates and fats, arginine supplementation (except in argininase deficiency) (see hyperammonemia algorithm, Fig. 7.2).

Disorders of Carbohydrate Metabolism

Galactosemia[43]

Defect: Deficiency of galactose-1-phosphate uridylyltransferase, *GALT* gene mutations; galactose epimerase deficiency, *GALE* gene mutations.

FHx: AR.

Presentation: Newborns w/ cataracts, vomiting, diarrhea (after 1st feeding), FTT. Neonatal death due to *E. coli* sepsis is common). Signs of increased ICP.

Other si/sx: Cataracts, hepatomegaly, jaundice.

Prognosis: Progressive truncal ataxia w/ coarse resting tremor of limbs. If not treated, can also result in severe mental retardation.

Dx: ***Imaging:*** Cranial ultrasound shows cerebral edema. ***Labs:*** Elevated urine reducing substances after feeding, glycosuria, albuminuria. Slit-lamp examination—punctate cataracts. ***Definitive dx*:** NBS, low erythrocyte galactose-1-phosphate uridyltranferase. *GALT* mutation analysis for carriers.

Rx: Immediate replacement of milk w/ lactose-free formula. IQ is low in many despite early and seemingly adequate therapy.

Glycogen Storage Diseases[44]

Defect: Defects of glycogen synthesis or catabolism leading to spectrum of phenotypes: severe hypoglycemia (neonatal), hepatomegaly, lactic acidosis, hypoglycemic seizures (infantile) to juvenile/adult exercise intolerance and skeletal muscle insufficiency (cramps, weakness).

GSD Ia—Von Gierke: glucose-6-phosphatase deficiency (80% cases) (*G6PC*)
GSD Ib—glucose-6-phosphate translocase defect (20% cases) (*SLC37A4*)
GSD II—Pompe: acid alpha-1,4-glucosidase deficiency (*GAA*)
GSD III—Cori: glycogen debranching enzyme deficiency (*AGL*)
GSD IV—Andersen: glycogen branching enzyme deficiency (*GBE1*)
GSD V—McArdle: myophosphorylase deficiency (*PYGM*)
GSD VI—Hers: hepatic phosphorylase deficiency (*PYGL*)
GSD VII—Tauri: muscle phosphofructokinase deficiency (*PFKM*)
GSD IXa—alpha subunit of phosphorylase kinase deficiency (*PHKA2*)
GSD IXb—beta subunit of phosphorylase kinase deficiency (*PHKB*)
GSD IXc—phosphorylase kinase deficiency (*PHKG2*)
GSD IXd—muscle phosphorylase kinase deficiency (*PHKA1*)
GSD X—phosphoglycerate mutase deficiency (*PGAM2*)
GSD XI—lactic dehydrogenase A deficiency (*LDHA*)
GSD XIII—beta-enolase deficiency (*ENO3*)
GSD XIV—phosphoglucomutase 1 deficiency (*PGM1*)

FHx: AR.

Presentation: Skeletal myopathy, myalgias, cardiomyopathy (type I), respiratory compromise. Type V (after exercise) (type XI, XIII)—often present only w/ muscle weakness.

Other si/sx: Growth retardation, short stature, hepatomegaly (liver adenomas type I), cardiomegaly (type II-infantile), xanthomas, & gout (type I). Late-onset Pompe does not have cardiac involvement but may have respiratory compromise first seen in supine position (do lying and sitting PFTs).

Prognosis: Variable. Type I, II (juvenile or late-onset forms), III, and V survive to adulthood.

Dx: ***Labs:*** ↑ CPK, ↑ uric acid (type I), myoglobinuria, EMG: myopathic changes or normal. ***Biopsy:*** Liver & muscle biopsy. ***Definitive dx:*** Enzymatic activity in erythrocytes, hepatocytes, or muscle. Mutational analysis (gene panel testing available).

Rx: High-protein diet, creatine supplementation, moderating level of exercise. Enzyme replacement therapy is available for some. Experimental BMT.

Lipid Metabolism Disorders

Cerebrotendinous Xanthomatosis[45] *(CTX)*

Defect: Deficiency of sterol 27-hydroxylase, (*CYP27A1*).

FHx: AR.

Presentation: Infantile-onset diarrhea, childhood-onset cataracts, juvenile- to young adult-onset tendon xanthomas (first on Achilles); adult: dementia, psychiatric disturbances, progressive ataxia and spasticity, dysphagia & dysarthria. Other si/sx: atypical PD, dystonia, peripheral neuropathy, seizures, myocardial infarction from premature atherosclerosis.

Prognosis: Severe disability w/o treatment.

Dx: ***Imaging:*** Cerebral and/or cerebellar atrophy. MRI focal hyperintense lesions (xanthomata; cholestanol storage) prominent in cerebellum but seen in cerebral, brainstem, or basal nuclei; abnormal white matter signal. ***Labs:*** Increased plasma and tissue cholestanol, low or normal cholesterol, increased urinary bile acids, chenodeoxycholic acid absent in bile. NCV: decreased velocities (demyelinating pattern). ***Biopsy:*** Tendon xanthomas (virtually every tissue has accumulation of cholestanol, skin for enzymatic analysis of culture fibroblasts. ***Definitive dx*:** *CYP27A1* mutation analysis. Enzyme activity in cultured fibroblasts.

Rx: Chenodeoxycholic acid 750 mg/d, inhibitors of HMG-CoA reductase (may cause muscle damage).

Neuronal Ceroid Lipofuscinosis Disorders[46] (NCL)

A group of neurodegenerative disorders (Batten disease; usually onset in early childhood) characterized by variant combinations of seizures, visual failure/blindness, dementia/development failure, and movement disorder that are associated with deficiency/dysfunction of at least 14 proteins in the lysosomal/autophagy pathways and characterized by lysosomal inclusions (Table 7.7). Juvenile- adult-onset types do not evidence visual failure.

Incidence: As a group, most common neurodegenerative disorder of childhood; 1 to 2.5/100,000, panethnic with enrichment in some populations (Scandinavian).

FHx: AR, except AD in some adult-onset forms.

Dx: Pathologic inclusions (granular, fingerprint, curvilinear) by EM ***Definitive dx:*** Enzyme testing (PPT1/CLN1; TPP1/CLN2) or by molecular testing (gene panels available).

Prognosis: Significant morbidity, early death.

Rx: Symptomatic management of seizures, behavioral difficulties, encephalopathy with blindness, spasticity, inability to feed orally; gene therapy trials ongoing (CLN2; intracerebral injections); enzyme replacement therapy trials (CLN2); immune modulatory therapy (CellCept; CLN3). Past stem cell therapy trials (intracerebral injections) were not successful.

Cholesterol Storage Disease: Smith–Lemli–Opitz Disease[47]

Defect: 7-dehydrocholesterold reductase deficiency (*DHCR7*).

FHx: AR.

Presentation: Pre- and postnatal growth retardation, microcephaly, moderate-to-severe cognitive failure and somatic malformations.

Other si/sx: Characteristic facial features: temporal narrowing, epicanthal folds, blepharoptosis, a broad nasal bridge and short nasal root, anteverted nares, cleft palate (40%–50%), often low-set and posteriorly rotated ears, and micrognathia; polydactyly, 2 to 3 toe syndactyly, ambiguous genitalia or hypospadius (males), severe congenital heart defect; behavioral problems (irritability, hyperactivity, self-injurious behavior); ASD (45%–55%); decreased sleep requirement.

Prognosis: Most patients do not survive infancy; some milder cases with subtle facial features, hypotonia, syndactyly, mild DD. **Dx:** ***Labs:*** Low levels of cholesterol (15%–27% of normal) and very high levels of

TABLE 7.7 The Neuronal Ceroid Lipofuscinosis Disorders

Disease	Prior Designation	OMIM No.	Inherit	Gene	Age of Onset	Clinical Phenotype	Early Symptoms and Signs	Usual Survival	EM Inclusions
CLN1	INCL	256730	AR	*PPT1*	6–24 mo	Classic infantile	Developmental failure, seizures, myoclonus, visual failure	2–6 y	GROD
					2–4 y	Late infantile	dev regression, seizures, visual failure	5–12+ y	GROD
					4– 6 y	Juvenile	Visual failure, seizures, behavioral, dementia	10–20 y	GROD
CLN2	cLINCL	204500	AR	*TPP1*	2–4 y	Classic late infantile (juvenile)	Malignant seizures, myoclonus, developmental & visual failure	6–12+ y	CL
CLN3	JNCL	204200	AR	*CLN3*	3–8 y	Classic juvenile	Visual failure, dementia, behavioral and motor difficulties, late seizures	20–40 y	vacuolated lymphs, FP
CLN4	Kufs [Parry type]	162350	AD	*DNAJC5*	teenage –30+	Juvenile to adult	Dementia, seizures, myoclonus, without visual loss	5–20 y	GROD
CLN5	fLINCL	256731	AR	*CLN5*	3–7 y	Variant late infantile (juvenile, adult)	Behavior abnl, cognitive decline, seizures, visual failure, myoclonus, motor difficulties	teenage+	CL, FP, RL
CLN6	vLINCL	601780	AR	CLN6	1.5–8 y	Variant late infantile	Visual failure, cognitive decline, seizures, myoclonus	teenage+	FP, CL
	Kufs, type A		AR		16–51 y	Adult-onset	Progressive myoclonic epilepsy		FP, GROD

CLN7	vLINCL	610951	AR	*MFSD8*	1.5–6 y	Variant late infantile (juvenile, adult)	Visual failure, dementia, seizures, myoclonus	teenage+	RL, FP
CLN8	vLINCL	600143	AR		1.5–7 y	Variant late infantile	Myoclonic seizures, visual failure, ataxia, cognitive decline	teenage+	GROD, CL (FP)
	EPMR	610003	AR	CLN8	5–10 y	Northern epilepsy	Seizures, slow dementia without visual loss	40+	GROD, CL
CLN10	CNCL	610127	AR	*CTSD*	Neonatal	Congenital (late infantile, adult)	Epileptic encephalopathy, microcephaly	< 1 y	GROD
CLN11		614706	AR	*GRN*	early 20s	Adult	Visual failure, myclonic seizures, ataxia, dementia	30+	FP
	FTLD-GRN	607485	AD		35–65 y	Adult	Myoclonic seizures, ataxia, cognitive decline	50+s	TDP-43
CLN12	Kufor-Rakeb	606693	AR	*ATP13A2*	8–12 y	Juvenile	parkinsonism, ataxia, dementia	30+	FP
CLN13	Kufs, type B		AR	*CTSF*	20–30 y	Adult	Movement abnl (ataxia, tremor) and dementia, rare seizures		FP (brain)
CLN14		611726	AR	*KCTD7*	8–9 mo	Infantile	Seizures, motor & speech regression, visual failure	teenage	FP (GROD)
	EPM3		AR		10 mo–3 y	Late infantile	without visual loss		none

7-dehydrocholesterol. **Biopsy:** Skin for enzyme assay. ***Definitive dx:*** Usually biochemical w/ cholesterol profile. Analysis of cultured skin fibroblasts is available. *DHCR7* mutational analysis, prenatal diagnosis.

Rx: Exogenous cholesterol (20–40 mg/kg/d).

Other Metabolic Neurological Diseases

Lesch–Nyhan Syndrome[48]

Defect: Hypoxanthine guanine phosphoribosyltransferase deficiency (*HPRT1*).

FHx: XR.

Presentation: Hypotonia at birth, followed by developmental delay and poor head control in first few months, then progressive axial dystonia in 1st y, chorea, ballism, spasticity in 2nd y and slowly progressive dementia, compulsive behaviors/self-mutilation after age 2 y.

Other si/sx: Compulsive self-mutilation (tongue, lips, fingers, & thrusting arms & legs), gout or nephrolithiasis.

Prognosis: Childhood death.

Dx: ***Labs:*** Elevated plasma and urine uric acid. ***Biopsy:*** Skin for enzyme assay in cultured fibroblasts. ***Definitive dx*:** Ultra-microassay of HPRT of chorionic villi sampled at ~10 wk of gestation; HPRT enzyme activity <1.5% normal in fibroblasts or leukocytes.

Rx: Symptomatic, allopurinol (gout), benzodiazepines, carbamazepine, SSRIs (behavior), L-dopa and deep brain stimulation (dystonia), restraints & removal of dentition.

Cockayne Syndrome[49] *(CS)*

Defect: Defects in the DNA excision repair (NER) system; CSA—ERCC8 (35% of cases); CSB—ERCC6 (65% of cases); mutations in respective genes, *ERCC8* or *ERCC6.*

FHx: AR.

Presentation: Profound global growth and progressive development failure; premature, accelerated, pathologic aging, and neurodegeneration.

Other si/sx: Cutaneous photosensitivity, ocular abnormalities (cataracts, progressive pigmentary retinopathy, decreased lacrimation, mitotic pupils), sensorineural deafness, dental caries, physical appearance of cachectic dwarf. **Prognosis**: Late childhood death.

Dx: ***Labs:*** Normal karyotype. ***Imaging:*** Leukodystrophy and/or mineralization of basal ganglia. ***Biopsy:*** Assay cultured fibroblasts—delay recovery of RNA synthesis after irradiation with UV light. ***Definitive dx:*** *ERCC6 or ERCC8* mutational analysis. Consider XP complementation group B, D, G if negative molecular testing.

Rx: Symptomatic, avoid sun or use sunscreen creams with SPF 50 to 100. Avoid valproic acid for seizure therapy.

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8 Mitochondrial Energy Metabolism Disorders

Patricia L. Musolino and Katherine B. Sims

INTRODUCTION

Mitochondrial oxidative-phosphorylation diseases are a clinically heterogeneous group of disorders that arise primarily as a result of dysfunction of the mitochondrial respiratory chain (electron transport chain [ETC]) and can present at any age. More than 70 different polypeptides interact on the inner mitochondrial membrane to form the respiratory chain. The vast majority of subunits are synthesized within the cytosol from nuclear DNA (nDNA) transcripts, but 13 essential subunits are encoded by the 16.5-kb mitochondrial DNA (mtDNA). See Figure 8.1.

CLINCAL PRESENTATION

Because of the presence of mitochondrial heteroplasmy (different amounts of mutant mitochondria) in different cells and tissues, some mitochondrial disorders may affect a single organ but more commonly involve multiple organ systems. Many disorders present with prominent neurologic (central, peripheral, and autonomic) as well as myopathic features. Moreover, variant mtDNA and nDNA mutations can present with the same clinical syndrome, or a single mutation can lead to different combinations of signs and symptoms. Common clinical features of mitochondrial disease include encephalopathy, seizures, dementia, migraine, stroke-like episodes,

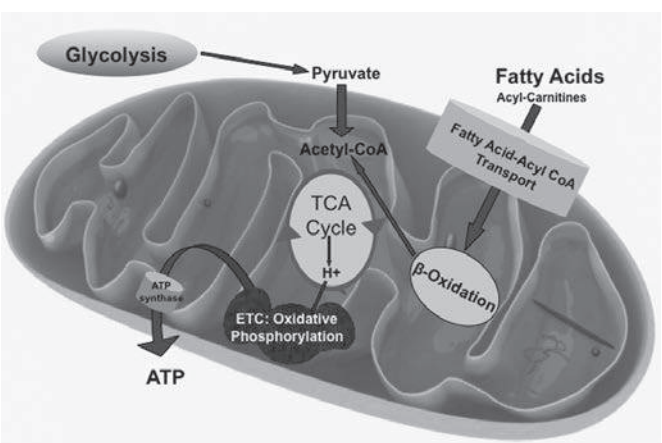


FIGURE 8.1 Simplified Energy Metabolic Pathways Affected in Mitochondrial Disorders.

ataxia, spasticity, ptosis, external ophthalmoplegia, myopathy (often with exercise intolerance), sensorineural hearing loss/deafness, optic atrophy/pigmentary retinopathy, and nonneurological symptoms (including cardiomyopathy, failure to thrive, hepatic failure, renal tubular acidosis, diabetes mellitus and other endocrinopathies, bone marrow failure, and immunologic alterations (Table 8.1). A high incidence of mid- and late pregnancy loss is a common occurrence that often goes unrecognized. Table 8.2 summarizes "red-flag" clinical S/S that should prompt the primary care team to trigger a mitochondrial disorder diagnostic work-up.

TABLE 8.1 Signs and Symptoms Suggestive of Mitochondrial Disorder

Neurologic	Cerebral stroke-like lesions in a nonvascular pattern Basal ganglia dysfunction or mineralization Encephalopathy: recurrent or w/ low/moderate dosing of valproate Neurodegeneration Epilepsia partialis continua, generalized or myoclonic seizures Myoclonus Ataxia MRI findings consistent w/ Leigh disease Characteristic MRS peaks (lactate peak at 1.3 ppm, TE at 35 & 135; succinate peak at 2.4 ppm)
Cardiovascular	Hypertrophic cardiomyopathy w/ rhythm disturbance Unexplained heart block in a child Cardiomyopathy w/ lactic acidosis Dilated cardiomyopathy w/ muscle weakness Wolff–Parkinson–White arrhythmia
Ophthalmologic	Retinal degeneration w/ signs of night blindness, color-vision deficits, decreased visual acuity, or pigmentary retinopathy Ophthalmoplegia/paresis Fluctuating, dysconjugate eye movements Ptosis Sudden- or insidious-onset optic neuropathy/atrophy
Gastroenterologic	Unexplained or valproate-induced liver failure Severe dysmotility Pseudo-obstructive episodes
Other	A newborn, infant, or young child w/ unexplained hypotonia, weakness, failure to thrive, and metabolic acidosis (particularly lactic acidosis) Exercise intolerance that is not in proportion to weakness Hypersensitivity to general anesthesia Episodes of acute rhabdomyolysis Short stature Autonomic dysfunction/postural orthostatic tachycardia syndrome (POTS)

Adapted from Haas RH, et al. Mitochondrial disease: a practical approach for primary care physicians. *Pediatrics*. 2007;120:1326–1333.[10]

DIAGNOSTIC APPROACH

In some individuals, the clinical picture is characteristic of a specific mitochondrial syndrome (e.g., LHON, NARP; see Table 8.2), and the diagnosis can be confirmed by molecular genetic testing of DNA extracted from a blood

TABLE 8.2 Clinical Syndromes of Mitochondrial Diseases

Disorder	Primary Features	Additional Features
	NUCLEAR DNA MUTATIONS	
Alpers-Huttenlocher syndrome	Hypotonia Seizures Liver failure	Renal tubulopathy
Leigh syndrome (LS)	Subacute relapsing encephalopathy Cerebellar, brainstem signs Infantile onset	Basal ganglia lucencies Maternal lineage history of neurologic disease, Leigh syndrome, or increased spontaneous abortions
Infantile myopathy and lactic acidosis (fatal and nonfatal forms)	Hypotonia in 1st y of life Feeding and respiratory difficulties	Fatal form may be associated with a cardiomyopathy and/or de Toni-Fanconi-Debre syndrome
	MITOCHONDRIAL DNA MUTATIONS	
Progressive external ophthalmoplegia (adPEO and arPEO)	External ophthalmoplegia Bilateral ptosis	Mild proximal myopathy Compatible with a normal life span
Kearns–Sayre syndrome (KSS)	PEO onset at age $<$20 y Pigmentary retinopathy One of the following: CSF protein $>$1 g/L Cerebellar ataxia Heart block	Bilateral deafness Myopathy Dysphagia Diabetes mellitus Hypoparathyroidism Dementia
Neurogenic weakness with ataxia and retinitis pigmentosa (NARP)	Late-childhood or adult-onset peripheral neuropathy Ataxia Pigmentary retinopathy	Basal ganglia lucencies Abnormal electroretinogram Sensorimotor neuropathy
Myoclonic epilepsy with ragged-red fibers (MERRF)	Myoclonus Seizures Cerebellar ataxia Myopathy	Dementia Optic atrophy Bilateral deafness Peripheral neuropathy Spasticity Generalized lipomatosis
Leber hereditary optic neuropathy (LHON)	Subacute painless b/l visual failure M:F, 4:1 Median age of onset 24 y	Dystonia Cardiac preexcitation syndromes

(continued)

TABLE 8.2 Clinical Syndromes of Mitochondrial Diseases (Continued)

Disorder	Primary Features	Additional Features
Mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes (MELAS)	Stroke-like episodes at age <40 y Seizures and/or dementia Ragged-red fibers and/or lactic acidosis	Diabetes mellitus Cardiomyopathy (initially hypertrophic, later dilated) Bilateral deafness Pigmentary retinopathy Cerebellar ataxia
Pearson syndrome	Sideroblastic anemia of childhood Pancytopenia Exocrine pancreatic failure	Renal tubular defects
Myoclonic epilepsy myopathy sensory ataxia (MEMSA or MIRAS)	Myopathy Seizures Cerebellar ataxia	Dementia Peripheral neuropathy Spasticity
Coenzyme Q_{10} deficiency	Encephalopathy, myopathy Seizures, cerebellar ataxia Cardiomyopathy Renal failure	Growth retardation Early infancy LS (severe form) Late onset: myopathy, ataxia, seizures, mild encephalopathy

Modified from genereviews.org. Chinnery PF. Mitochondrial Disorders Overview. 2000 Jun 8 [Updated 2010 Sep 16]. In: Pagon RA, Adam MP, Bird TD, et al., editors. GeneReviews™ [Internet]. Seattle (WA): University of Washington, Seattle; 1993–2013. Available from: http://www.ncbi.nlm.nih.gov/books/NBK1224/

sample. In many individuals, such is not the case, and a more structured approach is needed: family history, metabolic screening in blood, urine, and CSF, neuroimaging, cardiac evaluation, and muscle (or other tissue) biopsy for histologic, histochemical, or electron-microscopic evidence of mitochondrial disease, as well as ETC analysis or polography/ATP production (freshly frozen biopsy samples only). Molecular genetic testing for mtDNA and nDNA mutations is often best done in tissue. Diagnostic criteria have been developed[1,2] (Table 8.3). Although ability to rule out diagnosis is limited, a proposed algorithm for initial diagnostic work-up is summarized in Table 8.4. In terms of genetic work-up, the strategy is based on clinical constellation, likelihood of mtDNA mutation (clinical syndrome, maternal inheritance), availability of tissue for depletion analysis (muscle, liver), and evidence from biochemical testing.

GENETIC COUNSELING

Mitochondrial disorders caused by defects of nuclear DNA (nDNA) may be inherited in an autosomal recessive, autosomal dominant, or X-linked manner. mtDNA defects are transmitted by maternal inheritance. mtDNA deletions generally occur *de novo* and thus cause disease sporadically, with no significant risk to other family members. mtDNA point mutations and duplications may be transmitted down the maternal line. Thus both males and females can be affected by mtDNA pathologic lesions, but a male does not transmit the mtDNA mutation to his offspring. A female harboring a heteroplasmic mtDNA point mutation may transmit a variable amount of mutant mtDNA to her offspring (heteroplasmy), resulting in considerable

TABLE 8.3 Mitochondrial Disorders Diagnostic Criteria

Clinical Signs and Symptoms (max 4 Points)				
Muscular Presentation (max 2 Points)	**Cns Presentation (max 2 Points)**	**Multisystem Disease (max 3 Points)**	**Metabolic and Imaging Studies (max 4 Points)**	**Pathology (max 4 Points)**
Ophthalmoplegia[1]	Dev delay	Hematology	Elevated lactate[1]	Ragged-red/blue fibers[2]
Facies myopathica	Loss of skills	GI tract	Elevated L/P ratio	COX-negative fibers[2]
Exercise intolerance	Stroke-like	Endocrine/growth	Elevated alanine[1]	Reduced COX staining[2]
Muscle weakness	Migraine	Heart	Elevated CSF lactate[1]	Reduced SDH staining
Rhabdomyolysis	Seizures	Kidney	Urinary tricabon acid excretion[1]	SDH-positive blood vessels[1]
Abnormal EMG	Myoclonus	Vision	Ethylmalonic aciduria	Abnormal mitochondria/EM[1]
	Cortical blindness	Hearing	Stroke-like picture/MRI	
	Pyramidal signs	Neuropathy	Leigh syndrome/MRI[1]	
	Extrapyramidal signs	Recurrent/familial	Elevated lactate/MRS	
	Brainstem involvement			

Score 1: mitochondrial disorder unlikely; score 2–4: possible mitochondrial disorder; score 5–7: probable mitochondrial disorder; score 8–12: definite mitochondrial disorder.[1] scores 2 points.[2] If in a higher %, scores 4 points.

Modified from Morava E, *et al.* Mitochondrial disease criteria: diagnostic applications in children. *Neurology.* 2006;67:1823–1826, with permission.

TABLE 8.4 Screening Algorithm for Patients with Suspected Mitochondrial Disorder

For All Patients	**Family History and Pedigree** **Blood** Basic chemistries CBC, CPK LFTs, ammonia Blood lactate, pyruvate (lactate/pyruvate ratio), coenzyme Q_{10} (WBC, tissue) Quantitative plasma amino acids Plasma carnitines (free, total, esterified) and acylcarnitines **Urine** Quantitative urine organic acids **Echocardiogram & EKG** **Ophthalmologic examination** **Audiology testing**
If Neurological Symptoms: All of above plus:	**Brain MRI/MRS** **CSF** • Lactate and pyruvate • Quantitative amino acids, neurotransmitters, and biopterins • Routine studies, including cell count, glucose, & protein **Genetic consultation** **Child neurology consultation**
If Developmental Delays: All of above plus:	**Blood** • Karyotype • Fragile X syndrome molecular testing
If Myopathy Or Multiorgan Dysfunction Or Diagnostic Criteria are met	**EMG** (may be skipped if muscle atrophy or severe weakness) **Muscle biopsy** • Routine light microscopy + EM, histochemical stains, including SDH, COX • ETC enzyme analysis (needs freshly frozen sample on dry ice) • ETC enzyme and pology/ATP production (requires isolation and testing of fresh mitochondria) • Molecular studies (mtDNA and nDNA) (needs freshly frozen sample on dry ice) • Coenzyme Q_{10} measurement • Carnitines and acylcarnitines **Skin biopsy for EM and fibroblast culture** (collect at the same time of muscle biopsy)

Adapted from Haas RH, et al. Mitochondrial disease: a practical approach for primary care physicians. *Pediatrics.* 2007;120:1326–1333.[10]

intrafamilial as well as interfamilial clinical variability. Prenatal genetic testing, and interpretation of test results for mtDNA disorders, are difficult because of this mtDNA heteroplasmy and should be deferred to the genetic counselor or mitochondrial expert. nDNA-encoded mitochondrial disorders are increasingly recognized. Up to 1,200 nuclear genes, presumably associated with broad mitochondrial dysfunction, are being currently screened in clinical cohorts. The majority of nDNA-associated disorders, identified to

date, are those with infantile encephalopathy features. Increasingly, however, late-onset phenotypes are being recognized (myopathy, ataxia, PEO).

TREATMENT OF COMMON MANIFESTATIONS

- **Sensorineural hearing loss** has been successfully treated with cochlear implantation[3,4] (routine screening is appropriate).
- **Ptosis** can benefit from eyelid "crutches," blepharoplasty, or frontalis muscle-eyelid sling placement.
- **Progressive extraocular ophthalmoplegia (PEO)** and **retinopathy:** No therapy is available.
- **Exercise intolerance/poor stamina:** Low-aerobic and conditioning exercise is helpful in MELAS and other mitochondrial diseases.[5] Physical therapy should be implemented in individuals after strokes.
- **Seizures** respond variably to traditional anticonvulsant therapy. Valproic acid is contraindicated for prophylaxis given its effect on carnitine metabolism.
- **Migraine headaches** can be treated with standard analgesics. Beware as herald of stroke.
- **Cardiac manifestations** can benefit from standard pharmacologic therapy. Routine ECHO and EKG should be performed regularly. Holter monitoring is used with appropriate history suggesting arrythmia. Autonomic testing may support clinical suspicions (orthostasis, syncope, poor temperature regulation/cold or heat intolerance, GI dysmotility).
- **Diabetes mellitus** can often be managed by dietary modification alone, especially in thin individuals, or with oral hypoglycemic agents, but often requires insulin therapy.
- **Metabolic strokes:** Intravenous L-arginine, given acutely, has shown promise in treating stroke-like episodes in MELAS, although this remains unproven to date.[6] The role of daily prophylactic L-arginine remains unclear.
- **Cofactors:** Different combinations of vitamins, antioxidants, and minerals are used in weight-based dosing (for specific disorders, see their Rx section below).
- **Therapies under investigation:** Search ClinicalTrials.gov for access to information on clinical studies. Few studies have shown significant efficacy. Coenzyme Q_{10} studies are most heralded.

Respiratory Electron Transport Chain Disorders (RCD)

Defect: Mitochondrial or nuclear DNA mutations affecting different structural proteins, as well as those important in assembly, stability, or replication of the mitochondrial respiratory chain complexes. The mtDNA encodes 13 structural proteins [complex I (7), III (1), IV (3), V (2)]. It is estimated that there may be over 1,400 nuclear genes involved in mitochondrial structure or function which may lead to human disease.

Presentation and Syndromes: Most have some degree of myopathy or exercise intolerance. Other prominent neurologic symptoms include myoclonus (MERRF), parkinsonism-associated abnormalities (POLG & DNA helicase twinkle gene mutation, Leber hereditary optic neuropathy [LHON], MERRF), or dystonia (Leigh syndrome-complex I, IV, V defects, LHON mutations, MELAS, Kearns–Sayre syndrome [KSS]). *Other disturbances:* depends on the syndrome (external ophthalmoplegia, polyneuropathy, endocrinopathy, retinitis pigmentosa, multiorgan failure, symptoms involving

CNS, PNS, or autonomic nervous system, auditory & visual disturbances). Syndrome nomenclature represents the early-recognized phenotypes, but expanded clinical features are now clearly identified.

MELAS: Mitochondrial Encephalopathy w/ Lactic Acidosis & Stroke-Like Episodes

Defect: Mutation in several mtDNA genes, including *MT-TL1* (containing nucleotide 3243A>G, most common form), *MT-TQ*, *MT-TH*, *MT-TK*, *MT-TS1*, *MT-ND1*, *MT-ND5*, *MT-ND6*, & *MT-TS2.*

FHx: Exclusively maternally inherited.

Presentation: Onset in juvenile or early adulthood (infrequent early childhood) w/ sudden partially regressive neurologic attacks resembling strokes (hemiparesis, hemianopia, cortical blindness, aphasia). There is usually progressive sensorineural hearing loss (often earlier not recognized as heralding a metabolic disorder). Migraine-like headache, seizures, mental deterioration. Progressive external ophthalmoplegia (PEO; 10%). Often associated with short stature. Phenotypic expression depends on ethnic background. Asians with mtDNA mutation m.3243A>G have diabetes and sensorineural hearing loss as a restricted phenotype.

Prognosis: Variable. Usually, stroke-like episodes are transient, but can be permanent, resulting in progressive dementia & encephalopathy. SNHL is progressive. Early mortality.

Dx:

- Imaging: Serial alternating cortical & subcortical areas of destruction of the parieto-occipital lobes & basal ganglia (with calcifications) often sparing white matter (unique feature). MRI acute DWI bright lesions, not necessarily corresponding w/ vascular territories (ADC not necessarily dark). MRI spectroscopy (MRS) often w/ high lactate peak (doublet), but normal MRS does not exclude the diagnosis.
- Labs: CSF & blood-elevated lactic acid, abnormal urinary organic acids, elevated plasma alanine.
- Muscle biopsy: Ragged-red fibers (although clinically, exercise intolerance is rare).
- *Definitive dx:* Blood or tissue sequencing/ngs for mtDNA m.3243A>G (minority have other nucleotide mutations, including m.3271 or m.3291).

Rx: Acute intravenous L-arginine has shown promise in treating stroke-like episodes; coenzyme Q_{10} (ubiquinone, idebenone) has shown some beneficial effect. Idebenone, an analog of CoQ_{10} that crosses the blood–brain barrier more efficiently, has also been reported as beneficial in anecdotal reports.[7]

Reference: http://www.ncbi.nlm.nih.gov/books/NBK1233/

Leigh Syndrome: Infantile Subacute Necrotizing Encephalomyopathy

Defect: Mutations of nuclear or mitochondrial DNA. Most commonly affecting complex I, IV (COX), pyruvate dehydrogenase (PDH) or complex V (m.8993; high mutation burden).

Presentation: 75% with onset 3 to 12 mo; 25% adults. Developmental delay, FFT, hypotonia, spasticity, chorea, deafness, ataxia, dystonia, & peripheral neuropathy. Decompensation episodes: lactic acidosis, regression. Other disturbances: hypertrophic cardiomyopathy.

FHx: AR, X-linked, maternal inheritance only if mtDNA.

Dx:

- Imaging: T2 hyperintense bilateral brainstem & basal ganglia with small vessel hyperplasia, cavitating necrosis if severe.
- Labs: Elevated blood pyruvate and lactate with normal L/P ratio. Postprandial and glucose challenge can accentuate biochemical abnormalities.
- Biopsy: RRFs in muscle biopsy may be present (rare). Brain pathology shows small vessel hyperplasia (basal ganglia, tectum), sometimes necrotic lesions.
- *Definitive dx:* mtDNA mutation analysis.

Rx: Carbohydrate-restricted diet. High doses of thiamine. Coenzyme Q_{10}. NaHCO or dichloroacetate (DCA) if acidosis.

Reference: http://www.ncbi.nlm.nih.gov/books/NBK1173/

NARP: Neurogenic Weakness with Ataxia and Retinitis Pigmentosa

Defect: Mutation in mtDNA (*MT-ATP6*; m.8993T>G, C is found in 50% of pts with NARP.

Presentation: Late-childhood or adult-onset peripheral neuropathy, ataxia, retinitis pigmentosa, seizures, learning difficulties, and dementia. Other S/S: short stature, sensorineural hearing loss, PEO, cardiac conduction defects (heart block). High *MT-ATP6* mutation burden can express during infancy as Leigh syndrome.

FHx: Maternal inheritance.

Dx:

- Imaging: Cerebral and cerebellar atrophy.
- EMG/NCS: Sensory or sensorimotor axonal polyneuropathy.
- Labs: Sometimes can see elevated lactate in CSF & blood. Plasma amino acids may show elevated alanine concentration. Urine: lactic aciduria, dicarboxycyclic acid excretion.
- Biopsy/autopsy: RRFs in muscle biopsy may be present (rare). Necrotic lesions in the basal ganglia, thalamus, brainstem, dentate nuclei, and optic nerves.
- *Definitive dx:* mtDNA mutation analysis.

Rx: Sodium bicarbonate or sodium citrate for acute exacerbations of acidosis. High doses of thiamine. Coenzyme Q_{10}. Avoid valproic acid, barbiturates, anesthesia, and DCA.

Reference: http://www.ncbi.nlm.nih.gov/books/NBK1173/

Coenzyme Q_{10} Deficiency

Defect: Mutation in nuclear genes encoding the mitochondrial parahydroxybenzoic-polyprenyl transferase. Identified nuclear genes associated with primary coenzyme Q_{10} deficiency include *APTX*, *CABC1*, *COQ2*, *COQ9*, *PDSS1*, *PDSS2*.

FHx: AR.

Presentation: 5 major phenotypes: (1) encephalomyopathy w/ seizures & ataxia; (2) multisystem infantile form w/ encephalopathy, cardiomyopathy, & renal failure; (3) predominantly cerebellar w/ ataxia & cerebellar atrophy; (4) Leigh syndrome w/ growth retardation; (5) isolated myopathic form.

Prognosis: Variable.

Dx:

- Imaging: T2 hyperintense bilateral brainstem & basal ganglia.
- Labs: Decreased coenzyme Q_{10} (ubiquinone) in muscle biopsy, low activity in lymphocytes & fibroblasts (can be secondary deficiency). Measurable coenzyme Q_{10} deficiency can be best identified in muscle (blood may be normal).
- Biopsy: Muscle RRFs, abnormal mitochondria by EM. Fibroblasts may show deficiency.
- *Definitive dx:* Quantitative coenzyme Q_{10} in muscle or fibroblasts. mtDNA mutation analysis for nucleotide change, deletion/duplication or depletion.

Rx: Coenzyme Q_{10} (ubiquinone, up to 20 mg/kg/d).[8] Symptomatic.

Kearns–Sayre Syndrome

Defect: mtDNA deletions.

FHx: Predominantly sporadic. Rare maternal inheritance.

Presentation: Onset before 20 y w/ both chronic, PEO and pigmentary degeneration of the retina. Will also often have weakness of facial, pharyngeal, trunk, & extremity muscles & deafness. Other S/S: DM, cardiomyopathy, dysphagia from cricopharyngeal achalasia, small stature.

Prognosis: Progressive disability, often die of cardiac failure.

Dx:

- Imaging: Basal ganglia calcifications or normal.
- Labs: High plasma lactate & pyruvate. Marked increase in CSF protein.
- Biopsy: RRFs in skeletal muscle are common.
- *Definitive dx:* mtDNA deletion analysis (tissue). Current assays are sensitive to detect deletion at low heteroplasmic levels, making assay in blood possible.

Rx: Mitochondrial "cocktail" (including folinic acid, L-carnitine, coenzyme Q_{10}, antioxidants, creatine). Cardiac pacemaker if cardiac conduction block. Dilation of the upper esophageal sphincter to alleviate cricopharyngeal achalasia.

Reference: http://www.ncbi.nlm.nih.gov/books/NBK1203/

Leber Hereditary Optic Neuropathy (see also Chapter 12)

Defect: Many allelic variants of mtDNA. Primary LHON mutations include m.11778G>A (*MT-ND4*), m.3460G>A (*MT-ND1*), and m.14484T>C (*MT-ND6*); they are present in at least 90% of families. Secondary LHON mutations have never been associated with clinical phenotype when present alone. Complex I activity may be still normal in *in vitro* muscle assays.

FHx: Exclusively maternally inherited.

Presentation: Bilateral, painless, subacute central vision loss leading to central scotoma & blindness presenting at mean age of 27 to 34 y. Unilateral acute presentation usually followed by loss of vision in 2nd eye within weeks. Females carrying primary mutations at ~10% and males ~55% risk of disease expression. May see dopa-responsive parkinsonism, dystonia, or myoclonus ($LHON^+$).

Prognosis: Normal life span.

Dx:

- Imaging: Normal. Necessary to rule out ON compression from mass.
- Fundoscopic evaluation—acute: disk swelling, edema of the peripapillary nerve fiber layer, retinal telangiectasia, and increased vascular tortuosity; chronic: ON atrophy.
- *Definitive dx:* mtDNA mutation analysis.

Rx: Mitochondrial cocktail, coenzyme Q_{10}. Small trial showed that idebenone could benefit individuals at an early stage of the disease. L-dopa in postural tremor.

Reference: http://www.ncbi.nlm.nih.gov/books/NBK1174/

MERRF: Myoclonic Epilepsy w/ Ragged-Red Fibers

Defect: Produced by mutation in mtDNA, including *MTTK*, *MTTL1*, *MTTH*, *MTTS1*, *MTTS2*, *MTTF*. Four *MT-TK* mutations (m.8344A>G, m.8356T>C, m.8363G>A, and m.8361G>A; see Tables 8.1 and 8.3) account for ~90% of mutations in individuals with MERRF.

FHx: Exclusively maternally inherited.

Presentation: Onset in early childhood or adulthood w/ myoclonic epilepsy, followed by other epilepsy d/o, progressive ataxia, & cognitive impairment. Some present with myoclonus without epilepsy. Other S/S: exercise intolerance, hearing loss, short stature, diabetes mellitus, optic atrophy, and cardiomyopathy with Wolff–Parkinson–White (WPW) syndrome. Rarely, generalized lipomatosis.

Prognosis: Most patients typically progress to disabling ataxia & cognitive impairment.

Dx:

- Imaging: Brain atrophy and basal ganglia calcification.
- Labs: High serum and CSF levels of pyruvate & lactate.
- EEG: Generalized spike and wave discharges with background slowing.
- Biopsy: Skeletal muscle often shows RRFs. Often decreased activity of respiratory chain complexes, especially COX deficiency.
- *Definitive dx:* mtDNA mutation analysis for MERRF panel.

Rx: Mitochondrial "cocktail" (vitamins and cofactors, including coenzyme Q_{10}).

Reference: http://www.ncbi.nlm.nih.gov/books/NBK1520/

POLG-Related Disorders

Alpers-Huttenlocher syndrome (AHS), autosomal dominant PEO (adPEO), autosomal recessive PEO (arPEO), childhood myocerebrohepatopathy spectrum (MCHS) disorders, myoclonic epilepsy myopathy sensory ataxia (MEMSA), POLG-related ataxia neuropathy spectrum (ANS) disorders.

Defect: Caused by homozygous or compound heterozygous mutations in the nDNA-encoded polymerase-gamma gene (*POLG*) that affects mtDNA stability, leading to mtDNA depletion or deletions. 70% pts have one of three POLG mutations (p.Ala467Thr, p.Trp748Ser, and p.Gly848Ser), but the need to detect 2 mutant alleles in an individual with this autosomal recessive disorder usually requires full sequence analysis of the *POLG* gene. Infrequent autosomal dominant cases have been reported.

FHx: AR for most of the phenotypes except adPEO (autosomal dominant form).

Presentation: Continuum of overlapping phenotypes that exemplifies the diversity arising from a single gene mutation. Onset ranges from early childhood: **AHS** (see below) and **MCHS**: p/w developmental delay or dementia, lactic acidosis, and myopathy, FFT, liver failure, RTA, pancreatitis and hearing loss in the 1st few months of life up to 3 y and **MEMSA**; to late childhood/adulthood: **adPEO** usually associated w/ sensorineural hearing loss, axonal neuropathy, ataxia, depression, parkinsonism, hypogonadism, and cataracts; **arPEO**; and **ANS**, which encompasses phenotypes previously referred to as mitochondrial recessive ataxia syndrome (**MIRAS**) and sensory ataxia neuropathy dysarthria and ophthalmoplegia (**SANDO**).

Dx:

- Biopsy: RRFs in muscle (occasionally), respiratory chain defect, and/or a defect of mtDNA (depletion or multiple deletions) may be seen in affected tissues.
- *Definitive dx:* Direct sequencing of *POLG* gene or targeted mutation analysis.

Rx: L-dopa if parkinsonism symptoms; mitochondrial "cocktail" (vitamins and cofactors, including coenzyme Q_{10})

Reference: http://www.ncbi.nlm.nih.gov/books/NBK26471/

Alpers-Huttenlocher Disease

Defect: Mutation in the nuclear gene encoding mtDNA polymerase-gamma (*POLG*) that leads to mtDNA depletion/deletion.

FHx: AR.

Presentation: Onset in infancy or childhood w/ delayed milestones, followed by intractable partial seizures (at times, epilepsia partialis continua) and secondary generalized tonic–clonic seizures, psychomotor retardation, &, eventually, blindness. Other S/S: liver failure.

Prognosis: Poor w/ progressive neurologic deterioration. Life expectancy from months to a decade after onset of symptoms.

Dx:

- Imaging: MRI: T2 hyperintensities of brainstem. Can see cortical (occipital) and subcortical white matter, thalamus, basal ganglia, and cerebellar lesions.
- EEG: High-amplitude slow activity with smaller polyspikes or intermittent continuous spike-wave activity.
- *Definitive dx:* Direct sequencing of *POLG* gene or targeted mutation analysis. Postmortem examination of the brain & liver.

Rx: Low-carbohydrate diet, although not proven effective.

Reference: http://www.ncbi.nlm.nih.gov/books/NBK26471/

MNGIE: Myoneurogastrointestinal Encephalopathy

Defect: Mutation in the nuclear gene encoding thymidine phosphorylase (*TYMP* gene), locus 22q13.32-qter.

FHx: AR.

Presentation: Onset between 20 and 50 y w/ progressive gastrointestinal dysmotility and cachexia, ptosis, PEO, hearing loss, and demyelinating

peripheral neuropathy manifesting as paresthesias and symmetric distal weakness and myopathy.

Prognosis: Most pts die before 40 y.

Dx:

- Imaging: Signs of leukoencephalopathy in brain MRI.
- Labs: Elevated plasma deoxyuridine (5 μmol/L), thymidine (>3 μmol/L). Thymidine phosphorylase enzyme activity in leukocytes < 10% of the control mean.
- Biopsy: Ragged-red fibers in skeletal muscle.
- *Definitive dx:* Elevated plasma deoxyuridine (5 μmol/L) and thymidine (>3 μmol/L) are sufficient to make dx of MNGIE. Mutation analysis.

Rx: Mitochondrial cocktail (vitamins and cofactors, including coenzyme Q_{10}).

Reference: http://www.ncbi.nlm.nih.gov/books/NBK1179/

Pyruvate Dehydrogenase Deficiency[9]

Defect: PDH (E1 enzyme) is composed of 4 subunits (2αs and 2βs). Mutations in the E1-alpha unit, *PDHA1* (Xp22.2-p22.1), account for ~80% of cases.

FHx: X-linked dominant.

Presentation: One of the most common causes of primary lactic acidosis in newborn and children. Onset typically in newborn period as Leigh syndrome as episodic/acute attacks + chronic neurodegeneration. Acute: ataxia, dystonia, limb weakness, & encephalopathy. Chronic: axonal polyneuropathy, dystonia, chorea, & parkinsonism.

Prognosis: Neonatal or infantile death from metabolic failure.

Dx:

- Imaging: Putamen or tectal necrosis (T2 hyperintense).
- Labs: High lactate & pyruvate in blood & CSF. Low or normal lactate: pyruvate ratio.
- Biopsy: Fibroblast or tissue for enzyme analysis.
- *Definitive dx:* Low PDH activity in skin fibroblast or leukocytes. Prenatal testing available.

Rx: Vitamin B_1 (there are some thiamine-responsive forms of the disease) & ketogenic diet.

Fatty Acid Oxidation Metabolism

CPTII: Carnitine Palmitoyltransferase II Deficiency

Defect: CPTII deficiency (*CPT2*), chr 1p32. Carnitine transport system into mitochondria for long-chain fatty acids for beta-oxidation and production of ACoA and ketones.

FHx: AR.

Presentation: Three clinical presentations: (1) lethal neonatal form; (2) severe infantile hepatocardiomuscular form characterized by liver failure with hypoketotic hypoglycemia, cardiomyopathy, and seizures; and (3) myopathic form that can manifest from infancy to adulthood with exercise/fasting-induced muscle pain and weakness from recurrent episodes of rhabdomyolysis.

Prognosis: From early childhood death to normal life span w/o disabilities in the myopathic from.

Dx:

- Labs: Recurrent myoglobinuria and elevated CK during attacks. Tandem mass spectrometry of serum acylcarnitines (elevated palmitoylcarnitine & oleoylcarnitine w/ normal acylcarnitine).
- Biopsy: Skin fibroblast for enzyme analysis.
- *Definitive dx:* Analysis of cultured skin fibroblasts for enzymes of fatty acid metabolism (beta-oxidation pathway).

Rx: Supplement diet with oral or IV L-carnitine (accelerated conversion of toxic LCFA to acylcarnitines), large fraction of calories as carbohydrates, and one third of calories by medium-chain tryglycerides (MCT oil) that is independent of CPT metabolism. Avoid prolonged exercise and renal failure during rhabdomyolysis crisis. Bezafibrate restored the capacity for normal fatty acid oxidation in muscle cells in patients w/ a mild form of CPTII deficiency by stimulating the expression of the mutated gene.

Reference: http://www.ncbi.nlm.nih.gov/books/NBK1253/

Primary Carnitine Deficiency

Defect: Sodium ion-dependent carnitine transporter deficiency (*OCTN2*) resulting in impaired fatty acid oxidation in skeletal and heart muscles. Chr 5q31.1.

FHx: AR.

Presentation: Onset in childhood or teens w/ slowly progressive proximal (and often bulbar) weakness w/ sudden exacerbations. In systemic disease, episodic weakness corresponds to recurrent episodes of hepatic and cerebral dysfunction (lethargy, somnolence). Other S/S: hypoketotic hypoglycemia, hepatomegaly, dilated cardiomyopathy, underdeveloped muscles.

Prognosis: Depends on severity of disease (muscle-specific or systemic).

Dx:

- Labs: Decreased carnitines in plasma, muscle, and liver (<5%), NO myoglobinuria
- Biopsy: Skin fibroblast for transporter assay
- *Definitive dx:* NBS, impaired uptake of carnitine by skin fibroblasts

Rx: Metabolic decompensation, and skeletal and cardiac muscle function improves with 100 to 400 mg/kg/d oral L-carnitine if started before irreversible organ damage occurs.

Reference: http://www.ncbi.nlm.nih.gov/books/NBK84551/

MCAD: Medium-Chain Acyl-Coenzyme A Dehydrogenase Deficiency

Defect: Mutations in the *ACADM* gene, chromosome 1p31.

FHx: AR.

Presentation: Onset classically between 3 and 24 mo of age with hypoketotic hypoglycemia, vomiting, and lethargy triggered by a common illness or prolonged fasting in a previously healthy child. Seizures may occur. Other S/S: hepatomegaly and liver disease during an acute episode.

Prognosis: Depends on severity of disease. Better prognosis w/ later onset.

DX:

- Labs: Serum accumulation of C6 to C10 acylcarnitine species, with prominent octanoylcarnitine, hypoglycemia after fasting. Urine: medium-chain dicarboxylic acids are elevated, while ketones are inappropriately low.

- Biopsy: Skin biopsy for measurement of MCAD enzyme activity in cultured fibroblasts.
- *Definitive dx:* NBS & mutation analysis.

Rx: Frequent small carbohydrate feedings, dietary fat restriction (<30% of caloric intake), and carnitine supplementation reduces frequency of attacks.

Reference: http://www.ncbi.nlm.nih.gov/books/NBK1424/

VLCAD: Very Long-Chain Acyl-CoA Dehydrogenase Deficiency

Defect: Mutations or deletions in the *ACADVL* gene, chr 17p13.

FHx: AR.

Presentation: Three phenotypes: (1) severe early-onset hypertrophic or dilated cardiomyopathy, hypotonia, hepatomegaly, and intermittent hypoglycemia in the 1st months of life; (2) hepatic or hypoketotic hypoglycemic form p/w hypoketotic hypoglycemia and hepatomegaly during early childhood; and (3) later-onset episodic myopathic form with episodes of rhabdomyolysis, muscle cramps, and/or exercise intolerance.

Prognosis: Depends on severity of disease. Better prognosis w/ later onset.

Dx:

- Labs: Elevated C14:1, C14:2, C14, and C12:1 acylcarnitines during episodes (not present if patient is fed or given IV glucose). Recurrent myoglobinuria and elevated CK during attacks. VLCAD enzyme activity in leukocytes.
- Biopsy: Skin for fatty acid β-oxidation studies in cultured fibroblasts. Muscle shows lipid storage in type I fibers.
- *Definitive dx:* NBS & sequencing of *ACADVL* gene.

Rx: Frequent small carbohydrate feedings, dietary fat restriction (only MCT oil), & carnitine supplementation reduce frequency of attacks. IV glucose during acute decompensations, treatment of cardiac rhythm disturbance, and hydration/dialysis during rhabdomyolysis.

Reference: http://www.ncbi.nlm.nih.gov/books/NBK6816/

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9 Leukodystrophies

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GENERAL CONCEPTS

Leukodystrophies are inherited disorders that affect the white matter of the central nervous system with or without involvement of the peripheral nerve. Collectively leukodystrophies represent an important cause of progressive neurological disability in children. All disorders share glial cell or myelin sheath involvement. Brain MRI plays a large role in detection and diagnosis. Patterns of white matter involvement can be pathognomonic (Fig. 9.1). Diagnosis is important for palliative or experimental therapies that may offer benefits, as well as for reproductive counseling and family screening of currently unaffected individuals. Since the few treatments available are more effective in the early stages, timely referral to an expert is crucial.[1]

CLINICAL FEATURES

Age of Onset

First symptoms are usually neurological and appear, with few exceptions, in previously healthy children. Most leukodystrophies occur within a particular age group and can range in onset from early infancy to late adulthood. Within a leukodystrophy the phenotypes can vary, with more severe phenotypes usually starting in early childhood. Symptoms usually progress

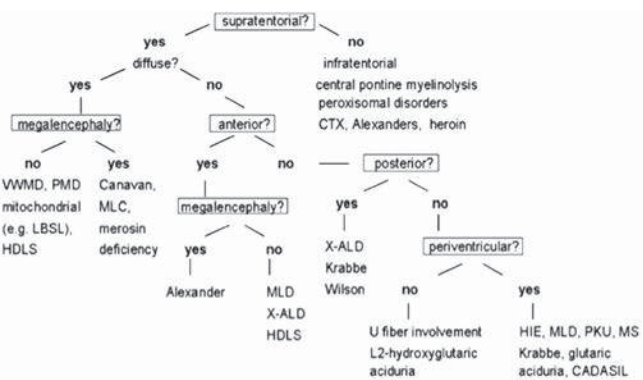


FIGURE 9.1 Algorithm for the Use of MRI Patterns in Distinguishing Disorders with White Matter Involvement (Reproduced with permission from Costello DJ, Eichler AF, Eichler FS. Leukodystrophies: classification, diagnosis, and treatment. *Neurologist.* 2009;15:319–328.)

TABLE 9.1 Most Common Leukodystrophies by Age of Onset of Symptoms

Leukodystrophies to Consider in Relation to Age of Patient at Onset

Patient age at onset of symptoms	Leukodystrophies (in order of probability)
Infantile (1st y of life)	Globoid cell leukodystrophy Pelizaeus–Merzbacher disease Canavan disease Vanishing white matter disease Megalencephalic leukodystrophy with cysts Aicardi–Goutières syndrome Hypomyelination with atrophy of the basal ganglia and cerebellum
Late infantile (1–5 y)	Metachromatic leukodystrophy Alexander disease Vanishing white matter disease Megalencephalic leukodystrophy with cysts Hypomyelination with atrophy of the basal ganglia and cerebellum Leukoencephalopathy with brainstem and spinal cord involvement and elevated lactate Giant axonal neuropathy type I
Juvenile	X-linked adrenoleukodystrophy Metachromatic leukodystrophy Vanishing white matter disease Megalencephalic leukodystrophy with cysts Alexander disease Leukoencephalopathy with brainstem and spinal cord involvement and elevated lactate
Adolescence, young adulthood	Metachromatic leukodystrophy Vanishing white matter disease Leukoencephalopathy with brainstem and spinal cord involvement and elevated lactate

Adapted from Kohlschutter A, Eichler F. Childhood leukodystrophies: a clinical perspective. *Expert Rev Neurother.* 2011;11:1485–1496.

slowly, with possible periods of stagnation. Phenotypes are variable depending on the severity of mutations. Starting from the age of the patient at onset of symptoms, certain types can be considered (Tables 9.1 and 9.2).

Neuroimaging

MRI of the head is the most important ancillary test. Standard investigation is T1- and T2-weighted and fluid-attenuated inversion-recovery (FLAIR) images. The distribution of white matter abnormalities (see Fig. 9.1) and certain specific patterns (Table 9.3) can assist in the differentiation of leukodystrophies. A systematic assessment of lesion location, presence of hypomyelination, cystic lesions, calcifications, contrast enhancement, and abnormalities on proton MR spectroscopy (MRS) is crucial. A rough classification of leukodystrophies according to their presentation on neuroimaging is shown in Table 9.3.[1,2]

TABLE 9.2 Differential Diagnosis of Leukodystrophies by Age of Onset

Childhood Onset

Primary CNS inflammation (ADEM, MS)
Primary CNS infection (encephalitis)
CNS neoplasia (glial tumors, lymphoma)
Toxic leukoencephalopathy (radiation, chemotherapy, biologic therapies)
Perinatal injury (hypoxic ischemic encephalopathy, periventricular leukomalacia)

Adult Onset

Infiltrative tumors (gliomas, gliomatosis cerebri, primary CNS lymphoma)
Toxic leukoencephalopathy (radiation, chemotherapy, organic solvents, biologic therapies, drugs of abuse)
Metabolic leukoencephalopathy (anoxia, carbon monoxide, mitochondrial)
Infection (encephalitis, HIV encephalopathy, progressive multifocal leukoencephalopathy)
Trauma (diffuse axonal injury) vasculopathies (ischemic, inflammatory, CADASIL), CNS inflammation (MS, ADEM, systemic disorders with CNS involvement)

CNS indicates central nervous system; ADEM, acute demyelinating encephalomyelitis; MS, multiple sclerosis, HIV, human immunodeficiency virus; CADASIL, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy.

Adapted from Costello DJ, Eichler AF, Eichler FS. Leukodystrophies: classification, diagnosis, and treatment. *Neurologist*. 2009;15:319–328.

TABLE 9.3 Childhood Leukodystrophies According to Major Neuroimaging Patterns

Disorders with Confluent MRI Lesions

Alexander disease[1]
Canavan disease
Globoid cell leukodystrophy
Leukoencephalopathy with metaphyseal chondrodysplasia
Metachromatic leukodystrophy
Metachromatic leukodystrophy with multiple sulfatase deficiency
Mitochondrial disorders
X-linked adrenoleukodystrophy

Disorders with Cavitating MRI Lesions

Cystic leukoencephalopathy without megalencephaly
Glycine leukoencephalopathy
Leukoencephalopathy with calcifications and cysts
Megalencephalic leukodystrophy with cysts
Progressive cavitating leukoencephalopathy

Disorders with Hypomyelination

Fucosidosis
Folate receptor defect
Hypomyelination with atrophy of the basal ganglia and cerebellum
Hypomyelination and congenital cataract
Hypomyelination, hypodontia, hypogonadotropic hypogonadism
Hypomyelination with monocarboxylate transporter-8 deficiency
Pelizaeus–Merzbacher disease
Pelizaeus–Merzbacher-like disease
Sialic acid storage disorder
Tremor–ataxia with central hypomyelination

TABLE 9.3 Childhood Leukodystrophies According to Major Neuroimaging Patterns *(Continued)*

Disorders with Calcifications
Aicardi–Goutières syndrome
Cerebrotendinous xanthomatosis
Leukoencephalopathy with calcifications and cysts

[1]Infantile type.

Adapted from Kohlschutter A, Eichler F. Childhood leukodystrophies: a clinical perspective. *Expert Rev Neurother.* 2011;11:1485–1496.

Physical and Neurological Exams

Most patients with leukodystrophies do not have any physical abnormalities. Some have a large head (Alexander disease, Canavan disease, megalencephalic leukodystrophy with cysts, and vanishing white matter disease). Very rarely, they can have dysmorphic features and skeletal abnormalities that resemble those seen in mucopolysaccharidoses (fucosidosis and metachromatic leukodystrophy [MLD] with multiple sulfatase deficiency). Dental abnormalities are seen in some forms of hypomyelination, such as hypomyelination, hypodontia, and hypogonadotropic hypogonadism (4H syndrome).[1]

MOST COMMON LEUKODYSTROPHIES (TABLE 9.4)

X-linked Adrenoleukodystrophy (ALD)

Defect: Mutations in the *ABCD1* gene lead to defects in peroxisomal beta-oxidation & very long chain fatty acid (VLCFA) accumulation. Locus Xq28.

Presentation: Cerebral ALD (only seen in males): Onset 4 to 8 y, 85% present initially with neurologic symptoms. Often begins with personality changes (resembles ADHD) and academic performance decline, followed by ataxia, spasticity, loss of vision and hearing. Dementia and seizures can occur later in the course. It often leads to total disability within 2 y. Adrenomyeloneuropathy (AMN) or adult form (males and some females): Onset after 20 y with spastic paraplegia, sensory peripheral neuropathy, sphincter disturbances, and impotence. **Other si/sx:** Adrenal insufficiency (mean onset 7.5 y, may be isolated). **Prognosis:** In cerebral ALD, there is progression to vegetative state and death by 3 y after onset (slower progression in adult cerebral ALD). **FHx:** X-linked, only males affected in cerebral form, up to 20% of female carriers will develop AMN.

Dx:

- Imaging: Cerebral form: T2-hyperintense confluent lesion that starts in the splenium of the corpus callosum and spreads to the posterior periventricular white matter and corticospinal tracts. A garland of peripheral contrast enhancement (Fig. 9.2). Adult form: Normal MRI or T2-hyperintense lesions of lateral spinal cord columns without contrast enhancement.
- Labs: High plasma VLCFA (concentration of C26:0, ratios of C24:0/C22:0 and C26:0/C22:0) is diagnostic in males (20% females have normal levels). Abnormal response to ACTH stimulation test. Low plasma cortisol in advanced cases.
- Biopsy: Skin for enzyme assay in cultured fibroblasts.
- *Definitive dx:* Gene sequencing for mutation analysis (>95% cases, 5–6% deletion/duplications). Newborn screening (to be instituted soon).

TABLE 9.4 Clinical, Imaging, and Pathophysiological Features of the Most Common Leukodystrophies

Disease	Inheritance	Clinical Features	Distinct Imaging Features	Diagnostic Tests	Pathophysiology
Adrenoleukodystrophy	X-linked recessive	Cerebral: behavioral changes, motor regression, acute progression AMN: chronic progressive spastic paraparesis	Cerebral: predominantly posterior-periventricular, contrast enhancement AMN: corticospinal tract involvement	Plasma very long chain fatty acids; ABCD1 mutation	Cerebral: brain inflammation AMN: oxidative stress?
Metachromatic leukodystrophy	Autosomal recessive	Behavioral changes, pyramidal sings, ataxia	Diffuse white matter abnormalities with sparing of U-fibers	Arylsulfatase A in leukocytes; high urinary excretion of sulfatides	Accumulation of sulfatides within lipid membranes
Globoid cell loukodystrophy (Krabbe disease)	Autosomal recessive	Developmantal regression, spasticity, opisthotonus; late-onset milder	Posterior-predominant periventricular; no enhancement	Galactosylceramide β-galactosidase in leukocytes	Psychosine cytotoxic to oligodendroglia?
Vanishing white matter disease	Autosomal recessive inheritance with age-dependent penetrance	Ataxia, spasticity, deterioration following minor head trauma and febrile illness	Progressive rarefaction and cystic degeneration of white matter	Mutation in eIF2B α., β, γ, δ, or ε	Abnoemal unfolded protein response?
Alexander disease	De novo mutations in majority	Megalencephaly, psychomotor regression, ataxia and seizures; adults with bulbar symptoms	Diffuse white matter abnormalities, often with anterior predominance	*GFAP* gene mutation	Toxic aggregates of GFAP?
Canavan disease	Autosomal recessive	Megalencephaly, hypotonia, psychomotor regression	Diffuse subcortical signal abnormalities; increased NAA on MRS	Aspartoacylase gene mutation	Poorly understood

Leukodystrophy with neuroaxonal spheroids	Unclear- most cases sporadic but familial inheritance described	Adult onset disease may masquerade as MS or dementia	Symmetric confluent or multifocal white matter signal abnormalities	Neuroaxonal spheroids and pigmented glia on brain biopsy	Poorly understood
Pelizaeus Merzbacher disease	X-linked recessive	Infanatile onset in majority; nystagmus, impaired vision, ataxia, seizures	Symmetric confluent white matter signal abnormalities	*PLP1* gene mutation	Poorly formed myelin
Pelizaeus-Merzbacher-like disease	Unclear, but probably autosomal recessive	Indistinguishable from PMD	Symmetric confluent abnormalities	*GJA12* gene mutation in some	Poorly understood
Megalencephalic leukoencephalopathy with subcortical cysts	Unclear, but probably autosomal recessive	Megalencephaly, slowly progressive ataxia and spasticity, seizures	Subcortical cysts in temporal poles and frontoparietal regions	*MCL1* gene mutation	Poorly understood
Leukoencephalopathy with brainstem and spinal cord involvement and elevated white matter lacate	Autosomal recessive	In early adulthood cerebellar ataxia, spasticity, cognitive impairment	Brainstem and spinal cord involvement and elevated lactate on MRS	*DARS2* gene mutation	Poorly understood
Aicardi-Goutieres syndrome	Predominantly autosomal recessive, except subtype 5 which is autosomal dominant	Neonatal form presents with microcephaly, spasticity developmental delay and regression; later-onset variants with milder phenotype	Extensive calcification, cerebral hypoplasia, white matter signal abnormalities	*TREX1* and *RNASEH2A*-C gene mutations	Dysfunction DNA repair?

ABCD1, ATP-binding cassette, subfamily D, member 1; AD, autosomal dominant; AMN, adrenomyeloneuropathy; AR indicates autosomal recessive; DARS2, mitochondrial asparty1-tRNA synthecase; eIF, eukaryotic translation initiation factor; GFAP, Glial fibrillary acidic protein; GJA12, gap junction protein ; MCL, Megalencephalic leukoencephalopathy with subcortical cysts; MRS, magnetic resonance spectroscopy; MS, multiple sclerosis; NAA, N-acetylaspartic acid; PLP, proteolipid protein; PMD, Pelizaeus-Merzbacher disease; RNASEH2A-C—aspartyl-tRNA synthetase; TREX-3-prime@repair exonuclease 1.

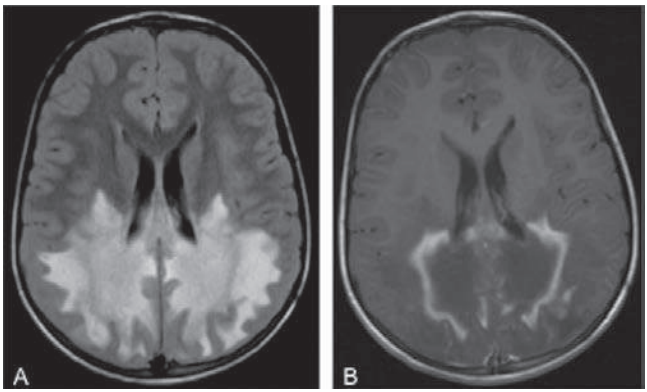


FIGURE 9.2 MRI of 7-year-old boy with cerebral X-linked adrenoleukodystrophy showing classic posterior confluent T2 hyperintensity on FLAIR **(A)** and contrast enhancement on T1-weighted image **(B)**.

Rx: Corticosteroid replacement therapy is life saving. Hematopoietic bone marrow transplantation, as soon as brain MRI shows lesion with contrast enhancement, is also life saving for cerebral ALD. Antiepileptic drugs (AEDs) for seizures.[3–5]

Zellweger Spectrum

Cerebrohepatorenal syndrome (infantile)

Defect: Mutations of genes involved in peroxisome biogenesis.

FHx: AR

Presentation: Continuum of 3 phenotypes: Zellweger syndrome (ZS), the most severe; neonatal ALD (NALD); and infantile Refsum disease (IRD), the least severe. Usually presents in the newborn period with severe hypotonia, feeding difficulties, and seizures, with facies, liver, and bone abnormalities. Older children have retinal dystrophy, sensorineural hearing loss, developmental delay with hypotonia, and liver dysfunction. **Other si/sx:** Biliary cirrhosis, arthrogryposis (limited extension of fingers & flexion deformities of knee & ankle), dysmorphic features (pear-shaped head: micrognathia, full cheeks, hypertelorism, high forehead), polycystic kidneys (PKD), retinal degeneration, chondrodysplasia punctata of patella & long bones.

Prognosis: Death by 1 y in the neonatal forms, can have slowly progressive course in older children.

Dx:

- Imaging: MRI-microgyria/pachygyria, heterotopias, and dysplasias of the inferior olive, areas of demyelination. X-rays of limbs with chondrodysplasia punctata (Fig. 9.3). Renal US: PKD.
- Labs: High plasma **VLCFA** (C26:0 and C26:1 and the ratios C24/C22 and C26/C22). High plasma pipecolic acid, phytanic acid, and/or pristanic acid. Very low C16 and C18 plasmalogens. High direct bilirubin, LFTs, and prolonged PTT from liver failure.

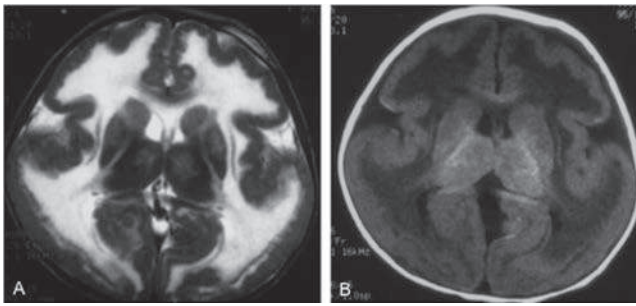


FIGURE 9.3 Zellweger Syndrome in a 5-Month-Old Girl. (A) T2-weighted MR image shows extensive areas of diffuse high signal intensity in the white matter. The gyri are broad, the sulci are shallow, and there is incomplete branching of the subcortical white matter, findings that suggest a migration anomaly with pachygyria. **(B)** On a T1-weighted MR image, the white matter abnormalities demonstrate low signal intensity.

- Biopsy: Skin for biochemical analysis of cultured fibroblasts confirms peroxisome biogenesis disorder.
- *Definitive dx:* Sequence analysis is available clinically for the following 12 genes: *PEX1* (68% of cases), *PXMP3* (*PEX2*), *PEX3*, *PEX5*, *PEX6*, *PEX10*, *PEX12*, *PEX13*, *PEX14*, *PEX16*, *PEX19*, and *PEX26*.

Rx: Symptomatic: gastrostomy to provide adequate calories, hearing aids, cataract removal in infancy, glasses, vitamin supplementation (K important to prevent bleeding disorders), primary bile acid therapy, AEDs, and possibly monitoring for hyperoxaluria.[6]

Metachromatic Leukodystrophy (Late Infantile, Juvenile, & Adult Forms)

Defect: Arylsulfatase A deficiency. Locus 22q13.31-qter. Also caused by saposin B deficiency (normal sulfatase activity). Locus 10q22.1.

FHx: AR

Presentation: *Late infantile form:* Normal development until age 2. Initially gait disturbances, peripheral neuropathy. Progressive distal to proximal lower extremity weakness with loss of DTR, ataxia, dysarthria, spasticity, blindness, mental retardation, and dementia. *Juvenile form:* Onset between 4 and 12 y. Behavioral/psychiatric symptoms with gait disturbances. Progressive truncal and limbs ataxia, spasticity, mental retardation, seizures, and dementia. *Adult form:* Onset after age 15 with psychiatric/schizophrenic symptoms. Mental retardation, seizures, and slowly progressive dementia follow. May have slow demyelinating polyneuropathy. **Other si/sx:** Optic atrophy. **Prognosis:** *Late infantile form:* Vegetative state, then death in late childhood. *Juvenile/adult form:* Vegetative state, then death within 10 y. *Adult form:* Vegetative state, then death within 20 y.

Dx:

- Imaging: MRI T2-hyperintense subcortical white matter with a streaky pattern sparing U fibers and posterior predominance. A scoring system is used to assess stages of disease, progression, and titrate therapeutic interventions[7] (Fig. 9.4).

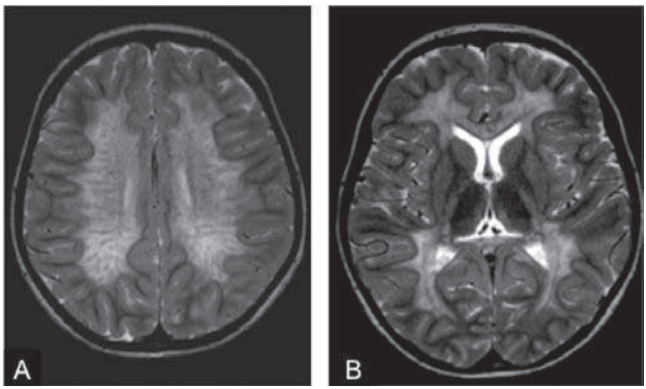


FIGURE 9.4 MRI in Juvenile Metachromatic Leukodystrophy. (A) The central white matter shows signal hyperintensity and a streaky pattern, while the subcortical U fibers are spared. **(B)** Involvement of corpus callosum and posterior limb of internal capsule. (Reproduced with permission from Kohlschutter A, Eichler F. Childhood leukodystrophies: a clinical perspective. *Expert Rev Neurother.* 2011;11:1485–1496.)

- Labs: Arylsulfatase A enzyme activity in leukocytes is less than 10% of normal controls (cannot distinguish from pseudodeficiency where activity varies from 5% to 20%). Urine: high sulfatides.
- NCS: Reduced motor conduction velocities (only late in the course of the juvenile/adult form).
- Biopsy: Skin for enzyme assay in cultured fibroblasts (useful in late onset). Metachromatic lipid deposits in nervous system tissue.
- *Definitive dx:* Low enzyme activity in peripheral leukocytes or cultured fibroblast. Newborn screening (not expanded yet). Prenatal dx from amniocentesis.

Rx: Bone marrow or unrelated umbilical cord blood transplantation in the early clinical stages.[8] AEDs. Antipsychotics for adult form when agitation and hallucinations are present.

Krabbe Disease: Globoid Cell Leukodystrophy (Infantile Form & Late-Onset Form)

Defect: Accumulation of galactosylceramide due to galactosylceramide beta-galactosidase deficiency. Locus 14q31.

FHx: AR

Presentation: *Classic infantile form:* Onset at 4 mo (range, 1–7 mo) with irritability and startle myoclonus, followed by developmental arrest, hypertonicity, → opisthotonos, terminally hypotonia. Peripheral neuropathy and seizures are common. *Late onset:* Onset from age 2 to 20 y. Progressive spastic paraparesis, dementia, and cortical blindness. **Other si/sx:** Macular cherry-red spot in infantile form. Optic nerve atrophy in late-onset form.

Prognosis: *Infantile form:* Death typically within 1 y. *Late onset:* Variable. Slow or rapid progression to disability and death.

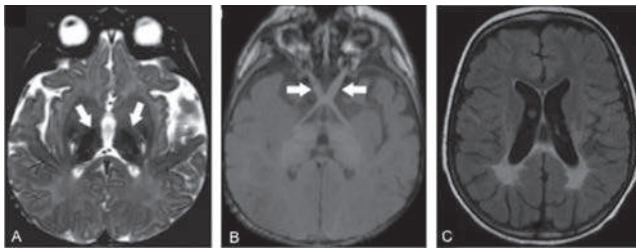


FIGURE 9.5 MRI of Infant with Krabbe's Disease. (A) Signal changes in T2-weighted images in the bilateral thalami, **(B)** optic nerve enlargement, **(C)** FLAIR hyperintensity affecting the posterior white matter. (Reproduced with permission from Krishnamoorthy KS, Eichler FS, Goyal NA, et al. Case records of the Massachusetts General Hospital.) Case 3–2010. A 5-month-old boy with developmental delay and irritability. *N Engl J Med.* 2010;362:346–356. doi:10.1056/NEJMcpc0907806.

Dx:

- Imaging: MRI T2-hyperintense diffuse white matter demyelination with parieto-occital cortex involved early (Fig. 9.5). A scoring system is used to assess stages of disease, progression, and titrate therapeutic interventions.[9]
- Labs: CSF—high protein. NCS—reduced motor conduction velocities.
- Biopsy: Skin for enzyme assay in cultured fibroblasts.
- *Definitive dx:* Low enzyme activity in peripheral leukocytes or cultured fibroblasts. Newborn screening (currently available only in NY).[10] Prenatal dx via amniocentesis.

Rx: Hematopoietic stem cell transplant from bone marrow or allogenic umbilical cord in infants before onset of symptoms may reverse and slow the course.[11]

Vanishing White Matter Disease (VWMD)

Defect: Caused by mutations in eukaryotic initiation factor 2B (eIF2B).

FHx: AR, with age-dependent penetrance.

Presentation: The prenatal/congenital (onset age <1 y) form is characterized by severe encephalopathy. In the later-onset forms (early childhood, onset age 1–5 y or late childhood 5–15 y), initial development is normal, followed by ataxia, spasticity, and seizures with a chronic progressive or subacute course. Chronic progressive decline can be exacerbated by rapid deterioration during febrile illnesses or following head trauma or major surgical procedures, or by acute psychological stresses, such as extreme fright. In the rare reports of adult-onset VWMD, the typical presentation consists of cognitive deterioration, pseudobulbar palsy, and progressive spastic paraparesis.

Other si/sx: Primary or secondary amenorrhea due to ovarian failure has been described (ovarioleukodystrophy).

Prognosis: Patients usually survive only a few years past the clinical onset, although the course is variable even among patients with mutations in the same eIF2B subunit.

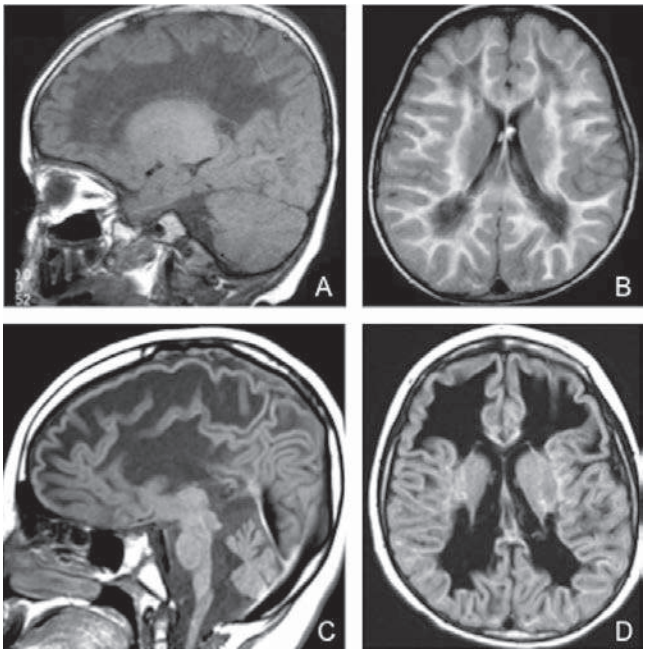


FIGURE 9.6 T1-weighted MR images of a child with vanishing white matter disease demonstrating abnormal signal affecting frontal, parietal, and occipital white matter at 3 y of age **(A&B)** and its progression over 4 y to the classic cavitations with preserved ventricular size **(C&D)**.

Dx:

- Imaging: Diffuse and symmetric abnormal white matter with signal intensity close to CSF on T1-weighted, T2-weighted, and FLAIR (Fig. 9.6).
- Labs: Routine labs and CSF are normal.
- *Definitive dx:* Sequence analysis to detect mutations in 1 of 5 genes (*EIF2B1*, *EIF2B2*, *EIF2B3*, *EIF2B4*, *EIF2B5*) encoding the 5 subunits of the eIF2B. If negative, deletion/duplication analysis should be performed.

Rx: Symptomatic: Physical therapy, ankle–foot orthotics, and AEDs for treatment of seizures and abnormalities of behavior and mood.

Alexander Disease

Defect: Mutations in GFAP, which encodes glial fibrillary acidic protein.

FHx: AD or sporadic de novo mutations.

Presentation: Disorder of cortical white matter that predominantly affects infants and children and usually results in death within 10 y after onset. Most individuals with Alexander disease present with nonspecific neurologic signs and symptoms. Three forms are typically recognized: infantile, juvenile, and adult. It has been suggested that the subset of infants with neonatal onset (i.e., within 30 d of birth) constitutes a separate neonatal

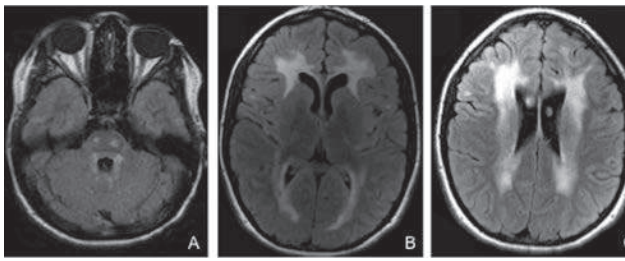


FIGURE 9.7 MRI of Juvenile Alexander Disease. (A) Signal abnormalities in the pons and the dentate nucleus, **(B)** anterior and posterior periventricular white matter, and **(C)** the peculiar garland-like structures along the ventricular wall.

form. Progressive psychomotor retardation with loss of developmental milestones, megalencephaly, seizures, hyperreflexia and pyramidal signs, ataxia, and hydrocephalus secondary to aqueductal stenosis.

Other si/sx: Megalencephaly and frontal bossing can be early sign in infantile form. In adult form, bulbar/pseudobulbar signs (including speech abnormalities) and swallowing difficulties occur.

Prognosis: Mostly progressive, but there can be periods of stagnation. Disease stabilization has also been observed in late-onset forms (personal observation).

Dx:

- Imaging: Diffuse cerebral white matter abnormalities with a frontal preponderance and a periventricular rim of decreased signal intensity on T2-weighted images and elevated signal intensity on T1-weighted images. Abnormalities of the basal ganglia, thalami, and brainstem. Contrast enhancement of one or more of the following: ventricular lining, periventricular rim, frontal white matter, optic chiasm, fornix, basal ganglia, thalamus, dentate nucleus, brainstem (Fig. 9.7).
- Labs: Sequence analysis of *GFAP* gene.
- Biopsy: Prior molecular testing; the demonstration of enormous numbers of Rosenthal fibers was prevalent.
- *Definitive dx:* Sequence analysis of *GFAP* gene.

Rx: Symptomatic: Physical therapy, ankle-foot orthotics, and AEDs for treatment of seizures and abnormalities of behavior and mood.

Canavan Disease

Defect: Aspartoacylase deficiency. Locus 17pter-p13. **FHx:** AR, Ashkenazi Jews.

Presentation: Early infancy with atonic neck muscles, hypotonia, hyperextension of legs and flexion of arms, blindness, severe developmental delay, and megalocephaly. Others present after 2 y, with mental retardation and extrapyramidal cerebral palsy. Seizures later in the course.[12] **Prognosis:** Death typically by 18 mo.

Dx:

- Imaging: MRI symmetric T2 hyperintensities in the basal ganglia, later diffuse leukodystrophy (Fig. 9.8). High *N*-acetylaspartic acid (NAA) peak on MRS.

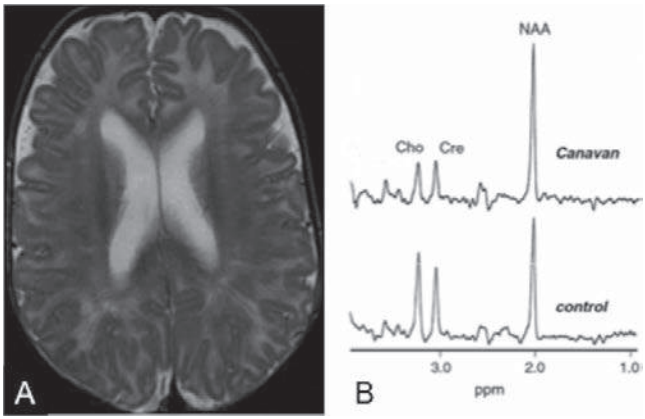


FIGURE 9.8 MRI of Canavan disease. (A) Megalencephaly with diffuse white matter T2-weighted hyperintensity, **(B)** MRS demonstrating high NAA peak in Canavan disease, compared with control. (Adapted from Costello DJ, Eichler AF, Eichler FS. Leukodystrophies: classification, diagnosis, and treatment. *Neurologist*. 2009;15:319–328.)

- Labs: Very high levels of NAA in the urine, plasma, & CSF.
- Biopsy: Skin for enzyme assay in cultured fibroblasts, postmortem brain spongy degeneration of astrocytes with normal neurons.
- *Definitive dx:* Targeted mutation analysis of ASPA gene (two mutations account for 98% of cases). If negative, sequence the ASPA gene. If not detected, perform deletion/duplication analysis. Prenatal dx via amniocentesis.[13]

Rx: Symptomatic, directed to providing adequate nutrition and hydration, managing infectious diseases, and protecting the airway. Physical therapy to minimize contractures. AEDs for seizures. A G-tube may be required to maintain adequate intake and hydration in the presence of swallowing difficulties. Acetazolamide seems to reduce intracranial pressure. Botox injections may be used to relieve spasticity.

Pelizaeus–Merzbacher Disease

Defect: *PLP1* gene.

FHx: X-linked or *de novo* mutations.

Presentation: Phenotypes range from Pelizaeus–Merzbacher disease (PMD) to spastic paraplegia 2. PMD typically manifests in infancy or early childhood with nystagmus, hypotonia, and cognitive impairment, followed by severe spasticity and ataxia. **Prognosis:** Shortened life span. SPG2 usually normal life span.

Dx: Clinical diagnosis of PLP1-related disorders depends on typical neurologic findings, X-linked inheritance pattern, and, usually, the finding of diffusely abnormal myelin on MRI. Molecular genetic testing of PLP1.

- Imaging: Diffusely increased signal intensity in the central white matter of the cerebral hemispheres, cerebellum, and brain stem; may not be definitive until a child is at least age 1 to 2 y.
- Labs: Molecular genetic testing of PLP1.

- *Definitive dx:* Molecular genetic testing of PLP1.
- **Rx:** Gastrostomy for individuals with severe dysphagia; AEDs for seizures; routine management of spasticity, including physical therapy, exercise, medications (baclofen, diazepam, tizanidine, botulinum toxin), orthotics, and surgery for joint contractures.

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10 Common Neurogenetic Syndromes

Anna L. Pinto and Jurriaan M. Peters

Genetics has become a promising and active research and clinical field within neurology. This young discipline applies molecular genetic techniques to the investigation of classical neurological disorders and symptoms. Novel genetic and metabolic tests are increasing the ability to provide an etiologic diagnosis for children with unexplained global developmental delay and deficits in intellectual development. A genetic etiology should be suspect in all patients who present with developmental delay, autism spectrum disorder (ASD), epilepsy, abnormal head size or shape, movement disorders, as well as dysmorphic features. Given the complexity and costs of genetic testing, clinicians should aim for a rational approach to an accurate etiologic diagnosis focusing on initial tests with high diagnostic yield.

PATTERNS OF INHERITANCE

Single Gene (Mendelian)

(1) AUTOSOMAL: Then defective gene is on a non-sex chromosome.

Dominant (AD): Monogenic AD disorders occur through the inheritance of a single copy of a defective gene found on a non-sex chromosome. The single defective copy is sufficient to override the normal functioning copy, resulting in abnormal protein functioning or expression.

Recessive (AR): Monogenic AR disorders occur through the inheritance of both copies of the defective gene, one from each parent.

(2) X-LINKED: The defective gene lies on the X sex chromosome.

Dominant (XD): Less frequent than recessive, both males and females can be affected. The exact pattern of inheritance varies, depending on whether the father or the mother has the trait of interest. All daughters of an affected father will also be affected, but none of his sons will be affected; and the mother of an affected son is also affected.

Recessive (XR): A female with a gene mutation on one X chromosome would be a carrier. On average, 50% of her sons will inherit the mutation and develop the disorder, and 50% of her daughters will inherit the mutation and become a carrier.

Non-Mendelian

(1) MULTIFACTORIAL INHERITENCE: >1 genetic factor is involved in developing a specific condition, and environmental (epigenetic) factors also participate in the causation of a disease.

(2) MITOCHONDRIAL INHERITANCE: Mitochondria contain their own DNA (mtDNA), distinct from nuclear (chromosomal) DNA. Mutation in the mitochondrial DNA can only be transmitted by the mothers to male or

female offspring. Not all mitochondrial disease comes from mtDNA; mutations in nuclear genes that code for mitochondrial proteins may be inherited in an AD, AR, or X-linked fashion.

(3) MISCELLANEOUS: Genomic imprinting is when differential monoallelic expression of a biallelic gene occurs, depending on the male or female parental origin of gene. Thus, with the silencing of imprinted alleles, there is *no* biparental contribution to the genome. This is done through DNA methylation (see below) or histone modifications. **Uniparental disomy (UPD)** occurs when both chromosome pairs come from a single parent. **DNA methylation** causes modification of regulation of gene expression without altering the DNA sequence. **Somatic mosaicism** occurs when different genotypes arise from a single fertilized egg cell, due to mitotic errors at first or later cleavages.

DIAGNOSTIC TOOLS

DETECTING CYTOGENETIC ABNORMALITIES: Chromosomal number and rearrangements can be tested at both structural and molecular levels. **Karyotype** (or chromosome) analysis enables the entire chromosome structure to be viewed at one time, but only detects aneuploidies and major structural rearrangements. **Fluorescence in situ hybridization (FISH)** is a molecular technique using specific loci-labeled probes spaced throughout the genome, and has higher sensitivity, specificity, and resolution, compared with chromosome analysis; however, small mutations and UPD can be missed. **Chromosomal microarray analysis (CMA)**, **also called comparative genomic hybridization (CGH) or array CGH (aCGH)**, is increasingly the first-line test of genetic screening and can be used in targeted conditions or applied to the whole genome for identification of copy number variation (CNV), including deletion/duplication. However, balanced structural rearrangements and small amounts of mosaicism can be missed. **Methylation studies** detect DNA methylation.

DETECTING MUTATIONS: Done with targeted tests or gene panels based on phenotype, and thus typically limited to a predefined number of sequence changes selected in advance. **Polymerase chain reaction (PCR)** is the 1st step in the vast majority of DNA analysis. **Amplification refractory mutation system (ARMS)** is a modified PCR technique, requiring a multiplex PCR reaction. **Single nucleotide polymorphism (SNP) arrays** detect the most common type of genetic variation among people, and may assist in the prediction of an individual's response to certain drugs (pharmacogenetics), susceptibility to environmental factors such as toxins, and risk of developing particular diseases. **Multiplex ligation-dependent probe amplification (MLPA)** has become a rapidly growing technique used in the detection of exon deletion. **Whole exome sequencing** is a highly advanced test developed for the identification of DNA changes causative or related to a medical condition in a patient. Exons or coding regions of thousands of genes are analyzed simultaneously using next-generation sequencing techniques. Interpretation of the results requires considerable expertise, and mapping the function of the entire human genome is a work in progress.

COMMON SPECIFIC CYTOGENETIC SYNDROMES

Trisomy 21[1] (Down Syndrome, DS)

EPIDEMIOLOGY: Most common autosomal anomaly and most common single cause of mental retardation. Incidence ~1 in 1,000 newborns, strongly associated with advanced maternal age (≥35 y).

GENETICS: Trisomy 21 is most common. Nonreciprocal translocation (~10%, often chromosome 21 to chromosome 14) has same clinical phenotype. Mosaicism (2%–3%) is associated with a higher intellectual development. **Karyotype analysis** shows presence of an extra chromosome 21 in all or some percentage of somatic cells. Recurrence/mode of inheritance in siblings of true trisomy is rare (<1%), and recurrence of translocation is more common (5%–15%).

PATHOPHYSIOLOGY: Thought to be in part related to overexpression of 21q22 region with a DS cell adhesion molecule (DSCAM, role in neuronal migration, axon guidance, neural connectivity) and a protein kinase (DYRK1, role in postembryonic neuronal cell proliferation).

CLINICAL PRESENTATION: Unusual association of common anomalies: **facial dysmorphism** (brachycephaly, flat nasal bridge, laterally upslanting and narrow palpebral fissures, epicanthal folds, simple C-shaped ear with deficient cartilage and narrow external auditory canal, open mouth with prominent protruding fissured tongue, low posterior hairline), **physical habitus** (short stature and neck, excessive skin at nape of neck, obesity, hypotonia with lax joints, broad hands with single palmar crease, brachy- and 5th-digit clinodactyly, wide 1–2 toe gap). **Mental retardation** (IQ, 25–49; average 43) with social skills better than expected from their IQ. Note that an adult with DS is considered competent to make medical decisions unless declared otherwise. **Multisystem involvement:** See Table 10.1.

TABLE 10.1 Down Syndrome: Common Associated Anomalies and Management

	Neonate–Children	Older Children–Adults	Management
Cardiac	Congenital heart disease: AVSD 45%, VSD 35%, ASD, PDA 10%, others	MVP 57%, AI, acquired valvular heart dz	Routine auscultation, echocardiogram, and cardiology consult as needed
GI	Duodenal or anal atresia, megacolon, Hirschsprung disease	Celiac disease	Monitor growth (length, weight), diarrhea, abdominal discomfort
Neurologic	Mental retardation: decline in 1st decade and plateau in adolescence, learning and language disorders (special education), autism 7% Infantile spasms or seizure disorder (GTCs and myoclonic seizures) 8% Hypotonia	Presenile dementia: 75% in >60 y Seizure disorder (SPS or CPS, others)	Clinical vigilance: seizures, loss of skills, apathy, personality change, focal neural deficits, psychiatric comorbidity. R/o medical conditions Management not specific to DS Management not specific to DS
Ophthalmologic	Congenital cataracts and glaucoma, refractive errors, strabismus, nystagmus	Cataracts, refractive errors, keratoconus	Ophthalmology consult q1y

TABLE 10.1 Down Syndrome: Common Associated Anomalies and Management (Continued)

	Neonate–Children	Older Children–Adults	Management
ENT	Conductive > sensorineural/mixed hearing loss 70% Recurrent acute and chronic otitis, middle ear effusions, endolymphatic hydrops	Hearing loss OSAS 50% Periodontal disease	Comprehensive hearing eval @ 6–12 mo. Auditory testing q2y. Rx recurrent otitis, surgical interventions (tubes, T&A) Speech Rx, communication enhancement, hearing aids Clinical vigilance, surgical interventions, CPAP Supervised brushing, dentist q6 mo
Endocrine	Hypothyroidism Primary gonadal deficiency	Hyper- & hypothyroidism Diabetes mellitus Obesity Gonadal deficiency with subfertility	TFTs at 0, 6 mo, then q1y Clinical vigilance, no routine testing DS growth charts, diet, Ca^{++}/vit. D, behavioral interventions, physical & social activities-Management not specific to DS
Musculoskeletal	Hypotonia JRA acquired hip dislocation	Atlantoaxial subluxation 15%–40% and cervical compressive myelopathy	Clinical vigilance: neck pain, gait, bowel/bladder control, pyramidal tract signs, torticollis, weakness Lateral X-ray neutral, flexion, extension, advanced imaging techniques
Mental health	Depression, OCD, aggression, conduct disorder, ADHD—all ~6%, autism 7% Sexual or physical abuse	Same	Psychopharmaca, interventions not specific to DS
Hematologic	Polycythemia, macrocytosis, and transient myeloproliferative disorder (neonates) AML (1:300) and ALL (1:300)		Clinical vigilance Interventions not specific to DS

(continued)

TABLE 10.1 Down Syndrome: Common Associated Anomalies and Management (Continued)

	Neonate–Children	Older Children–Adults	Management
Misc	Xeroderma Hyperkeratotic lichenification Other dermatologic	Testicular cancer Reproduction & sexuality Orthopedic/ podiatric	Annual clinical examination, gynecologic surveillance, psychosocial assessment, counseling, refer as indicated

ADHD, attention deficit hyperactivity disorder; AI, aortic insufficiency; ALL, acute lymphoblastic leukemia; AML, acute myelocytic leukemia; ASD, atrial septum defect; AVSD, atrioventricular septum defect; CPAP, continuous positive airway pressure; CPS, complex partial seizure; ENT, ear nose throat; GTC, generalized tonic–clonic seizure; JRA, juvenile rheumatoid arthritis; MVP, mitral valve prolapse; OCD, obsessive compulsive disorder; OSAS, obstructive sleep apnea syndrome; PDA, patent ductus arteriosus; Rx, therapy or treatment; SPS, simple partial seizure; TFTs, thyroid function tests; VSD, ventricular septum defect.

PRESENILE DEMENTIA: Increasing prevalence with age (3rd decade, 10%; 4th, 10%–25%; 5th, 28%–55%; 6th, 30%–75%). Early signs and symptoms include speech and gait deterioration, later include adult-onset seizures and myoclonus, apathy, behavioral or personality change, psychiatric comorbidity, focal neurological signs, urinary and fecal incontinence, sleep disorders, cognitive and memory impairment. Pathophysiology parallels Alzheimer disease (AD) with overexpressed amyloid-β precursor protein from 21q21 region. Gender (male), estrogen deficiency, elevated expression of beta-site APP-cleaving enzymes (BACE), valine polymorphism of prion protein gene, and carriers of apolipoprotein E4 allele may have accelerated decline. Imaging may show premature aging, calcifications of basal ganglia, and cerebellar folia; age-related atrophy resembles the pattern of brain atrophy in early stages of AD. Management and diagnosis are not specific to DS.

PROGNOSIS: Multiple factors affect outcome, including associated conditions. Life expectancy is in the mid-50s. Many people with this syndrome form meaningful relationships and eventually marry.

Klinefelter Syndrome[2]

EPIDEMIOLOGY: Affects 1 in 500 to 1,000 males and does not occur in females.

GENETICS: 47,XXY variant is found in 80% to 90% of patients, and about 10% of patients will have mosaicism. Karyotypes include 46,XY/47,XXY; 46,XY/48,XXXY; and 47,XXY/48,XXXY.

PATHOPHYSIOLOGY: Involves the extranumerary X chromosome whose genes play roles in many body systems, including testicular function, brain development, and growth. As the number of X chromosome increases, somatic and cognitive developments are more likely to be affected. Whether the morbidity associated with the syndrome results from the hormonal abnormalities or abnormal function of the X chromosome-linked genes is unclear. Besides cytogenetic analysis, androgen receptor gene quantitative real-time PCR (AR-qPCR) is a reliable screening method for disorders involving aberrant number of X chromosome. The recurrence risk is not increased above that in the general population.

CLINICAL PRESENTATION: Shortage of testosterone is associated with small testes, gynecomastia, reduced facial and body hair, and infertility. In addition, patients can present with tall stature, narrow shoulders, broad hips, osteoporosis, varicose veins, thromboembolic disease, or diabetes mellitus. Neurologically, epilepsy, learning disabilities, and difficulty with speech and language development are seen.

MANAGEMENT: Multidisciplinary team approach should address three major aspects of the disease: hypogonadism, gynecomastia, psychosocial and developmental problems (including speech impairment, academic difficulties, and behavioral problems). **Monitoring and health maintenance:** Endocrinology for testosterone replacement therapy, routine bone density screening for risk of osteopenia and osteoporosis. Hypercoagulability screening, given the increased risk for deep venous thrombosis and pulmonary embolism. Adult males have an increased risk of developing breast cancer and immunologic disease such as systemic lupus erythematosus.

PROGNOSIS: Generally good; patients are at risk for developing the aforementioned comorbidity.

22q11.2 Microdeletion Syndromes (DiGeorge and Velocardiofacial Syndrome,[3] and Phelan/McDermid Syndrome[5])

EPIDEMIOLOGY: Prevalence ~1:5,000 (velocardiofacial [VCF]) and ~1: 2–4,000 (DiGeorge).

GENETICS: Most frequent microdeletion of 22q11.2. High-resolution chromosome analysis; FISH for a chromosome region 22q11 deletion. Recurrence will depend on the parental status. Parental carrier frequency is ~10%. Most patients carry a de novo mutation. If DiGeorge is suspected but testing is negative, consider *TBX1* gene sequencing and consult with clinical geneticist.

PATHOPHYSIOLOGY: The microdeletion includes genes that affect, in part, the migration of neural crest cells and early development of the branchial arches.

CLINICAL PRESENATION: Velo (69%; overt or submucous cleft palate, velopharyngeal insufficiency with rhinolalia aperta), **cardio** (conotruncal defects, including tetralogy of Fallot, ventricular septal defect, interrupted aortic arch, and truncus arteriosus), **facial** (prominent bulbous nose w/ squared root, hypertelorism, micrognathia), and parathyroid deficiency with hypocalcemia (20%). Immunodeficiency (77%), feeding problems (30%), renal anomalies (37%), conductive and sensorineural hearing loss, laryngotracheoesophageal anomalies, growth hormone deficiency, autoimmune disorders, seizures (without hypocalcemia), and skeletal abnormalities. **Neurologically**, learning difficulties or mild mental retardation (MR; 70%–90%). Associated with perisylvian and frontal polymicrogyria and epilepsy. Associated with a variety of psychiatric disorders, including schizophrenia. **DiGeorge syndrome**[4] involving thymic hypoplasia and hypocalcemia at birth is also a common finding, clinically one sees to feeding difficulties (poor sucking and swallowing problems). Immunodeficiency of the T-cell lines. Facial features include low-set ears, hypertelorism, and narrow upper lip. Neurological manifestations include global development delay, learning disabilities, and hypotonia. **Monitoring and health maintenance** includes absolute lymphocyte count in the peripheral blood; ionized calcium and parathyroid hormone level. Mental health care for ADHD, depression, and other behavioral disorders.

TABLE 10.2 22q11.2 Deletion Syndromes: Common Problems, Management

System, Condition	Monitoring/Intervention
Cardiac: tetralogy of Fallot, interrupted aortic arch, ventricular septal defect, and truncus arteriosus	Cardiology referral Management not specific to 22q11.2 deletion syndromes
GI: feeding difficulties	Modification of spoon placement when eating, treatment for gastroesophageal reflux with acid blockade, prokinetic agents, and postural therapy
Immunology: infections Lymphocyte deficiency	Aggressive Rx Avoid live vaccines. Rare: prophylactic antibiotics, IVIG therapy, thymic transplantation
Misc: low Ca^{++}	Ca^{++} supplementation, endocrine evaluation
Palatal abnormalities	Craniofacial team
Ectopic internal carotid arteries	MRA prior to palate repair surgery
Developmental delay	Early intervention w/ ST, OT, PT
Renal abnormalities	Renal U/S
Vertebral abnormalities	Chest XR

Ca++, calcium; IVIG, intravenous gammaglobulin; MRA, magnetic resonance angiography; OT, occupational therapy; PT, physical therapy; Rx, therapy or treatment; ST, speech therapy; U/S, ultrasound; XR, x-ray.

Adapted from 22q11.2 Del syndrome. In: *Gene Reviews*. Available at www.ncbi.nlm.nih.gov/bookshelf.

MANAGEMENT: Check calcium serum in newborns and in any patient at any age with VCF syndrome, and monitor for seizure disorder. Perform immune studies, including T-cell marker studies. Cardiac evaluation. Outcome depends on the severity of the cardiac problem. (See Table 10.2).

Smith–Magenis Syndrome[6]

EPIDEMIOLOGY: ~1:15,000 births.

GENETICS: Mutation or deletion of the *RAI1* gene on chromosome 17p11.2. Diagnosis is made by cytogenetic analysis, FISH, or CMA. Virtually all occurrences are de novo.

PATHOPHYSIOLOGY: Unknown, haploinsufficiency of the *RAI1* may affect gene/protein function.

CLINICAL PRESENTATION: Minor skeletal (brachycephaly, brachydactyly, short stature) and craniofacial features (*cherubic* appearance with prominent forehead, midface hypoplasia, prognathism, epicanthal folds, upslanting palpebral fissures, synophrys), hoarse voice, obesity. Neurological manifestations include infantile hypotonia, complacency, and lethargy. Later speech delay with or without hearing loss, psychomotor and growth retardation with broad flapping gait, behavioral problems.

MANAGEMENT: See Table 10.3.

16p11 Deletion/Duplication[7]

EPIDEMIOLOGY: ~3 in 10,000 births.

GENETICS: Pathophysiological mechanism unknown. FISH, MLPA, and quantitative PCR (qPCR) can be used for initial detection of the deletion

TABLE 10.3 Smith–Magenis Syndrome: Common Problems, Management

	Infant–Child	Adolescent–Adult	Management
Language & hearing	Speech delay Hearing loss (conductive and/or sensorineural) Recurrent otitis media	Typically stable. Better communication with better behavior	Early intervention, hearing evaluation, augmentative communication programs
Behavior	Stereotypies Self-abusive behaviors	Impulsivity, aggression Rage outbursts Self-injurious behaviors Attention seeking Mood lability Disobedience	Rule out medical cause for behavior Medication (anecdotal), polypharmacy is typical: stimulants, lithium, valproic acid, atypical neuroleptics, SSRI, beta-blockers, melatonin. In general, management not specific to SMS
Neurologic	Seizure disorder Sleep disturbances: short sleep cycle, early risers, frequent nighttime awakenings and daytime naps, snoring, enuresis Peripheral neuropathy (decreased pain sensation, hyporeflexia, nonprogressive)	Sleep problems become chronic	Management not specific to SMS Melatonin (anecdotal) Management not specific to SMS
Misc	Hypercholesterolemia, obesity, pes planus/cavus, abnormal thyroid function tests	Scoliosis, obesity	Management not specific to SMS Avoid medications that increase appetite

SMS, Smith–Magenis syndrome; SSRI, selective serotonine reuptake inhibitor.

Adapted from Gropman AL, Duncan WC, Smith AC. Neurologic and developmental features of the Smith-Magenis syndrome (del 17p11.2). *Ped Neurol*. 2006;34(5):337–350.

and are used as confirmation of CGH findings. CGH and qPCR are used to determine the size of the microdeletion and to test relatives of a proband with a known deletion. Inheritance is AD, but typically de novo mutations are found.

CLINCAL PRESENTATION: Obesity and tall stature are common. Cataracts, cardiac defects, obesity, dysmorphic features, including a prominent forehead. Schizophrenia is associated with microduplications. Neurologically, may present with developmental delay, epilepsy, intellectual disability, and ASD. Expressive language more affected than receptive language.

MANAGEMENT: Close monitoring of height and weight. Consider cardiac evaluation with echocardiography. Screening for hypertension and diabetes in the overweight patients. Assessment for cognitive and behavior disorders, and management of ASD.

1q21.1 Deletion Syndrome[8]

EPIDEMIOLOGY: ~0.2% of individuals with developmental delays, intellectual disabilities.

GENETICS: Microdeletion of 1q21.1 with reduced penetrance and variable expressivity.

PATHOPHYSIOLOGY: There is a poor genotype–phenotype correlation as individuals with the deletion may be normal, and those affected present with large phenotypic variability. Haploinsufficiency of one or more of the deleted genes associated with 1q21.1 microdeletion syndrome likely contributes to the phenotype. AD inheritance, and 18% to 50% are de novo deletions.

CLINICAL PRESENTATION: Facial dysmorphism (mild) and microcephaly, eye abnormalities, cardiac defects, genitourinary anomalies, skeletal malformations. Neurologically, may present with ASD, schizophrenia, sleep disorders, epilepsy, ADHD, developmental delays, and learning difficulties.

MANAGEMENT: Symptomatic, management not specific to identified medical and developmental issues. Developmental screening and routine pediatric care.

Beckwith–Wiedemann Syndrome (BWS)[9]

EPIDEMIOLOGY: ~1:13,700 births.

GENETICS: Mutations in *CDKN1C*. Cytogenetic abnormalities of chromosome 11p15 are found in 1%. Paternal UPD (20%) and gain of methylation at imprinting center 1 (IC1; 5%) and loss of methylation at imprinting center 2 (IC2; 50%) lead to abnormal regulation of gene transcription on chromosome 11p15.5. Finally, sequence analysis of *CDKN1C* identifies mutations in ~40% of familial cases and 5% to 10% of cases with no family history. The risk to the siblings of a child with BWS depends on the genetic basis of BWS in the proband.

CLINICAL PRESENTATION: Disorder of abnormal growth, resulting in macrosomia, macroglossia, visceromegaly, embryonal tumors (e.g., Wilms tumor, hepatoblastoma, neuroblastoma, and rhabdomyosarcoma), omphalocele, neonatal hypoglycemia, ear creases/pits, adrenocortical cytomegaly, and renal abnormalities. Typically have normal development unless suffer complications from hypoxia and untreated hypoglycemia. Autism has been reported.

MANAGEMENT: Close monitoring for hypoglycemia, especially in the neonatal period. Abdominal wall repair for omphalocele. Macroglossia may warrant endotracheal intubation (acute compromise of airway), nasogastric tube feeding, surgical reduction of the tongue, and speech therapy. Embryonal tumor screen by abdominal US every 3 mo until age of 8 y. Serum alpha-fetoprotein (AFP) monitoring every 2 to 3 mo in the first 4 y for early detection of hepatoblastoma. Annual renal US for nephrocalcinosis and other renal findings. Significant growth asymmetry in limbs or face may require orthopedic or craniofacial surgery. Early death may occur from complications of prematurity, hypoglycemia, cardiomyopathy, macroglossia, or tumors. After childhood, prognosis is generally favorable.

Charge Syndrome[10]

EPIDEMIOLOGY: Incidence ~1:10,000 births.

GENETICS: *C*oloboma, *H*eart defects, choanal *A*tresia, *R*etarded growth and development, *G*enital abnormalities, and *E*ar anomalies result from mutations of the *CHD7* gene. This gene is from the chromodomain-helicase-DNA-binding family, and its product forms complexes with different proteins essential for neural crest gene expression and cell migration. Sequence analysis of the *CHD7* gene detects mutations in ~60% to 70% of cases. AD inheritance with variable expressivity, so with affected parents the risk to the siblings is 50%. If neither parent is affected, the empiric risk to sibs of a proband is ~1% to 2%.

CLINICAL PRESENTATION: Uni- or bilateral coloboma of the iris, retina-choroid, and/or disc with or without microphthalmos; unilateral or bilateral choanal atresia or stenosis; abnormal outer ears, ossicular malformations, cochlear defect, absent or hypoplastic semicircular canals; cryptorchidism in males and hypogonadotrophic hypogonadism in both males and females; cardiovascular malformations; growth deficiency; orofacial clefts; and tracheoesophageal fistula. Neonates with CHARGE syndrome often have multiple life-threatening medical conditions. Feeding difficulties are a major cause of morbidity in all age groups. Neurological associations include (severe) developmental delay and several cranial nerve abnormalities resulting in hyp- or anosmia, facial palsies, impaired hearing, and swallowing problems.

MANAGEMENT: Neonates require immediate evaluation of the airway, feeding, heart, and hearing. Management involves tracheostomy and surgical correction of choanal atresia as needed; a multidisciplinary approach to feeding therapy, including specialists in speech-language pathology, occupational therapy, and nutrition and gastrostomy as needed; routine care for heart defects; and hearing aids and hearing habilitation as soon as hearing loss is documented. Psychological/school evaluations should be performed by a team that includes specialists in deafblindness when dual sensory loss is present. Regular ophthalmologic and audiologic evaluations. Testing for hypogonadotropic hypogonadism if puberty has not occurred by age 13 to 14 y.

Fragile X Syndrome[11]

EPIDEMIOLOGY: ~1:2,000 to 3,600 males or ~1:8,000 females, carriers are ~10× more common.

GENETICS: X-linked inheritance. Large amplification of trinucleotide repeat (CGG) sequence in fragile X gene (*FMR1*): normal, 5–44 repeats; "gray zone," 45–54 repeats; premutation, 54–200 repeats; and full mutation, >200 repeats. The abnormal fragile X MR protein (FMRP) leads to impaired control of cytoskeletal organization with abnormal dendritic spine morphology and synapse formation during neuronal development. Cytogenetic analysis of the "fragile" site at chromosome Xq27.3 is false negative in ~20%, so standard is karyotype and DNA analysis (PCR or Southern blot). Other mutations in *FMR1* gene may give same phenotype. Complex multigenerational inheritance, variable phenotype, implications for other family members. Female premutation carriers are at risk for having offspring with full mutation since expansion of CGG repeat occurs with oogenesis more so than with spermatogenesis. Daughters from male premutation carriers will be obligate carriers too.

CLINICAL PRESENTATION: Most obvious post puberty: subtle facial dysmorphism with long face with prominent brow, jaw, large ears, squared chin,

macroorchidism, and hyperextensible skin and joints. Neurological symptoms include moderate to severe mental retardation, hypotonia, normo- or macrocephaly, autism (30%–70%), epilepsy (15%, most common in young children), hyperactivity, and behavioral problems. In males IQ decreases over time. **Carriers:** Female—ovarian dysfunction (elevated FSH), 20% premature ovarian failure (cessation of menses <40 y); male—milder phenotype with behavioral (attentional, hyperactivity, anxiety, autism spectrum) and learning problems. **Mosaicism** (coexistent small and large amplications) is associated with a milder phenotype too. **Tremor/ataxia syndrome (FXTAS):** Late-onset (>50 y) neurodegenerative disorder in up to 40% of male fragile X carriers. Clinical presentation includes intention tremor, cerebellar gait and limb ataxia, parkinsonism, cognitive decline (dementia, disinhibition, decline in executive function, processing speed, and working memory), neuropathy, and psychiatric features (anxiety, depression) with T2/FLAIR prolongation in the middle cerebellar peduncles on MRI. More CGG repeats and older age carry a higher risk.

MANAGEMENT: Screening for scoliosis should be done. Common problems include GERD, sinusitis, and otitis media. Early childhood focus attention on hip dislocation, hernias, and hypotonia. Overall life expectancy is unchanged unless significant medical complications.

Williams (–Beuren) Syndrome[12]

EPIDEMIOLOGY: ~1:7,500 to 20,000 births.

GENETICS: 7q11.23 microdeletion involves *ELN* gene encoding for elastin. Autosomal dominant, but most cases are from a de novo mutation with a single occurrence in the family. Over 99% of patients will have the deletion detected by FISH for gene deletion or targeted mutation analysis.

CLINICAL PRESENTATION: Multisystem disorder with (1) **characteristic dysmorphism** involving an unusual and remarkably uniform elfinlike facies: medially flaring eyebrows, stellate iris, bitemporal narrowing, depressed nasal bridge with epicanthal folds, full nasal tip with anteverted nares, prominent earlobes, wide mouth with full lips and cheeks. Adults may appear prematurely aged with graying of hair and sagging skin. (2) **Connective tissue** (hyperextensible joints) and **cardiovascular involvement** with hypertension and supravalvular aortic stenosis, elastin arteriopathy, and peripheral pulmonary stenosis. (3) **Endocrine abnormalities** with poorly understood tendency for hypercalcemia and calciuria (leading to stones), hypothyroidism, and pubertas praecox. (4) **Neurological issues** include hypotonia with early feeding difficulties and failure to thrive, and a specific cognitive profile with unique personality characteristics: mild to moderate mental retardation with better verbal abilities than nonverbal, and a tendency for excessive socialization. May have exceptional musical abilities or interest. Sometimes not diagnosed until adulthood if less classic presentation with mild intellectual impairment, neuropsychiatric disorders, diverticular disease, mitral valve prolapse, and hypertension.

MANAGEMENT: Prominent and complex medical needs require coordinated, specialized care in setting of underlying condition rather than fragmented problem-specific care. Outcome often with no or noncompetitive employment and nonindependent living arrangements. (See Table 10.4).

Angelman and Prader–Willi Syndromes

Prader–Willi syndrome (PWS) and Angelman syndrome (AS) are the result of genomic imprinting. This can result from the absence of the paternal

TABLE 10.4 Williams Syndrome: Medical Monitoring in Adults

System, Condition	Monitoring/Examination
Cardiovascular: supravalvular aortic or pulmonary stenosis, other pulmonary stenoses, mitral valve prolapse, abdominal aortic aneurism, hypertension	Cardiological consultation q3–5y Clinical examination q1y If hypertensive, check kidneys, valvular and vascular stenoses, calcium
Endocrine: hypercalcemia (15%), nephrocalcinosis, calcium arteriopathy, hypercalciuria. Impaired glucose tolerance and diabetes (75%)	Serum Ca^{++}, BUN, creatinine, U/A, spot urine Ca^{++}-to-creatinine ratio q0.5–1y, renal and bladder U/S q10y OGTT q5y, HbA1c poor sensitivity
(Subclinical) hypothyroidism	TFTs q3y
Neurologic: stroke, neuropsychiatric d/o (anxiety, depression, others), hypertonia and contractures, Chiari I with acute hydrocephalus or chronic posterior fossa compression and compressive cervical myelopathy	Clinical examination Neurology consult Neuroimaging as indicated (no baseline or routine needed)

BUN, blood urea nitrogen; OGTT, oral glucose tolerance test; TFT, thyroid function test; U/A, urine analysis.

Adapted and abbreviated from Pober BR, Morris CA. Diagnosis and management of medical problems in adults with Williams–Beuren syndrome. *Am J Med Genet C Semin Med Genet.* 2007;145C(3):280–290.

copy of 15q11-q13 (Prader–Willi) or of the maternal copy of 15q11-q13 (Angelman) due to deletion, UPD, or by methylation changes due to a mutation in the imprinting center.

Prader–Willi Syndrome[13]

EPIDEMIOLOGY: Incidence ~1:10 to 30,000 births.

GENETICS: 95% partial (15q11-q13) or complete absence of paternal chromosome 15, remainder imprinting center mutations. A methylation pattern of maternal inheritance only on methylation analysis can detect the responsible molecular abnormalities responsible in >95% of patients with PWS: aberrant imprinting, UPD, and deletions. UPD studies and FISH/qPCR (deletions) have lower yield. Sequence analysis of imprinting regions is rarely needed. Genetic counseling is recommended to assess risks in siblings. The metabolic mechanisms of hyperphagia remain yet to be elucidated, although there may be a role for ghrelin and obestatin, two homeostatic hormones with counterregulatory effects on hunger.

CLINICAL PRESENTATION: Long face, narrow forehead, almond-shaped eyes, small hands and feet. Breech presentation, hypothermia, and feeding difficulties in infancy. Later short stature, hypogonadism, strabismus. Hyperphagia, obesity, hypersomnolence, and daytime hypoventilation are very common. Neurologically, present with prominent neonatal hypotonia, moderate to severe cognitive impairment, and seizures (15%–20%).

MANAGEMENT: Multidisciplinary approach required. Growth hormone treatment can improve height growth and metabolic status (decreased obesity), and may impact cognitive function. Strictly enforced diet and exercise programs, calcium supplementation, monitoring of bone health. Cryptorchidism may resolve spontaneously. Evaluate for sleep disorders

(OSAS), speech and learning disabilities, behavioral and psychiatric problems, strabismus, and scoliosis. Obesity and related comorbidity (diabetes mellitus, thrombophlebitis) contribute to a higher mortality rate in patients with PWS than in other patients with intellectual disability.

Angelman Syndrome[14]

EPIDEMIOLOGY: Incidence ~1:12 to 20,000 births.

GENETICS: 75% maternal 15q11-q13 deletion, 2% with paternal UPD, 5% imprinting center mutations, 8% *UBE3A* mutations, remainder unexplained. Pathophysiology related to deficient expression or function of the maternally inherited *UBE3A*. DNA methylation analysis is, just like in PWS, the study of choice. In 20% this test is normal, and *UBE3A* sequencing is typically done. Together, these tests confirm diagnosis in ~90%. The risk to siblings and extended (maternal) family depends on the genetic mechanism leading to the loss of *UBE3A* function.

CLINICAL PRESENTATION: Historical name, "happy puppet," describes hyperexcitability, gait ataxia, and tremulous, jerky movement combined with a characteristic triangular face, with prognathia, wide mouth with wide-spaced teeth and protruding or thrusting tongue. Multisystem involvement, with hypotonia, drooling, sucking/swallowing and feeding issues during infancy, scoliosis, small hands, constipation. Neurologically, have severe mental retardation, microcephaly with flat occiput and a typical occipital groove, puppetlike jerky but not ataxic movements with paroxysmal unprovoked laughter. Expressive speech delay disproportionate to cognitive function, autistic spectrum disorder, and fascination with water. Early-onset seizures of any type, myoclonic, generalized tonic–clonic, unilateral clonic and atypical absences > others, infantile spasms are rare. Typical EEG with bifrontally dominant high-amplitude, notched sharp and slow waves ("shark fins"), may be in 2- to 3-Hz runs augmented by eye closure and sleep. No alteration in EEG with AEDs.

MANAGEMENT: Associated movement abnormalities may be misjudged as seizures, with risk of inappropriate use of AEDS. Moreover, EEG abnormalities persist even with controlled seizures. Possible adverse reactions to neuroleptic drugs. Exercise and diet can help limit scoliosis and obesity. Several anticonvulsants, including carbamazepine, vigabatrin, and tiagabine, may exacerbate seizures and nonconvulsive status epilepticus. Most live in institutions or supervised housing setting. Life expectancy may be normal, but there is a paucity of data.

Rett Syndrome[15]

EPIDEMIOLOGY: Prevalence ~1:20,000 females, 2nd most common cause of mental retardation in females.

GENETICS: Most commonly sporadic (99.5%) *MECP2* gene mutation (70%–80%) on Xq28 from paternal origin. Females have random X inactivation, leading to survival (males die in utero) and phenotypic variation. Rett-like presentations can also be found with *CDKL5* and *FOXG1* mutations, although less commonly. *MECP2* gene contains transcriptional repression domain but exact pathophysiological mechanism unknown. *MECP2* mutations can also be found in X-linked mental retardation, in males with mosaicism, in girls with autism and other neurodevelopmental disorders. Genetic testing for *MECP2*-related disorders is done by sequence analysis and deletion testing. *CDKL5* and *FOXG1* should be investigated in patients with negative *MECP2* testing.

CLINICAL PRESENTATION: Clinical criteria and guidelines, for the diagnosis and molecular evaluation of classic and variant forms of Rett, have been published. [15] Rett syndrome is a neurodevelopmental disease with a heredodegenerative character: initial normal development (may be placid or mildly hypotonic), then regression with early decelerated head growth at age 2 to 5 mo, insidious or rapid loss of intellectual capabilities, speech, and purposeful hand use at age 12 to 18 mo and stereotyped hand movements. Later seizures, MR with autistic features, gross motor regression with ataxia, breathing abnormalities, and vasomotor changes are seen. MRI will show nonspecific low cerebral volume and atrophy. Other associations include bowel dysmotility, functional megacolon, and gallbladder dysfunction. Scoliosis and osteopenia are frequent. Staging to track and anticipate clinical course:

I. Developmental arrest at 6 to 18 mo: gross motor delay, decelerated head growth, less eye contact, play and cuddling.

II. Rapid or insidious regression at 1 to 4 y. Loss of intellectual capabilities, speech, and purposeful hand use (12–18 mo), periods of inconsolable screaming. Stereotyped hand movements include washing motions, hand rubbing, hand-to-mouth licking, grasping of hair or clothing, and others. Also seizures, MR with autistic features, gross motor regression with ataxia, and breathing abnormalities both during sleep and wakefulness, disturbed sleep pattern.

III. Pseudostationary stage at 2 to 20 y, lasts years. Some improvement in behavior, nonverbal communication and social interaction, hand use, gait, seizures.

IV. Late motor deterioration onset >10 y. May need wheelchair.

MANAGEMENT: See Table 10.5. Patients typically survive into adulthood, but the incidence of sudden unexplained death is significantly higher than in the general population.

Cornelia de Lange Syndrome (CdLS)[16]

EPIDEMIOLOGY: Incidence, 1:50,000 births.

GENETICS: *NIPBL* gene mutation on 5p13.3. *NIPBL* is human analogue of Nipped-B, a *Drosophila* fly gene involved in notch signaling, regulating cell proliferation, and neuronal plasticity. 99% sporadic but AD inheritance for mildly affected parent may lead to recurrence of 50% instead of 0.5% to 1.5% population risk. *SMC1A* mutations are a more rare cause.

CLINICAL PRESENTATION: Syndrome of multiple congenital anomalies characterized by a distinctive facial appearance, prenatal and postnatal growth deficiency, feeding difficulties, psychomotor delay, behavioral problems, and associated malformations that mainly involve the upper extremities. Features include marked growth retardation evident at birth with continued failure to thrive, hypertonia, micro- and brachycephaly, severe mental retardation (some w/ autistic features and stereotypies), feeding difficulties, a low-pitched growling cry, dysmorphisms (low anterior hairline, bushy eyebrows and synophrys, long curly eyelashes, maxillary prognathism with long philtrum "carp mouth"), hirsutism, and various malformations of hands and feet (micromelia, proximal implantation of thumbs, 5th-digit clinodactyly, syndactyly of 2nd and 3rd toes). Miscellaneous associations include hypoplastic external male genitalia, undescended testes, small labia majora, seizures (23%), hearing loss, GI problems (including GERD, various obstructions, including volvulus). Diaphragmatic hernia in infancy, aspiration pneumonia, congenital heart defects, and apnea are common causes of death.

TABLE 10.5 Rett Syndrome: Medical Monitoring

System, Condition	Monitoring/Intervention
Growth and nutrition	Aggressive nutritional support
Deceleration of head growth, later wgt and length, small hands and feet	Evaluate for GERD, need for gastrostomy feedings
Constipation, feeding impairment	BMD studies, screaming episodes may indicate occult fracture or GERD
Bone mineral deficits	Consider vitamin D, calcium supplements, and bisphosphonates
Cardiovascular	Review FH, consider EKG parents. Yearly EKG for prolonged QTc
Sudden, unexpected death from autonomic instability	Avoid drugs that prolong QT, consider beta-blockage
Autonomic dysfunction: tachycardia, cold hands & feet, peripheral vasomotor disturbances, drooling	Clinical examination, refer as indicated
Neurologic	
Epilepsy: complex partial, tonic–clonic, tonic, myoclonic seizures; prev 70%–80% (overreported?), intractable in ½, status in >⅓	May need video-EEG to r/o nonepileptic recurrent behaviors: breath holding, stereotypies, hyperventilation, behavioral arrests inappropriate screaming or laughter, motor or eye abnormalities (tremor, limpness, twitching, jerking, slumping, pupillary dilation) and others. Seizure management not specific to Rett
Motor dysfunction:	
Rigidity, dystonia, hypo- and bradykinesia, quadriparesis	Physical, occupational, and communication therapy, supportive care, orthotics
Neurogenic scoliosis	Restraining or splinting hand(s) may improve interaction, decrease agitation, and self-injurious behavior
Broad-based, ataxic–apraxic gait with hesitancy, freezing, and retropulsion	Serial examination and clinical vigilance for scoliosis, early referral to orthopedics
Stereotyped hand movements	Avoid overtreatment of nonepileptic behaviors (see above)
Bruxism, myoclonus, intermittent strabismus, abnormal eye movements	Anoxic seizures occur only with apneas, not with disorganized breathing or desaturations alone. Naltrexone, magnesium citrate, and topiramate anecdotally improve breathing
Breathing: episodes of hyperventilation (hypocapnia) alternating w/ 20–120s hypoventilation or apnea (hypoxemia)	Consider contribution from GERD, seizures, OSAS. Behavioral interventions, avoid late bright-light exposure, caffeine, and exercise. Short-acting nonbenzodiazepine receptor agonists and melatonin are of some benefit
Sleep disturbances:	
80% have sleep problems with irregular sleep times, periodic awakenings with disruptive behavior, decreased total nighttime sleep with daytime somnolence. Breathing abnormalities are usually less during sleep	

GERD, gastroesophageal reflux disease.

MANAGEMENT: See Table 10.6. Anatomic abnormalities of the face and neck may cause difficulties during intubation, and malignant hyperthermia, which has been reported with anesthesia in a few children with CdLS. If uncomplicated, life expectancy appears to be normal.

TABLE 10.6 Cornelia de Lange Syndrome: Clinical Findings by System and Interventions in Adulthood

	Childhood	Adult	Management
Cardiac	Congenital heart disease	Typically stable	Echocardiography if never had
GI	Pyloric stenosis requiring surgery GERD (may worsen over time) Malrotation may be present	Constipation Barrett esophagus Risk for volvulus, intestinal perforation	Diet, medications as needed Regular gastrointestinal follow-up Biopsies every 1–3 y after Barrett diagnosis All patients need upper GI series, warning about presenting signs of volvulus (e.g., bilious vomiting)
Neuro	Seizure disorder	Peripheral neuropathy	Management not specific to CdLS
Eye	Lacrimal duct malformations	Myopia, retinal detachment	Regular ophthalmology visits, surgery as needed
ENT	Extraction of retained primary teeth Secondary teeth eruption delayed Sinusitis and/or nasal polyps may produce symptoms Cleft palate—should be repaired	Lingual caries w/ GERD Same Same NA	Panorex X-ray (Pediatric) dental visits q4–6 mo ENT visits as needed, consider polypectomy Craniofacial team visits as needed
Renal	Renal malformation, VUR	Same	Renal ultrasound on all patients, VCUG as indicated clinically
Ortho	Hip dislocations	Leg length difference, scoliosis, bunions	Orthopedic visits as needed
Mental health	Behavioral issues (self-injurious behavior, anxiety, aggression)	Same	Psychopharmaca, interventions not specific to CdLS, refer to psychiatrist or psychologist as needed

CdLS, Cornelia de Lange syndrome; ENT, ear nose throat; GERD, gastroesophageal reflux disease; GI, gastrointestinal; VUR, vesicouteral reflux.

Wolf–Hirschhorn Syndrome (WHS)[17]

EPIDEMIOLOGY: ~1:20 to 50,000, twice more common in females than in males. Also known as 4p syndrome, monosomy 4p, and includes Pitt-Rogers-Danks syndrome.

GENETICS: Contiguous gene syndrome with partial loss of chr 4p (4p16.3 is the critical region). The WHS critical region (WHSCR) involves *WHSC1* (role in normal, early development) and has in its close proximity *LETM1*

(role in seizures) and *FGFRL1* (role in craniofacial dysmorphism). Cytogenic analysis detects about half of the deletions in WHS, FISH detects up to 95%.

CLINICAL PRESENTATION: Greek warrior helmet facial appearance with frontal bossing, a prominent glabella, and a broad and beaked nose, high frontal hairline, hypertelorism with protruding eyes and epicanthal folds, distinct mouth with downturned corners, micrognathia. Common associations include cleft lip and palate, congenital heart defects, urinary tract defects and genital abnormalities, growth retardation, and skeletal abnormalities (equinovarus, split hand), abnormal tooth development, hearing loss due to recurrent otitis and sensorineural etiology. Neurological manifestations include structural CNS defects, including hypoplasia of the corpus callosum microcephaly, hypotonia with lower leg atrophy, severe (or moderate) mental retardation.

MANAGEMENT: Heart defects may need monitoring. Behavior, social and motor skills improve with age and are amenable to (early) intervention. Standard care is recommended for skeletal anomalies, ophthalmologic abnormalities, congenital heart defects, and hearing loss. Intense management of (refractory) seizures, some epilepsy may become easier to control during late toddlerhood and childhood.

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ONLINE RESOURCES

Specific Disorders

GeneTests – www.genetests.org – provides information on genetic testing and its use in diagnosis, management, genetic counseling, and promotes the appropriate use of genetic services in patient care (Note GeneTest.org is migrating into NCBI and URL may change).

Gene Reviews – via www.genetests.org, click on GeneReviews - online collection of peer-reviewed articles that describe specific gene-related diseases.

OMIM – www.ncbi.nlm.nih.gov/omim – Online Mendelian Inheritance in Man is a compendium of human genes and genetic phenotypes that is freely available and updated daily with focus on the relationship between phenotype and genotype.

Genome Data

Ensemble Genome browser – www.ensembl.org – genome databases for vertebrates and other eukaryotic species, and makes this information freely available online.

Human genome project – www.ornl.gov/sci/techresources/human_genome/home.shtml – the sequence of the human DNA is stored in databases available to anyone on the Internet.

NCBI gene – http://www.ncbi.nlm.nih.gov/gene – database provides highly summarized information about genes for all species where it is available.

UCSC genome browser – www.genome.ucsc.edu the site contains the reference sequence and working draft assemblies for a large collection of genomes.

Neurogenetics Databases

NCBI SNP database– www.ncbi.nlm.nih.gov/projects/SNP – database of Single Nucleotide Polymorphism.

DECIPHER (Database of Chromosomal Imbalance and Phenotype in Humans Using Ensemble Resources) is an interactive web-based database which incorporates a suite of tools designed to aid the interpretation of submicroscopic chromosomal imbalance.

11 Cerebral Dysgenesis

Jeffrey Bolton, Jurriaan M. Peters, and Annapurna Poduri

DISORDERS OF NEURULATION

OVERVIEW: Failure of the embryonic neural tube to close during fetal development results in the group of disorders classified as neural tube defects. The specific disorder largely depends on the site at which fusion is disrupted. Rostral defects cause anencephaly or encephalocele, and caudal defects lead to spina bifida and similar conditions.

Anencephaly

DEFINITION: Congenital absence of both cerebral hemispheres with accompanying cranial vault defect. A soft, angiomatous mass of neural tissue is covered by skin with no overlying skull. The forebrain and upper brainstem are present.

PATHOPHYSIOLOGY: Failure of closure of the rostral neural tube occurs between days 21 to 26 of gestation. Exact mechanism is unclear, but may be associated with low maternal folate levels. Other associations include maternal hyperthermia, infection, low socioeconomic status, chromosomal abnormalities, and extremes of maternal age.

DIAGNOSIS: Prenatal ultrasound, prenatal MRI, increased alpha-fetoprotein (AFP).

MANAGEMENT: Prenatal folate supplementation may decrease incidence in at-risk populations. Spontaneous abortions or stillbirths are common (75%). If delivered, will die shortly after birth.

Encephalocele

DEFINITION: Herniation of intracranial contents through a midline skull defect. Three subsets based on location: sincipital (orbit, nose, or forehead), basal, or occipital (most common form). There is accompanying hydrocephalus in about 50% of cases and strong association with agenesis of the corpus callosum.

PATHOPHYSIOLOGY: Largely unknown and likely multifactorial. Hyperthermia around days 20 to 28 has been implicated. Rare associations with known genetic syndromes, such as Meckel syndrome and Walker–Warburg syndrome.

DIAGNOSIS: Prenatal ultrasound, fetal MRI, increased AFP.

TREATMENT/OUTCOME: Surgical intervention to repair the deficit in the neonatal period. Endocrinologic evaluation for those with the basal form. Hydrocephalus, if present, may also require surgical intervention. Majority of children have some degree of neurologic deficit, many quite severe. Frontal form tends to have better neurologic outcome than occipital form. Outcome is also dependent on any genetic association.

Myelomeningocele (MMC)

DEFINITION: Incidence ~0.5 to 2.5 per 1,000 live births. Spinal neural tube defect with cleft in the vertebral column, exposing spinal cord and meninges; may be covered by thin membrane. Up to 80% have lumbosacral involvement. Majority are associated with hydrocephalus, particularly with thoracolumbar location.

PATHOPHYSIOLOGY: Similar to encephalocele, though with defect occurring in the caudal neural tube closure. Low maternal folate levels are implicated as one etiology. Other factors include chromosomal abnormalities, teratogens (valproic acid, thalidomide), and maternal hyperthermia and obesity.

DIAGNOSIS: Prenatal ultrasound, fetal MRI, elevated levels of alpha-fetoprotein. Prevention with prenatal folate supplementation.

MANAGEMENT: Great advances in fetal surgery have led to push for prenatal surgical repairs, with good outcomes. Delivery should be via planned C-section with close attention to infection prevention, followed by early postnatal closure. Children should be closely followed for hydrocephalus, and require long-term multidisciplinary follow-up by neurology, neurosurgery, renal, and orthopedics. Many patients will have impaired gait and bowel/bladder function. Most have normal cognition.

Occult Dysraphic States

DEFINITION: Subtle anomalies of caudal neural tube formation accompanied by overt dermal and vertebral abnormalities, due to nondysjunction of overlying ectoderm from the neural tube. Neural injury results from both *tethering*, i.e., traction injury to the cord from differential growth of vertebrae and spinal cord, as well as *fixation*, leading to limitation of the lower spinal cord mobility and injury upon flexion and extension of the trunk. See Table 11.1 for more details.

DISORDERS OF PROSENCEPHALIC DEVELOPMENT

OVERVIEW: After caudal neural tube closure, a single prosencephalic vesicle is formed. This is the precursor of the cerebral hemispheres and deep nuclei. Various errors may occur between weeks 4 to 20 of gestation in the development of the prosencephalon. This includes defects in formation of the prosencephalon (wk 4–5), prosencephalic cleavage (wk 5–6), and midline prosencephalic development (wk 7–12, corpus callosum wk 9–20). These disorders are often accompanied by significant facial/midline abnormalities. (See Table 11.2.)

Holoprosencephaly (HPE)

DEFINITION: Incidence ~1:10,000 live births. Characterized by failure of prosencephalic cleavage. Divided into 3 subtypes. **Alobar HPE** is characterized by a single spheroid cerebral structure with common ventricle, fused basal ganglia and thalamus, membranous roof of the 3rd ventricle with posterior cystic extension, agensis corpus callosum (ACC), absent olfactory system, and a hypoplastic or single optic nerve. Limbic characteristics of cortical architecture and absent supralimbic cortex. Often associated with neuronal migration disorder. **Semilobar HPE** is characterized by anterior fusion with some cleavage present posteriorly, less fusion of the deep nuclei, and ACC. **Lobar HPE** is the mildest form and is characterized by near or total separation of cerebral hemisphere with fusion of only the most rostral

TABLE 11.1 Disorders of Neurulation

D/o, Mechanism, Timing	Anatomy/Pathology	RF, Genetics, Associations	Management/Outcome
Cranioraschisis totalis Total failure of neurulation ~D20–22	Anencephaly plus myeloschisis	Possible link to planar cell polarity pathway[1]	Dx: routine US Miscarriage, death in utero
Anencephaly Failure of anterior NT closure, ~D24	Soft angiomatous mass of neural tissue covered by skin with no overlying skull Forebrain and upper brainstem present	Positive family history, ↓ SES, Caucasian, female, young/old maternal age	Dx: routine US 2nd trimester, increased AFP levels 75% die in utero, 25% in neonatal period Prevention with folic acid prior to conception
Myeloschisis Failure of posterior NT closure, ~D24	Neural plate-like spinal cord with flat, velvety structure and no vertebral or dermal covering	Overlap with more restricted NT defects, e.g., myelomeningocele	Dx: routine US 2nd trimester, increased AFP Most are stillborn
Encephalocele Restricted disorder of neurulation involving *anterior* NT closure, ~D26 Later closure defects have no neural elements involved, termed meningocele	Typically protruding occipital mass with cortex and white matter 3 types Sincipital (frontoethmoidal) Basal Occipital ± hydrocephalus 50% Chiari III: low occipital-type encephalocele with Chiari II (see below), cerebellar abnormalities, ± agenesis corpus callosum (2/3), abnormal venous drainage (1/2)	AR inheritance, maternal hyperthermia D20–28 Subependymal nodular heterotopia Meckel syndrome: encephalocele, microcephaly, microphthalmia, cleft lip/palate, polydactyly, polycystic kidneys, ambiguous genitalia Walker–Warburg syndrome (see below)	Dx: routine US 2nd trimester Surgical interventions when appropriate, variable neurological outcome Sincipital form has better outcomes

MMC Restricted disorder of neurulation involving *posterior* NT closure, ~D26 (0.5–2.5 per 1,000 live births)	Dorsally displaced neural plate or neural tube-like structure, resulting in sac on the back Defects in axial skeleton, dermal covering 80% lumbar involvement (lumbar, thoracolumbar, or lumbosacral) Hydrocephalus 85%–90% with lumbar involvement, less with others. Etiology Chiari II (blocked 4th V. or flow through posterior fossa) > aqueductal stenosis	Genetics & environmental etiology: see *anencephaly*, plus maternal DM, obesity, hyperthermia, low B_{12}, folate Other causes: (1) multifactorial inheritance, (2) single mutant genes (e.g., Meckel syndrome autosomal recessive), (3) chromosomal abnormal incl. trisomies and duplications, (4) specific rare syndromes of uncertain mode of transmission, (5) teratogens (e.g., valproate, carbamazepine, thalidomide), (6) specific phenotypes of uncertain etiology (e.g., cloacal exstrophy and myelocystocele) Deficits in motor, sensory, sphincter function, reflexes ~segmental innervations Hydrocephalus Brainstem dysfunction: stridor, central, or obstructive apnea, cyanotic spells, reflux, aspiration, feeding difficulties Cognitive impairment, seizures 20%–25% Scoliosis Urologic complications (retention, incontinence, recurrent UTI)	Dx: routine US, increased AFP levels Prevention with folic acid prior to conception Intrauterine surgical repair more common, good results Delivery by C-section Early postnatal closure and broad-spectrum antibiotics <24–72 h (infection, outcome—both controversial) Hydrocephalus (late, insidious), common at 2–3 wk, 80% at 6 wk; should be followed by serial US Early ventriculoperitoneal shunting Brainstem dysfunction: supportive care Orthopedic and urological complications: specialty care
Chiari II Malformation	Chiari II: (1) inferior displacement medulla and 4th V. into upper cervical canal, (2) herniation cerebellum through foramen magnum, (3) elongation, embryonic angulation, and thinning upper medullar, lower pons, (4) variable defects foramen magnum, occiput, upper cervical vertebrae, (5) MMC • Chiari II is associated with cortical dysgenesis in 92% (40% polymicrogyria, 44% neuronal heterotopia, 8% other)		

(continued)

TABLE 11.1 Disorders of Neurulation (Continued)

D/o, Mechanism, Timing	Anatomy/Pathology	RF, Genetics, Associations	Management/Outcome
Occult dyspraphic states Subtle anomalies of caudal NT formation accompanied by overt dermal and vertebral abnormalities, due to nondysjunction of overlying ectoderm from NT	**Myelocystocele**—cystic dilation of central canal of caudal neural tube. Association with cloacal exstrophy, omphalocele, imperforate anus, severe vertebral defects, and others **Diastematomyelia, diplomyelia**—bifurcation of the spinal cord **Meningocele–lipomeningocele**—rare as an isolated lesion, not a disorder of neurulation. Association with fibrofatty tissue contiguous with subcutaneous lipoma **Lipoma, teratoma, others**—tumors originating from germinative caudal tissue **Dermal sinus ± (epi)dermoid cyst**—lumbosacral cutaneous dimple with sinus tract ± cyst, can infect, tether, or compress **Tethered cord** (isolated)—prolonged conus, fatty fibrous filum and fibrous bands fixing caudal cord	Vertebral defects >85% (laminae, sacrum, widened spinal canal) Dermal findings 80% (hair tufts, subcutaneous mass, cutaneous dimples or tracts, superficial cutaneous hemangioma, skin tag, pigmented macule) Later: gait problems, abnormal sphincter function, pes cavus or equinovarus, pain, motor and sensory deficits, scoliosis, recurrent meningitis (rare)	Spinal X-ray insensitive US sufficient if no neurological abnormalities If clinically suspect or equivocal US, perform MRI (superior) Early microsurgical repair with electrophysiologic intra-op monitoring of cord function to prevent neurological symptoms Sudden deterioration: consider vascular compromise

ACC, agenesis of corpus callosum; AFP, alpha-fetoprotein; D, day of gestation; MMC, meningomyelocele; MRI, magnetic resonance imaging; NT, neural tube; US, ultrasound; UTI, urinary tract infection.

TABLE 11.2 Disorders of Prosencephalic Development

Mechanism, Timing	Anatomy	Etiology and Associations	Management
Aprosencephaly and atelencepaly Total failure of *prosencephalic formation*, absence of diencephalon and telencephalon, wk 4–5	Small cranium with minimal volume above supraorbital ridge, but with intact skull and dermal coverings • Facial anomalies, including cyclopia or absence of eyes • Anomalies of limbs and genitalia	Unknown. May be postneurulation encephaloclastic event	Lethal, rarely make it to neonatal stage
HPE and holotelencephaly Failure of *prosencephalic cleavage* with marked abnormalities of (diencephalon and) telencephalon, wk 5–6 Etiologies: • Chromosomal anomalies 60% (chr 13 > 18 > 2, 3, 7, 21) • Monogenic syndromes 25% (Smith–Lemli–Opitz, pseudotrisomy 13, Pallister–Hall, Meckel, velocardiofacial) • Monogenic nonsyndromic 15%–20% (*SHH, PTCH, GLI2, TGIF, TDGF, FAST1, Z1C2*)	• **Alobar:** single spheroid cerebral structure with common ventricle, fused basal ganglia and thalamus, membranous roof 3rd ventricle with posterior cystic extension, absence CC, absence olfactory system, hypoplastic or single optic nerve. Limbic characteristics of cortical architecture and absence of supralimbic cortex. Often also neuronal migration d/o. • **Semilobar**: anterior fusion, presence of some cleavage posterior, less fused deep nuclei, absent anterior CC	• **Alobar**: thalamic fusion with aqueductal stenosis leads to hydrocephalus, large dorsal 3rd ventricular cyst • **Semilobar and lobar**: microcephaly • Facial anomalies: absent, rudimentary, or malformed nose, absent, single, or hypoteloric eye(s), cleft lip/palate with absent philtrum. Severe facial abnormality indicates severe HPE, while severe HPE can have normal face • Other anomalies: cardiac, skeletal, GU, GI • Neurological: wide range of cognitive deficits, motor abnormalities incl dystonia, hypothalamic endocrinopathies, seizures, neonatal apnea, and stimulus-sensitive tonic spasms	• Neurological management of seizures, motor abnormalities, development not specific • Multiple systems affected (neurological, cardiac, skeletal, GU, GI, endocrine) requires coordinated effort of clinical care

(continued)

TABLE 11.2 Disorders of Prosencephalic Development (Continued)

Mechanism, Timing	Anatomy	Etiology and Associations	Management
• Teratogenic: maternal diabetes, others disputed • Sporadic	• **Lobar**: Near or total separation of cerebral hemispheres and deep nuclei, small anterior CC • **Syntelencephaly**: Fusion of onormaly posterior frontal and parietal cerebrum, abnormal body CC	• Mild cases are detected later • Etiologies: see left panel. Detailed examination of parents and relatives for detection of hypotelorism, coloboma, single incisor, microcephaly, mild cognitive deficits; may indicate autosom dominance	
ACC, wk 9–20 **ASP**, wk 20 **SOD** **SOHD** Disorders of *midline prosencephalic development* with failure of development of commissural, chiasmatic and hypothalamic plates	• **ACC:** everted cingulate gyri, crescentric lateral ventricles lined by uncrossed *Probst* bundles. Partial ACC is typically posterior (except in HPE, see above). On imaging superiorly displaced 3rd V., colpocephaly, longitudinal *Probst* bundles, radial orientation of gyri ("sunburst") **ASP:** virtually never isolated. HPE, ACC, SOD, hydrocephalus, Chiari II, porencephaly/hydranencephaly from encephaloclastic event *in utero*, schizencephaly (see panel on right), basilar encephalocele **SOD/SOHD:** often associated with hypothalamic–pituitary endocrinopathies	• **ACC:** assoc with Chiari II, vermian hypoplasia, encephalocele, d/o of neuronal migration 25%–45% • **Aicardi syndrome** (female with ACC, periventricular nodular heterotopia, polymicrogyria, and chorioretinal lacunae): infantile spasms, other seizures, mental retardation, X-linked **ASP:** syndrome of ASP with schizencephaly: uni > bilat cerebral cleft or narrowing at level of primary fissures, heterotopias, gyral abnormal's (hemi- or quadriparetic, seizures, mental retardation) Cavum septum pellucidum ± mild cognitive deficits (doubtful, usually coincidental finding) **SOD/SOHD:** hypothalamic–pituitary endocrinopathies 72% (multiple, DI, hypogonadism, neonatal hypoglycemia). Seizures, cognitive deficits ± neuronal migration d/o	• As a rule: neuronal migration occurs concurrently and d/o should be suspected • MRI better than US and CT • Neurological management of seizures, motor abnormalities, development not specific • Multiple systems affected (neurological, cardiac, skeletal, GI, endocrine, GU) requires coordinated effort of clinical care

ACC, agenesis corpus callosum; ASP, agenesis of septum pellucidum; CC, corpus callosum; CT, computed tomograph; DI, diabetes insipidus; d/o, disorder; GI, gastrointestinal; GU, genitourinary; HPE, holoprosencephaly; MRI, magnetic resonance imaging; SO(H)D, septo-optic (hypothalamic) dysplasia; US, ultrasound; wk, week of gestation.

and ventral aspects. The majority of the corpus callosum is formed, except for the genu.

PATHOPHYSIOLOGY: Over 60% of HPE cases are due to underlying chromosomal/genetic causes. Maternal factors also play a role, including alcohol, retinoic acid exposure, and maternal diabetes. Common chromosomal abnormalities include trisomy 13 and 18. Monogenic syndromes such as Smith–Lemli–Opitz and Pallister–Hall syndrome and nonsyndromic monogenic mutations in *SHH* (7q36), *PTCH* (9q22), and *TGIF* (18p11) genes have been implicated.

DIAGNOSIS: Prenatal ultrasound may detect alobar HPE, but is not sensitive for the more mild forms. Fetal MRI can better characterize the malformation if ultrasound is suggestive. Prenatal genetic testing is available for families with prior children with HPE. After birth, mild cases may be diagnosed with MRI after clinical concerns arise.

MANAGEMENT: Large majority have severe neurologic impairment as well as epilepsy. There may be endocrinologic abnormalities which need to be closely monitored. Due to the medical complexity of these patients, a multidisciplinary approach is suggested. Many will require long-term support such as gastrostomy tubes and in-home nursing care.

Agenesis of the Corpus Callosum (ACC)

DEFINITION: Corpus callosum fails to develop. May range from complete to partial agenesis. Partial agenesis may refer to either thinning of the full structure or segmental loss. Often associated with Chiari II malformation, but seen in wide array of genetic and metabolic syndromes.

PATHOPHYSIOLOGY: Thought to be due to disruption in prosencephalic segmentation around week 10 to 20 gestation.

DIAGNOSIS: Prenatal US (should be visualized by 20 wk), fetal MRI; if partial, may be diagnosed later in life via MRI.

MANAGEMENT: Isolated ACC, particularly partial ACC may be relatively asymptomatic. When associated with specific metabolic or genetic syndrome, outcome is largely determined by underlying condition.

Septo-Optic Dysplasia (SOD)

DEFINITION: Characterized by optic nerve hypoplasia, hypothalamic and pituitary hypoplasia, plus midline and forebrain abnormalities (ACC, absent septum pellucidum). SOD is often associated with other cortical malformations.

PATHOPHYSIOLOGY: Disruption in prosencephalic segmentation; most cases are sporadic, though an association with *HESX* gene has been described.

DIAGNOSIS: MRI, dilated ophthalmologic exam, screening endocrinologic labs.

MANAGEMENT: Management of any endocrine abnormalities. May require adaptations for visual impairments. Many patients have mild to moderate cognitive deficits and seizures if an associated cortical malformation is present.

NEURONAL PROLIFERATION DISORDERS

OVERVIEW: After neural tube formation and prosencephalic development, neuronal proliferation, neuronal migration, neuronal organization, and finally myelination follow (these periods span from 2nd mo of

gestation to adult life). Neuronal progenitor cells in the subventricular zone (subependyma of the developing brain) *proliferate* in the 3rd and 4th mo of gestation, through early symmetrical and, later, asymmetrical division (cortical neurons, astrocytes, oligodendrocytes). Disorders may be attributed to either abnormally increased proliferation or decreased proliferation. (See Table 11.3.)

Congenital Microcephaly

DEFINITION: Characterized by occipitofrontal head circumference (OFC) being >2 standard deviations (SD) below the mean for patients' age. **Microcephaly vera (MV)** is defined as congenital microcephaly (typical >3 SD) with no other abnormalities.[2]

PATHOPHYSIOLOGY: Underlying etiology can be environmental or genetic. Environmental factors include infections (CMV, HSV, toxoplasmosis, rubella, etc.), intrauterine toxic/teratogen exposures, and prenatal hypoxic-ischemia. MV is inherited via an autosomal recessive pattern with several genes being implicated (*ASPM* is the most common). The various genes linked to MV play a role in regulation of cell cycle and cell division during early cortical development. Congenital microcephaly is also associated with known syndromes such as Smith–Lemli–Opitz, Pelizaues–Merzbacher disease, and Cornelia de Lange syndrome.[3]

DIAGNOSIS: OFC measurement 2 to 3 SD below mean. MRI to assess for any associated malformation.

MANAGEMENT: Patients with MV and no other malformations may have mild cognitive impairment or even normal neurologic function. The syndromic/genetic mircrocephalies tend to have much poorer outcomes and often refractory epilepsy.

Hemimegalencephaly

DEFINITION: Characterized by unilateral enlargement of one cerebral hemisphere. The abnormal hemisphere may also have associated cortical malformations such as abnormal gyral pattern, blurring of gray–white matter boundaries and gray matter heterotopias.[4]

PATHOPHYSIOLOGY: Can be seen in isolation or associated with neurocutaneous syndromes such as hypomelanosis of Ito, linear sebaceous nevus syndrome, or Klippel–Trénaunay–Weber syndrome. Thought to be a sporadic, noninherited condition (although possible tissue mosaicism and association with mutations in *AKT3* and other mTOR pathway genes).

DIAGNOSIS: Patients often present with focal seizures, and the malformation is discovered by MRI. A thorough skin exam can rule out associated neurocutaneous syndromes.

TREATMENT/OUTCOME: For refractory epilepsy, hemispherectomy may be warranted. Patients will often already have some degree of a baseline hemiplegia, and cognitive impairment is common.

Megalencephaly

DEFINITION: Characterized by abnormally large brain size/weight, measuring >2 SD or >98% for age. Can be subdivided into anatomic vs. metabolic etiologies.

PATHOPHYSIOLOGY: Anatomic megalencephaly results from overproliferation of normal neuronal cells or lack of normal apoptosis during brain

TABLE 11.3 Disorders of Neuronal Proliferation

Abnormality	Anatomy	RF, Genetics, Associations	Management
Primary micrencephaly[1–] *Familial* AR: MV, RB AD: rare X-linked, or unclear with ocular abnormalities) *Teratogenic (T)* *Syndromic (Sy)* *Sporadic (Sp)*	**MV:** small brain, simplified gyral pattern–4 to –12 SD below mean **RB:** very rare, extremely small (<50 g; nL, 350 g), nearly normal-formed brain **T:** irradiation, hyperphenylalanemia, alcohol and cocaine, CMV, rubella **Sy:** multiple systemic abnl chromosomal, monogenic, sporadic **Sp:** nonsyndromic, most common cause of micrencephaly vera	**MV:** subtle neuro deficits, often no seizures MV gene mutations: microcephalin, CDK5RAP2, ASPM (most common), CEP152, WDR62, CENPJ, and STIL; CASK if cerebellum is also small	**RB:** death 0–30 d Others: management of psychomotor development not specific
Macrencephaly[2–] *Isolated* *Familial* AR ARD *Sporadic* *Growth disturbance* *Achondroplasia* *Sotos*[3]	**AD/spor**: large brain (with prominent extra-axial CSF space called benign external hydrocephalus), usually mild or no neurological deficits, normal dev >50%, MR 10% **AR:** more MR, seizures, motor deficits **NF**: increased white matter volume due to glial proliferation, glial tumors, associated neuronal migration defects	Clinical spectrum from normal to subtle, to severe MR with intractable seizures, some with associated growth and neurocutaneous disturbances **FAD**: incr parental head circumf **NF**: AD NF1 mutation on chr 17, >5 café-au-lait spots >5 mm 40%, macrocephaly >40%, optic nerve glioma, plexiform neuroma of eyelid	Management of psychomotor development and seizures not specific in most conditions **TSC, SW, NF**—see Chapter 12 **HMG**: early hemispherectomy > late, outcome related to function of contralateral hemisphere

(continued)

TABLE 11.3 Disorders of Neuronal Proliferation (Continued)

Abnormality	Anatomy	RF, Genetics, Associations	Management
Neurocutaneous disorder Several d/o with hemangiomatosis, lipomas, lymphangiomas, pseudopapilema, asymmetric hypertrophy, varicosities, telangiectatic lesions, flame nevus of the face[3] Neurofibromatosis (NF) Tuberous sclerosis (TSC) Sturge-Weber (SW) Epidermal nevus syndrome (ENS) **Chromosomal disorder** Fragile X, Klinefelter (see Neurogenetics section) **HMG** Sporadic Syndromic (ENS, Proteus, hypomelanosis of Ito)	**SW:** MRI > CT—leptomeningeal angiomatosis with cortical and white matter changes, atypically located congested deep veins, enlarged choroid plexus due to deficit in superficial cortical veins, CT > MRI calcifications at ~6 mo **TSC:** abnl proliferation, migration, and differentiation of neurons and glia. MRI: cortical tubers, subependymal nodules, radial white matter disturbances, subependymal giant cell astrocytomas (SEGAs) **HMG:** abnl proliferation, migration, and organization, increased size one hemisphere, abnormal gyration, disordered and thick cortex, heterotopias	**SW**: port-wine stain, glaucoma, seizures, cognitive deficits more with bilateral than unilateral disease **TSC**: depigmented, ash, leaf-shaped skin macules, seizures, cardiac rhabdomyomata, renal angiomyolipomas, subependymal nodules, cortical tubers. TSC1 gene (chr 9, codes for hamartin), TSC2 (chr 16, tuberin), AD but 80% sporadic. Phenotype associated with TSC2 mutations is more severe **HMG**: severe seizures with sometimes characteristic EEG (large-amplitude triphasic complexes), neurological impairment **ENS:** midline linear nevus, HMG **Proteus:** uni > bilateral hypertrophy of body, thick and hyperpigmented skin, macrodactyly, abnormal foot sole	

AD, autosomal dominant; AR, autosomal recessive; CT, computed tomograph; dev, development; ENS, epidermal nevus syndrome; HMG, hemimegalencephaly; MRI, magnetic resonance imaging; MV, micrencephaly vera; NF, neurofibromatosis; RB, radial microbrain; SEGA, subependymal giant cell astrocytoma; Sp, sporadic; SW, Sturge–Weber syndrome; Sy, syndromic; T, teratogenic; TSC, tuberous sclerosis complex.

[1]Excludes congenital microcephaly secondary to destructive disease, e.g., infection or hypoxic-ischemic injury occurring after proliferation.

[2]Excludes skull formation abnormalities, subdural collections, hydrocephalus, metabolic & neurodegenerative disease (e.g., Canavan, Alexander).

[3]Full table, details in Volpe JJ. *Neurology of the Newborn*. 5th ed. Philadelphia, PA: WB Saunders; 2008:59.

development. May be familial, which typically occurs in isolation with no other associated malformations. Megalencephaly may also be associated with neurocutaneous disorders such as Sturge–Weber, neurofibromatosis type I, and tuberous sclerosis complex. Metabolic megalencephaly is due to either edema or accumulation of metabolites and not considered a congenital malformation.

DIAGNOSIS: OFC measurement 2 SD above the mean for age. MRI is recommended to assess any other associated malformations. Parental OFC measurement may be useful in cases of familial megalencephaly. A careful skin exam can rule out a neurocutaneous syndrome.

OUTCOME: When occurring in isolation, particularly in familial cases, megalencephaly may be associated with normal neurologic development. The majority, however, will have underlying neurologic disorders, including autism, epilepsy, and developmental delays. When associated with a neurocutaneous syndrome, outcome is determined by the specific syndrome.

NEURONAL MIGRATION AND ORGANIZATION DISORDERS

OVERVIEW: Neuronal migration peaks between 3 and 5 mo of gestational age. Neural progenitor cells in the subventricular zone migrate *radially* from the posterior germinal matrix to the cerebral cortex (projection neurons) and deep nuclei, and *tangentially* from the anterior germinal matrix to the cerebral cortex (GABA-ergic interneurons). Gyration and cortical organization peaks between 26 and 28 wk of gestation. Gyration results from increasing surface area of the outer cortical compared with that of the inner cortical layers, resulting in compression, and from white matter axons formed in the cortex ("tension-based morphogenesis"). Corpus callosum abnormalities are also common since prosencephalic development co-occurs in time and corticocortical fibers that thicken the corpus callosum require migration of neurons to the cortices.

Lissencephaly Type I

DEFINITION: Lissencephaly ("smooth brain") type I is characterized by abnormally thickened cerebral cortex with a smooth surface lacking any gyral or sulcal formation. The overall cytoarchitecture of the cortex is abnormal, most commonly containing only 4 primitive layers. **Pachygyria** and **subcortical band heterotopia (SBH)** are malformations that fall under the scope of lissencephaly. **Pachygyria** is abnormally formed cortex with a few coarse gyri. **SBH**, also called "double cortex," consists of a symmetric, circumferential band of cortex lying in the white matter just below typical cortex. The outer cortex may be normal or have shallow sulci or pachygyria. (See Table 11.4.)

ETIOLOGY: Lissencephaly is commonly associated with *LIS1* or *DCX* (X-linked) genes. With deletions in *LIS1*, a more widespread presentation may occur, coined **Miller–Dieker syndrome (MDS)**. MDS consists of lissencephaly (posterior more affected than anterior), microcephaly, facial dysmorphism (temple narrowing, prominent forehead, hypertelorism, upward slanting palpebral fissures, and prominent philtrum), syndactyly, and visceral abnormalities.[5] Mutations in the *DCX* gene may give diffuse or anterior predominant lissencephaly in males, or SBH in females.[6]

DIAGNOSIS: Typically not appreciated on routine prenatal US. Postnatal MRI for developmental delay or seizures will reveal the malformation. Genetic testing should then be considered depending on clinical presentation. EEG may show a characteristic pattern of high-amplitude fast activity, bursts of spike and waves with periods of voltage depression.

TABLE 11.4 Neuronal Migration Disorders, Part I: Schizencephaly and Lissencephaly

Abnormality	Anatomy	RF, Genetics, Associations	Clinical Aspects
SE **L1, pachygyria, and SBH** **L2 "cobblestone"** with associated congenital muscular dystrophy (CMD)	**SE:** agenesis of a portion of the germinal matrix, agenesis of portion of cerebral wall, cleft with deep pial-ependymal seam, cleft wall with thick pachy- or polymicrogyric cortex, gray matter heterotopia, focal cortical dysplasias. Uni- more often than bilateral, often perirolandic or -sylvian. Wide separation of cleft wall ("separated or open lips"), dilation of lateral ventricles, hydrocephaly. *Porencephaly* and *hydranencephaly* are later, destructive lesions with *no* gray matter lining of cleft **L1:** decreased (pachygyria) convolutions with cortical thickening and smooth cerebral surface. Abnormal cortical cytoarchitecture with 4 primitive layers	**SE:** heterogeneous etiology: CMV (dysgenetic and destructive), vascular events, genetic (families reported, *EMX2* not validated, consider *WDR62* if microcephaly present). Spectrum of neurological outcome ~ extent and distribution: MRI bilateral 100%, unilateral 24%, frontal and open-lipped lesions have motor impairment. Seizures, hydrocephalus 50%, agenesis septum pellucidum 70%, septo-optic dysplasia and/or agenesis corpus callosum ~25% **L1:** *LIS1* chr 17; L1 > SBH. If L1 then posterior > anterior. Rare causes of L1: vascular events month 2–4 of gestation, fetal CMV infection, metabolic dz (PDH def, Zellweger, NKH)	**SE:** early developmental delay and diffuse hypotonia, later spastic quadriplegia. Seizures >90%, infantile spasms very common **L1:** acquired microcephaly, early developmental delay, hypotonia, later spastic quadriplegia and MR, paucity of movement and feeding disturbances, seizures as above. Characteristic EEG with high-amplitude fast activity, bursts of spike and waves with periods of voltage depression **XLAG:** severe neonatal seizures 2/2 GABA-ergic interneuron involvement, hypothermia, cryptorchidsm, and micropenis

	SBH: bands of gray matter are interposed in the white matter between the cortex and lateral ventricles. Overlying cortex structurally normal with shallow sulci, at times pachygyria **L2:** lissencephaly with protrusions of neurons over the brain surface into the subarachnoid space, 2/2 failure of termination of radial migration. White matter interdigitations give "cobblestone" appearance on MRI. Associated with defects in glycosylation of α-dystroglycan	**SBH:** *DCX,* X chr; SBH > L1. If L1 then anterior > posterior. Females may have normal MRI and only mild cognitive impairment with favorable X-inactivation **Miller–Dieker:** *LIS1* and contiguous gene deletions with severe posterior > anterior L1, dysmorphisms and additional malformations **XLAG** (*ARX* on X chr), and LCHb (lissencephaly with cerebellar hypoplasia b, Reelin on chr 7, microcephaly at birth, severe hypoplasia of entire cerebellum, no folia): rare **L2:** Fukuyama CMD (9q31, Fukutin), Walker–Warburg syndrome (9q34, *POMT1*), and muscle–eye–brain disease (1p34, *POMGnT1*)	**Walker–Warburg:** macrocephaly, retinal malformations, CMD, cerebellar malformation, L2, hydrocephalus, Dandy–Walker, encephalocele. Clinically as L1, but with elevated CK, hypotonia, death in 1st y of life

CK, creatinine kinase; CMD, congenital muscular dystrophy; CMV, cytomegalovirus; GABA, gamma-aminobutyric acid; L1, type I lissencephaly; L2, type II lissencephaly; MRI, magnetic resonance imaging; NKH, nonketotic hyperglycinemia; SBH, subcortical band heterotopia; SE, schizencephaly; XLAG, X-linked lissencephaly with ambiguous genitalia, agenesis corpus callosum.

MANAGEMENT: The majority of patients with lissencephaly have epilepsy, often beginning in early life with infantile spasms, and often very refractory. Overall neurologic function is also significantly compromised in the vast majority of patients.

Lissencephaly Type II

DEFINITION: Characterized by lissencephaly with protrusions of neurons over the brain surface into the subarachnoid space, secondary to failure of termination of radial migration. White matter interdigitations give "cobblestone" appearance on MRI.

ETIOLOGY/GENETICS: Associated with defects in glycosylation of α-dystroglycan. Three most commonly associated syndromes are **Walker–Warburg, Fukuyama**, and **Muscle–eye–brain disease**. All three of these syndromes fall under the umbrella of **congenital muscular dystrophies** and have associated neuromuscular findings (see neuromuscular chapter).

Walker–Warburg, associated with mutations in *POMT1* gene, is characterized by cobblestone cortex, brainstem and cerebellar malformations, and often an occipital encephalocele. **Fukuyama's congenital muscular dystrophy**, linked to *FCMD* gene, consists of a less severe cobblestone cortex plus congenital muscular dystrophy, which may be quite severe.

Muscle–eye–brain disease, associated with *POMGnT1* gene, is characterized by cobblestone cortex, complicated ophthalmologic abnormalities, and congenital muscular dystrophy.

DIAGNOSIS: Typically diagnosed with MRI prompted by seizures or severe congenital muscular dystrophy. Since these conditions are almost exclusively caused by AR mutations, appropriate genetic studies should be performed.

MANAGEMENT: Like lissencephaly type 1, a significant proportion will have epilepsy, often severe. The patients may have very limited motor development due to associated congenital muscular dystrophy.

Schizencephaly

DEFINITION: Characterized by a deep cleft extending from cortical surface to ventricle. The cleft is often lined by polymicrogyria (PMG) cortex. May be unilateral or bilateral with the sylvian fissures a common area of involvement. When there is wide separation of the cleft wall with the space being filled with CSF, it is termed open-lip schizencephaly. Less-involved lesions may have their walls touching and are termed closed-lip schizencephaly.

ETIOLOGY: Most cases are likely due to encephaloclastic (destructive) events. Agenesis of a portion of the developing germinal matrix leads to agenesis of the cerebral wall. Vascular events, particularly in the middle cerebral artery territory, are likely a large contributing factor. Congenital CMV has also been implicated. Much less commonly, familial cases have been described.

DIAGNOSIS: Severe cases of schizencephaly may be seen on 3rd trimester ultrasounds. Most likely the malformation will be discovered via postnatal MRI.

MANAGEMENT: The range of neurologic impairment is quite broad and depends on the extent of the lesion. Bilateral, open-lipped lesions typically have worse prognosis with epilepsy and significant developmental delay. Children with open-lip schizencephaly are also more prone to developing hydrocephalus.

Polymicrogyria (PMG)

DEFINITION: Characterized by multiple small placations of the cortical surface in a festoon-like or glandular formation, resulting in a malformed cortex with numerous small gyri. PMG is further subclassified based on location. (See Table 11.5.)

Bilateral frontoparietal PMG (BFPP) is characterized by PMG in the frontal and parietal cortex and presents with developmental delay, epilepsy, and pyramidal signs. BFPP is also associated with brainstem and cerebellar hypoplasia.

Congenital Bilateral Perisylvian PMG (CBPS) is characterized by PMG involving the bilateral perisylvian regions. Patients with CBPS present with swallowing difficulty, facial diplegia, plus developmental delay and epilepsy.

Bilateral generalized PMG (BGP) constitutes a more diffuse pattern and clinically presents with cognitive and motor delay plus epilepsy. Other forms include bilateral frontal, bilateral mesial parieto-occipital, and bilateral occipital PMG.

ETIOLOGY/GENETICS: Most cases of PMG are sporadic. There is a known associate with deletions of 22q11. BFPP may be associated with mutations of the *GPR56* gene and perisylvian with Xq28 mutations.[10] PMG may be seen in association with other congenital syndromes such as Aicardi, Zellweger, and congenital CMV.[11]

DIAGNOSIS: These malformations are rarely picked up with prenatal ultrasound. MRI in the 1st y of life may be difficult to distinguish PMG from pachygyria.

POSTERIOR FOSSA ABNORMALITIES[9]

Dandy–Walker Malformation

DEFINITION/CHARACTERISTICS: Characterized by hypoplasia of the cerebellar vermis and cystic dilatation of the 4th ventricle with increased volume of the posterior fossa, elevated tentorium and hydrocephalus. Often is associated with other CNS anomalies, including agenesis of the corpus callosum, gray matter heterotopias, and gyral malformations. (See Table 11.6.)

DIAGNOSIS/TREATMENT: The malformation is typically seen on prenatal ultrasounds and then later confirmed with postnatal MRI. Various techniques for management of hydrocephalus have been attempted. The most common intervention is ventriculoperitoneal shunting, but more recently 3rd ventriculostomy and choroid plexus cauterization have been used.[12] Outcome typically depends on associated malformations or syndromes.

Joubert Syndrome

DEFINITION: Joubert syndrome is characterized by a small dysplastic cerebellar vermis with batwing-like, triangular 4th ventricle. There are often multiple brainstem and nuclear abnormalities plus absent pyramidal, pontine, and superior cerebellar peduncle decussation.

DIAGNOSIS/CLINICAL FEATURES: "Molar tooth" appearance of posterior brainstem on MRI and thinning of the pontomesencephalic junction. Clinically the patient may have cognitive impairment, hypotonia, abnormal eye movements, ataxia, episodic hypopnea.

TABLE 11.5 Neuronal Migration Disorders, Part II: Polymicrogyria, Neuronal Heterotopia, and Cortical Dysplasia

Abnormality	Anatomy	RF, Genetics, Associations	Clinical Aspects
Polymicrogyria (PMG) Neuronal heterotopias periventricular (PVH) laminar (subcortical band heterotopia (SBH) nodular (focal/diffuse) ocal cortical dysplasias (FCD)	**PMG:** multiple small placations of cortical surface in festoon-like or glandular formation Subdivided based on location: Bifrontal Bilateral frontoparietal Bilateral perisylvian Occipital Mesial parieto-occipital **Heterotopias:** collections of neurons in the periventricular or subcortical white matter, arrested during radial migration—spectrum ranges from coincidental findings at autopsy to severe migrational disorders **FCD:** area of focal cerebral cortical dysgenesis ± polymicrogyria, abnormal cortical lamination, and subcortical heterotopia—heterogeneous, may not represent single entity	**PMG association w/ Zellweger:** severe hypotonia and weakness, refractory seizures, absent high-level response to stimuli, craniofacial dysmorphism, hepatomegaly, renal cysts, calcified patellae. Other peroxisomal d/o too, as well as dysgenetic syndromes, e.g., Aicardi, Joubert (see above) **Sporadic PMG:** broad clinical spectrum, poorly defined **Bilateral symmetric PMG syndromes:** frontal, (sporadic), frontoparietal (*GPR56*), perisylvian (Xq28 and others), generalized (16q), and more. Occipital—LAMC3 **PVH:** X-linked,[7] (Xq28, *FLNA* gene, Filamin A), autosom rec (20q11, *ARFGE*)[8] **SBH:** see type I lissencephaly **Nodular heterotopias:** associated with metabolic d/o, myotonic dystrophy, neurocutaneous syndromes, multiple congenital anomaly syndromes, chromosomal abnormalities, fetal toxin exposure **FCD:** dysmorphic large neurons, with or w/o multipotent balloon cells. May cause intractable epilepsy.[9]	**Bilateral symmetrical perisylvian PMG:** pseudobulbar palsy with feeding disturbances, facial weakness, and early seizures **Unilateral PMG:** congenital hemiplegia **PMG:** MRI difficult to interpret in neonatal period 2/2 poor gray–white matter differentiation and hypomyelination Seizure disorder, severe. Often MRI description only, at time of resection (epilepsy surgery) often findings of abnormal proliferation, migration, and organization. Clinical symptoms dependent on location and extent; e.g., occipital—congenital hemianopia, frontal—focal seizures (clonic, myoclonic), hemiparesis, left frontotemporal—developmental dyslexia, bilateral perisylvian—facial diplegia, dysarthria, dysphagia, mental retardation

TABLE 11.6 Cerebellar Malformations and Posterior Fossa Fluid Collections

Abnormality	Anatomy	RF, genetics, associations	Clinical aspects
Primary vermian Dandy–Walker (DW) Joubert syndrome (JS) Rhombencephalon synapis (rare) **Primary hemispheric** Prematurity (white matter injury), familial, lissencephaly (see above), congenital msc dystrophies, metabolic d/o, CMV infection	**DW:** (1) (partial) agenesis vermis, (2) cystic dilation 4th V., (3) increased-volume posterior fossa, elevated tentorium, and torcula, (4) hydrocephalus (late) **JS:** small dysplastic vermis ("batwing"-like triangular 4th V), multiple brainstem and nuclear abnl's, absent pyramidal, pontine and sup cerebellar peduncle decussation ("molar tooth"-like posterior brainstem), thinning of pontomesencephalic junction **Rhombencephalosynapsis:** fusion of cerebellar hemispheres w/ absence or hypoplasia of vermis. Also fusion of cerebellar dentate nuclei and superior cerebellar peduncles	**DW:** assoc CNS abnl 70% have ACC, cerebral gray matter heterotopia and gyral malformation, aqueductal stenosis, abnormal nuclei, occipital encephalocele. Systemic abnormalities in 30%–40% (cardiac, urinary) **JS:** autosom rec ("familial vermian agenesis," JBTS1-5 gene loci), cognitive impairment, hypotonia, abnormal eye movements, ataxia, episodic hyperpnea **Rhombencephalosynapsis:** wide clinical spectrum from subtle cerebellar signs to profound delay and cerebral palsy	**DW:** lateral ventricular shunt given aqueductal stenosis and (later) posterior fossa shunt[13] **JS:** management of psychomotor development not specific to JS, respiration improves in 1st mo
Posterior fossa fluid collections Trapped 4th V. Enlarged Cisterna Magna (ECM) Arachnoid cyst (AC)	**Trapped:** postinfectious or posthemorrhagic, hydrocephalus **ECM:** no cystic dilation 4th V., no increase of posterior fossa, vermis present. Isolated or assoc with other abnormalities **AC:** not communicating with subarachnoid space or 4th V.	**Trapped:** expansion with brainstem dysfunction and increased ICP **ECM:** asymptomatic; hypotonia, tremor, nonprogr macrocephaly **AC:** signs and symptoms of posterior fossa mass (infant, child), obstructive hydrocephalus	**Trapped:** lateral ventricular shunt and/or 4th V. shunt **ECM:** no surgical intervention needed **AC:** may need shunting or marsupialization

4th V, fourth ventricle; AC, arachnoid cyst; ACC, absent/agenesis corpus callosum; CMV, cytomegalovirus; DW, Dandy–Walker; ECM, enlarged cisterna magna; JS, Joubert syndrome.

TABLE 11.7 Congenital Hydrocephalus

Mechanism	Anatomy	RF, Genetics, Associations	Management
Neonatal AS, Dandy–Walker Chiari II communicating hydrocephalus Less common: infection, neoplasm, hemorrhage, vascular malformation **Fetal** Holoprosencephaly, myelomeningocele see neonatal	Marked ventriculomegaly, attenuation or absence of recognizable cerebral mantle, compressed basal ganglia, variety of cystic herniations, associated anomalies. Expansion of mantle and partial restoration of normal anatomy after surgical intervention Dandy–Walker (see above) Isolated mild fetal ventriculomegaly (radiological diagnosis: 10–15 mm between lateral ventricles level of atrium)	AS: nonfamilial > X-linked (adducted thumbs, ACC, mental retardation), autosom recessive, associated VACTERL Neonatal: enlarged head, full fontanel, splayed sutures, good neurological, eye, skin, & morphologic examination (limbs, cranium, spine) Fetal: major associated anomalies 80% (CNS > 60%, extraneural > 40%), affects neurological outcome Isolated mild fetal ventriculomegaly: 10%–35% have mild neurological handicap ~ assoc neural anomalies	Serial exams, head US (Fetal) MRI for size of cerebral mantle, assoc migrational anomalies, signs of parenchymal destruction, localization of obstruction Early surgical intervention, consider fetal surgery (very rare, controversial) or termination Delivery by C-section Outcome ~ associated anomalies (major), infection (major), size of mantle, timing of intervention Neurological management of seizures, psychomotor development not specific

ACC, agenesis of corpus callosum; AS, aqueductal stenosis; CNS, central nervous system; MRI, magnetic resonance imaging; US, ultrasound; VACTERL, vertebral, anal, cardiovasc, tracheo-esophageal, renal, limb defects.

CONGENITAL HYDROCEPHALUS

Onset occurs in utero, and may be diagnosed in the fetal stage via prenatal ultrasound or in neonatal period, with either ultrasound, CT, or MRI. May result from heterogeneous causes, often abnormal development of brain with resultant abnormal CSF circulation/flow. Common causes of congenital hydrocephalus include aqueductal stenosis, Chiari II w/ MMC, communicating hydrocephalus, Dandy–Walker (see above) (Table 11.7).

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12 Neuro-oncology and Neurocutaneous Syndromes

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NEURO-ONCOLOGY

Brain Tumors

DEFINITION: Brain tumors are a diverse group of primary tumors arising from one of many different cell types within the central nervous system. Diagnosis, treatment, and prognosis depend on the tumor cell of origin and pattern of growth. See overview in Table 12.1.

EPIDEMIOLOGY: Brain tumors constitute 20% to 25% of all pediatric malignancies and are the most common solid tumors in children as well as the most common cause of cancer death in children <15 y.[1] Most cases of brain tumors in children are sporadic, although 5% are associated with hereditary syndromes that predispose to neoplasia (Table 12.2). Environmental exposures such as ionizing radiation have been implicated in meningiomas, gliomas, and nerve sheath tumors. No convincing evidence has demonstrated a link with trauma, occupation, diet, or electromagnetic fields.

CLINICAL PRESENTATION: Clinical presentation is often influenced by the age of onset, tumor location (supratentorial often present in ≤ 3 yo and >10 yo; infratentorial often in 4 to 10 yo), tumor histology, and rate of growth. Additionally, the chronicity of symptoms may provide an indirect correlate of tumor biology and prognosis.[2] Symptoms can be grossly divided into focal neurologic signs and symptoms that are directly referable to the tumor location and diffuse symptoms that indicate either larger regional involvement or symptoms suggestive of increased intracranial pressure (ICP; Table 12.3).

HEADACHES: The most common presenting symptom of children with brain tumors. It is estimated that 41% of children will experience headaches at the time of presentation, often due to increased ICP, and ⅔ of patients will experience headaches over the course of the illness.[2] Headaches are typically described as a pain that awakens the patient from sleep, occurs in the early morning, and/or can be worsened with coughing or Valsalva maneuver, is often bilateral, and is described as a pressure-like feeling. Patients should be evaluated for communicating or noncommunicating/obstructive hydrocephalus since cerebrospinal fluid volume may be increased due to impaired reabsorption (secondary to blood from subarachnoid hemorrhage, increased protein from meningitis, or overpopulation with malignant cells) or overproduction. Indirect causes of headache in children with brain tumors include surgery (hemorrhage, vascular injury, perioperative stroke, CSF leak), chemotherapy (retinoids, antibiotics, cytokines, leukoencephalopathy, venous sinus thrombosis), supportive therapy (steroids, antihistamines, antiemetics), radiotherapy (acute edema, radionecrosis, secondary tumor, vascular changes), and other causes (infarction, fever, infection, post lumbar puncture).[2]

TABLE 12.1 Pediatric Neuro-oncology

Tumor Type	Incidence	Location	Diagnostic Features	Treatment	Prognosis
Astrocytic					
Grade I/Pilocytic astrocytoma	20% of astrocytomas Male = Female Peak, 5–14 yo Increased in NF1	Cerebellum (most) Brainstem Optic pathway Hypothalamus	CT/MRI: 50% well circumscribed Cyst with mural nodule Contrast enhancing Solid parts with low attenuation relative to cerebellar parenchyma Path: Rosenthal fibers	Maximal surgical resection ± Chemotherapy ± RT	Total surgical resection is curative in 95%–100% May stabilize for long periods
Grade II/ Diffuse astrocytoma	15% of astrocytomas Peak, 2–4 yo and early adolescence	Frontal and temporal lobes > brainstem and spinal cord	MRI: heterogeneous CT: solid parts are low density Path: ⇑ cellularity, diffuse infiltration of neighboring brain structures	Maximal surgical resection ± Chemotherapy ± RT	With gross total resection, 80%–100% survival With partial resection, 50%–95% survival Worse prognosis if tumor is midline
High-grade astrocytoma Anaplastic astrocytoma/ Grade III Glioblastoma/ Grade IV	10% of pediatric tumors Peak, 9–10 yo	Most are supratentorial	CT/MRI: often with mass effect, variable contrast enhancement, areas of necrosis (if grade IV), restricted diffusion MRS: low choline, high citrate Path: increased cellularity, atypia; grade IV with vascular proliferation and necrosis	Maximal surgical resection ± Chemotherapy and RT	5-y survival rate is 15%–30% for supratentorial lesions, <10% for pontine

(continued)

TABLE 12.1 Pediatric Neuro-oncology (Continued)

Tumor Type	Incidence	Location	Diagnostic Features	Treatment	Prognosis
Astrocytic					
Pleomorphic xanthoastrocytoma	<1% of all astrocytomas; typically develops in children and adolescents	Cortical/hemispheric predominance Most common origin = temporal lobe	MRI: peripheral hemispheric mass w/heterogeneous enhancement post contrast Solid parts show signal intensity similar to gray matter	Maximal surgical resection Seizure management	Recurrence-free survival rates of 72% at 5 y and 61% at 10 y
Subependymal giant cell astrocytoma	Almost exclusive to TSC patients Peak, 1st decade	Most in lateral ventricle, near foramen of Monro	MRI: circumscribed, homogenously enhancing mass characteristically located within the lateral ventricle	Maximal surgical resection Seizure management CSF diversion mTOR inhibitors	Survival ~95% at 5 y
Oligodendroglioma Well-differentiated/WHO grade II) Anaplastic/WHO grade III)	1% of childhood brain tumors	Supratentorial	CT: presence of dense nodular calcification suggests diagnosis; osseous remodeling of skull inner table to the skull is common, mineralization frequent MRI: predominantly solid mass centered peripherally in the cerebral hemispheres Histology: honeycomb/ground glass appearance	Maximal surgical resection ± Chemotherapy and RT if recurrence	10-y survival rate up to 80%

Ependymoma	8%–10% of childhood brain tumors Peak, 0–5 yo; 30% < 3 yo	Posterior fossa (60%) Supratentorial tend to occur in a periventricular location May have drop metastases at presentation (10%) or at recurrence	MRI: usually heterogeneously enhancing, along the ventricular lining; cerebellopontine predilection; tend to extend through the outlet foramina of the 4th ventricle; mineralization, necrosis, and hemorrhage common, isointense to gray matter LP: check for leptomeningeal spread	Maximal surgical resection ± RT Chemotherapy may delay RT	Prognosis depends on extent of resection, age, and tumor location
Choroid plexus Choroid plexus papilloma (CPP) Choroid plexus carcinoma (CPC)	2%–4% If <1 yo, 10%–20% (80% CPP, 20% CPC) Peak, 0–5 yo	Lateral ventricle (50%); 4th ventricle (40%) Associated with Li–Fraumeni	MRI: markedly lobulated, often frond-like, solid mass within ventricle CPC is more heterogeneous ± necrosis and parenchymal invasion ± CSF dissemination Both will enhance post administration of IV contrast MRS: CPP marked inc of myoinositol; CPC marked inc choline	Maximal surgical resection Multiagent chemotherapy for CPC	CPP: 10-y survival, 85% if gross total resection CPC: 5-y survival, 26% (most deaths occurring within 7 mo of surgery) May metastasize if associated with Li–Fraumeni

(continued)

TABLE 12.1 Pediatric Neuro-oncology (Continued)

Tumor Type	Incidence	Location	Diagnostic Features	Treatment	Prognosis
Neuronal and mixed neuronal–glial					
Dysembryoplastic neuroepithelial tumor (DNET)	Overall incidence of ~1%. In one study, 18%–19% of patients undergoing temporal lobe resection for refractory epilepsy had a DNET Often presents with seizures	Always centered in cerebral cortex (temporal > frontal lobes)	CT: peripherally located, low density mass MRI: circumscribed mass centered within the cerebral cortex; involvement of subcortical WM is not uncommon and tends to show a centripetal tapering Cystic components are common (soap bubble appearance) MRS: normal Pathology: may have surrounding areas of dysplasia	Maximal surgical resection	Have potential for recurrence following complete surgical resection Seizure control may be challenging
Ganglioglioma	3% of brain tumors; 6% of all supratentorial tumors in children Peak, adolescence Often presents with seizures	Cerebral cortex, most commonly the temporal lobe	CT: mineralization common MRI: peripherally located, intra-axial, wholly solid or partly cystic	Maximal surgical resection	Potential for recurrence following complete surgical resection Seizure control may be challenging

Germ cell tumors					
Germinoma nongerminomatous germ cell tumor (NGGCT)	1%–2% of childhood brain tumors Mean age at diagnosis, 10–12 y M:F = 2–3:1	Suprasellar more common in females; pineal more common in males Can have synchronous or consecutive tumors	MRI: predominantly solid, suprasellar mass with signal characteristics approximating that of gray matter If suprasellar, often pituitary bright spot is absent Labs: for germinoma, markers negative; for NGGCT, elevated α-fetoprotein and βHCG	Diagnostic biopsy if markers negative RT for germinoma RT+ chemotherapy for NGGCT May require CSF diversion	Germinoma: most localized germinomas can be cured with RT therapy alone, survival is 65%–95% @ 5 y NGGCT survival, 40%–70% @ 5 y. High-dose chemotherapy and stem cell rescue at relapse
Teratoma	2nd most common germ cell tumor of the pineal region Most common neonatal tumor	Usually pineal	MRI: Benign form—marked heterogeneity; coexistence of cystic, solid enhancing, fatty, and mineralized components Malignant form—a predominantly solid, enhancing mass without associated fat or mineralization	Diagnostic biopsy if markers negative May require surgical resection May require CSF diversion	Survival is dependent upon location and the patient's ability to tolerate gross total resections

(continued)

TABLE 12.1 Pediatric Neuro-oncology (Continued)

Tumor Type	Incidence	Location	Diagnostic Features	Treatment	Prognosis
Parenchymal tumors of pineal gland					
Pineoblastoma Pineocytoma	Each account for up to 45% of all tumors in the pineal region Peak, 1st decade (pineocytoma are most common in 25–35 yo)	Pineal	MRI: Pineoblastoma—heterogeneous enhancement post contrast administration; leptomeningeal dissemination may occur, and/or necrosis and hemorrhage Pineocytoma—partially cystic mass, commonly associated with mineralization Pathology: pineoblastoma; (small round cell tumor; histology similar to PNET)	Diagnostic biopsy with resection if possible May require CSF diversion May consider markers to exclude NGGCT Pineoblastoma-related RT + chemotherapy	Operative morbidity high Pineocytoma often has metastases at diagnosis, prognosis is poor, survival is 86% @ 5 y Pineoblastoma survival is 58% @ 5 y after treatment with various modalities
Primitive neuroectodermal tumors (PNET)					
Supratentorial PNET	5% of all supratentorial tumors in children Peak, 0–5 yo	Hemispheric	CT: calcification and osseous erosion MRI: large, heterogeneous, often with necrosis, cystic degeneration, and hemorrhage; heterogeneous enhancement; isodense to gray matter MRS: markedly elevated choline peak	Maximal surgical resection Chemotherapy + RT	Prognosis is dependent upon risk category Local relapse is a more significant failure pattern in supratentorial PNET than in medulloblastoma

Primitive neuroectodermal tumors (PNET)					
Medulloblastoma	15%–20% Peak, 5–9 yo M:F = 2.4:1	Posterior fossa	MRI heterogeneous; enhancing mass; 30%–40% disseminated at diagnosis MRS: elevated choline peak LP: check for leptomeningeal spread	Maximal surgical resection Multiagent chemotherapy If >3 yo, craniospinal RT with focal boost	Standard risk, 85% survival High risk, 65% survival Poorer prognosis in infants, large cell/anaplastic variant Molecular stratification will guide future therapies
Atypical teratoid rhabdoid	1.5–2.1% of childhood CNS tumors Peak, <2 yo	Posterior fossa Can be supratentorial	MRI: signal intensity similar to gray matter; heterogeneous secondary to frequent necrosis and sometimes hemorrhage Path: loss of INI1 staining on immunohistochemistry	Maximal surgical resection Multiagent (+intrathecal) hemotherapy If >3 yo, craniospinal RT with focal boost	5-y survival 35%
Meningeal					
Meningioma (wide range of histopathologic appearances that classify them as WHO grade I/II/III)	Rare in children and adolescence May be associated with NF2 or prior history of RT	Most commonly vertex or orbital in children	CT/MRI: homogeneous enhancement is the rule with dural tail Hyperostosis of adjacent osseous structures is suggestive	Maximal surgical resection if symptomatic Seizure control	After surgical resection, WHO grade I recur in 7%–20%; grade II in 29%–40%; grade III in 50%–78% Malignant histologic features correlate with shorter survival times

(continued)

TABLE 12.1 Pediatric Neuro-oncology (Continued)

Tumor Type	Incidence	Location	Diagnostic Features	Treatment	Prognosis
Sellar/Suprasellar					
Pituitary adenoma	Increased incidence with improved detection 17% of all pituitary neoplasms (and only a minority are symptomatic) Prolactinoma type is the most common	Hormonally active > inactive macroadenoma >1 cm; microadenoma <1 cm	MRI: relative hypoenhancement compared with normal surrounding pituitary glandular tissue A significant fraction of macroadenomas are hemorrhagic	Hormonal therapy If surgical intervention required, trans-sphenoidal surgery is treatment of choice	Initial remission rate of 83%
Craniopharyngioma (WHO grade I)	7%–10% of all childhood brain tumors Peak, 2nd decade and 4th–5th decades	Originate within the sellar or suprasellar region	MRI: large multilobulated heterogeneous masses with cystic and solid component; may be T1 hyperintense secondary to high cholesterol or protein content CT: may show calcification Path: most with adamantinomatous histology	Maximal surgical resection RT if incomplete resection or recurrence Chemotherapy not helpful	Postoperatively often with panhypopituitarism May need stress-dose steroids 10-y progression-free survival rate 60%–93% in a large series, the most significant prognostic factor associated with tumor recurrence is the extent of surgical resection

Hypothalamic hamartoma	Rare and most occur sporadically; may be associated with TSC or Pallister–Hall syndrome (10%)	Hypothalamus	CT: appears as a gray matter density, suprasellar mass MRI: round or ovoid mass centered at, or pedunculated from, the tuber cinereum. Does not enhance with contrast	Endoscopic disconnection if possible Seizure control	Dependent upon ability to treat seizures (manifesting as several types, including gelastic) in addition to endocrinological and behavioral side effects
Spinal cord					
	2%–4% of all primary CNS tumors, 1/3 in the intramedullary compartment	Extradural Metastases (neuroblastoma, sarcoma, medulloblastoma, ependymoma) Intradural—extramedullary Meningiomas, nerve sheath tumors (schwannoma, neurofibroma) Intradural—Intramedullary Astrocytoma, ependymoma, myxopapillary ependymoma	MRI: mass; appearance depends on tumor type	Surgical resection is the mainstay of treatment Observation for low-grade tumors postresection Systemic therapy for relapse after maximal surgery and/or radiation Consideration for radiation therapy depending on histology Metastases have added increased risk for spinal cord compression	Depends on tumor histology

AA, anaplastic astrocytoma; ADC, apparent diffusion coefficient; AT ataxia; CPC, choroid plexus carcinoma; CPP, choroid plexus papilloma; CSF, cerebrospinal fluid; CT, computed tomography; DFA, diffuse fibrillary astrocytoma; DIPG, diffuse intrinsic pontine glioma; DNET, dysembryoplastic neuroepithelial tumor; FLAIR, fluid-attenuated inversion recovery; GBM, glioblastoma multiforme; JPA, juvenile pilocytic astrocytoma; LCH, Langerhans cell histiocytosis; MRI/S, magnetic resonance imaging/spectroscopy; NF-1, neurofibromatosis type 1; NGGCT, nongerminomatous germ cell tumor; OAC, oligoastrocytoma; ODG, oligodendroglioma; PBL, pineoblastoma; PCY, pineocytoma; PNET, primitive neuroectodermal tumor; PXA, pleomorphic xanthoastrocytoma; RT, radiation therapy; TSC, tuberous sclerosis complex; VHL, von Hippel–Lindau; WM, white matter.

From Louis DN, Ohgaki H, Wiestler OD, et al. *WHO Classification of Tumors of the Nervous System*. Lyon, France: IARC; 2007 and Paldino, Faerber EN, Poussaint TY. Imaging tumors of the pediatric central nervous system. *Radiol Clin North Am*. 2011;49:589–616, with permission.

TABLE 12.2 Hereditary Cancer Syndromes Associated with Brain Tumors in Children

Cancer Syndrome	Gene	Classification	Tumors
Li–Fraumeni	*TP53*	Tumor suppressor	Soft tissue and bone sarcoma, leukemia, breast carcinoma, brain tumor, adrenocortical carcinoma
Familial retinoblastoma	*Rb*	Tumor suppressor	Retinoblastoma, osteosarcoma, pineal tumors
Wilms tumor syndromes WAGR syndrome Denys–Drash syndrome Frasier syndrome	*WT-1*	Tumor suppressor	Wilms tumor
Neurofibromatosis type 1	*NF1*	Tumor suppressor	Neurofibromas, optic pathway tumors, other brain tumors, leukemia, malignant peripheral nerve sheath tumors
Neurofibromatosis type 2	*NF2*	Tumor suppressor	Vestibular schwannoma, schwannoma, meningioma
Von Hippel–Lindau	*VHL*	Tumor suppressor	Renal cell carcinoma, vascular tumors, retinal and central nervous system hemangioblastoma, pheochromocytoma
Tuberous sclerosis	*TSC1, TSC2*	Tumor suppressor	Subependymal giant cell astrocytomas, cortical tubers, hamartomas, renal and extrarenal angiomyolipoma, renal cell carcinoma, cardiac rhabdomyomas
Familial breast and ovarian cancer syndrome	*BRCA-1*	Tumor suppressor	Breast carcinoma, ovarian carcinoma[1]
Familial breast cancer syndrome	*BRCA-2*	Tumor suppressor	Breast carcinoma, Fanconi anemia, brain tumor[1]
Familial adenomatous polyposis	*APC*	Tumor suppressor	Colorectal carcinoma, hepatoblastoma, brain tumors (typically medulloblastoma)[1]
Familial melanoma	*P16*	Tumor suppressor	Melanoma[1]
Nevoid basal cell carcinoma/Gorlin syndrome	*PTCH*	Tumor suppressor	Basal cell carcinoma, medulloblastoma, cardiac and ovarian fibroma
Cowden syndrome	*PTEN1*	Tumor suppressor	Breast cancer, hamartoma
Multiple endocrine neoplasia type 2 (MEN)	*RET*	Oncogene	Thyroid and parathyroid carcinomas, pheochromocytoma[1]
Ataxia telangiectasia	*ATM*	DNA repair	Leukemia, lymphoma
Nijmegen breakage syndrome	*NBS1*	DNA repair	Lymphoma, medulloblastoma, glioma, rhabdomyosarcoma
Rhabdoid predisposition syndrome	*SNF5, INI1*	Growth arrest, DNA repair	Rhabdoid tumors of kidney and brain, choroid plexus tumor

[1]No primary involvement of peripheral or central nervous system.

TABLE 12.3 Brain Tumors in Children: Presenting Signs and Symptoms

Focal Symptoms	Diffuse Symptoms
Seizures	Headache
Focal motor/sensory deficits	Nausea/vomiting
Cranial nerve function	Ataxia/gait changes
Nystagmus	Lethargy
Cranial nerve palsies	Cognitive decline/memory impairment
Parinaud syndrome[1]	Behavioral/personality changes
Visual acuity/visual field dysfunction	Infants
Hormonal changes	Failure to thrive
Diabetes insipidus	Irritability
Delayed or precocious puberty	Macrocephaly/increased head circumference
Growth abnormalities	Bulging fontanelle
Hypogonadism	
Pain	
Back pain	
Neck pain	

[1]Dorsal midbrain syndrome: Limited upgaze with preserved downgaze, downgaze at rest (sunsetting), lid retraction, pseudo-Argyll Robertson pupils (poorly reactive to light but constrict with convergence), convergence–retraction nystagmus (on fast upgaze, the eyes converge and the globes retract). See Neuro-ophthalmology chapter.

EPILEPSY: 15% to 25% of children with brain tumors have seizures. Those that predispose to seizures include low-grade glioma, oligodendroglioma, ganglioglioma, pleomorphic xanthoastrocytoma, and dysembryoplastic neuroepithelial tumor.[3,4] Cortical gray matter involvement also increases risk of seizure activity.[5] Among the putative causes of seizures are the tumor itself, presence of concurrent surrounding areas of dysplasia, focal cortical irritation, surrounding edema, hyperexcitability, altered level of neurotransmitters, presence of blood products, and scar formation (gliosis).[5] The greatest risk for seizures is in the immediate post–tumor resection period.

DIAGNOSTIC WORKUP:

***IMAGING*:** Modern neuroimaging techniques have helped refine tumor classification, assess the spread of disease, and plan for surgical resection.[6,7] For some tumor types, the appearance of a tumor on MRI, magnetic resonance spectroscopy (MRS), or positron emission tomography (PET) is sufficient to establish a diagnosis, without the need for biopsy. Postoperative imaging (ideally in the 1st 48 h after surgery) can also provide information regarding residual tumor volume and be useful in staging. **MRI with gadolinium administration:** Highly sensitive, although CT scan is useful if calcification or hemorrhage is suspected. FLAIR and T2 abnormalities may indicate regions where the blood–brain barrier has broken down, thus suggesting edema and/or infiltration. The location of the tumor is paramount to identifying its type. Low-grade tumors often present as an infiltrating lesion without mass effect. Some brain tumors in children may present with metastatic lesions, including germ cell tumors, ependymomas, medulloblastomas, and primitive neuroectodermal tumors (PNET). **Follow-up:** Cranial and spinal MRI scans are often performed serially during the treatment phase. In the follow-up period, they are typically performed every 3 mo for 1 y; every 6 mo for the 2nd y, and then annually assuming there is no evidence of tumor recurrence.

MRS: Frequently used as a diagnostic tool to define the metabolic composition of a region of interest. Choline and choline-to-creatinine ratios correlate with the degree of cell proliferation, as can be increased in gliomas and other rapidly growing tumors. Decreased choline, creatin\ine, and NAA (*N*-acetylaspartate; a marker of neuronal loss that decreases with destruction or replacement of neurons) levels may suggest areas of necrosis within the tumor itself or in a region that was exposed to radiotherapy. The presence of a lipid signal may also indicate necrosis.

Functional MRI (fMRI): Performed in patients with tumors in regions of eloquent cortex in order to allow for better cortical mapping preoperatively.

PET: Measures regional blood flow, which may be increased in lesions with high metabolic activity.

***HISTOLOGY*:** Classification and staging in pediatric brain tumors are based on adult tumor classification. There are numerous classification systems, which generally are based on histology, degree of anaplasia, and location. The most frequently used classification system is the World Health Organization classification scheme.[8] Measurements of cell proliferation may, in concert with histologic data, help predict the behavior of tumors. One such example is immunostaining of the Ki-67 nuclear antigen by MIB-1, expressed during selective phases of the cell cycle. A significant association has been noted between low MIB-1 staining and progression-free survival. **CSF cytology analysis:** Should be performed in order to assess for metastases, particularly in medulloblastoma, PNET, ependymoma, and germ cell tumors. Children with pineal tumors should also have CSF and serum tested for mixed germ cell tumor markers (αFP and βchorionic gonadotropins).

MANAGEMENT AND TREATMENT: Treatment for a primary brain tumor may involve a combination of surgery, chemotherapy, radiation therapy, and transplant; specific tumor-directed therapy is tailored to the underlying tumor type and location in children (see Table 12.1). The specific combinations depend upon tumor histology, location, patient age, and risk factors specific to the individual tumor subgroup.[9]

***SURGERY*:** Usually the initial step in brain tumor management, because it reduces tumor volume and allows for the determination of tumor histology. The current availability of adjuncts such as neuronavigation (e.g., intraoperative MRI), fMRI, and neurophysiological monitoring of sensorimotor pathways makes the removal of tumors much safer. This may not be possible in tumors that have an MRI appearance of infiltrative growth in a region such as the brainstem. Endoscopic procedures have been used as an approach to intraventricular or deep-seated parenchymal lesions or even hydrocephalus using endoscopic third ventriculostomy.[10] **Surgery for recurrence:** Reports conflict as to whether or not outcome is improved by treating presymptomatic radiographic recurrences, but additional surgery and aggressive adjuvant therapy in children with well-localized recurrence often achieve long-term disease control. **Deficits and long-term effects resulting from neurosurgery:** These are multifactorial and depend on tumor location, attempted degree of resection, age of the patient, and presurgical performance status. Direct sequelae from surgical removal can include perioperative stroke, hemiparesis, hemisensory deficits, seizures, and cerebellar mutism (posterior fossa syndrome). Cerebellar mutism occurs postoperatively in 15% to 25% of patients. There is thought to be a delay of 12 to 48 h after surgery, and symptoms include a loss of verbal expression, pseudobulbar dysfunction, irritability, and ataxia.[11] In addition, poor attention and

eye contact, vomiting, incontinence, and emotional lability are common. Speech and neurocognitive recovery range from days to months.[12]

***CHEMOTHERAPY*:** Commonly used for many tumor types and is often guided by clinical trials conducted by multi-institutional consortia, such as the Children's Oncology Group. Autologous bone marrow transplantation or peripheral blood stem cell reconstitution may be used when delivering otherwise marrow-ablative levels of chemotherapy to the tumor.

Antiangiogenesis strategies, monoclonal antibodies, gene therapy, and immunotherapy (e.g., monoclonal antibodies, vaccine therapies, and direct fusion of activated lymphocytes that are modified to specifically recognize tumor antigens) have been used in an attempt to improve access to the CNS across the blood–brain barrier and may be administered concurrently with chemotherapeutic agents.[9,13,14]

***RADIATION*:** Radiation therapy remains an important component of cancer treatment in children. Craniospinal irradiation is used for lesions prone to dissemination along the neuroaxis. Major advances have been made in the development of conformal and fractionated techniques that tailor the treatment field to the tumor and thus minimize the irradiation of surrounding structures.[15,16] Experimental approaches to radiation therapy include the development of biologic modifiers that are intended to increased radiation sensitivity and decrease radiation resistance. **Deficits and long-term effects resulting from radiation therapy:** Major limitations with radiation include acute toxic effects such as fatigue, erythema, desquamation, otitis media, and/or local alopecia. Late toxic effects include cognitive impairment (several studies showing a 20- to 30-point drop in IQ with 3,600 cGy),[17] altered growth and development (via growth hormone deficiencies or direct spine irradiation), glandular function (hypothyroidism, adrenal insufficiency, or direct gonadal injury),[18] radiation vasculopathy (leading to cerebral infarcts, chronic cerebral ischemia, or moyamoya),[19] and risk for the development of secondary malignancies.[20] Care should be taken to routinely assess pre- and postoperative hormonal function in these patients.

***GENE THERAPY*:** Future studies will likely modify therapy on the basis of genomic data. For tumors that have specific pathway alterations, molecularly targeted agents may have therapeutic applications.[9,14,21]

PROGNOSIS/COMPLICATIONS: Outcome depends on the tumor type, extent of resection, and any tumor- and/or treatment-related complications. In general, younger age, high-performance status, and lower pathologic grade have more favorable prognosis. Importantly, in the modern treatment era, >60% of children diagnosed with a brain tumor are expected to become long-term survivors; however, survival is not without serious long-term effects and many individuals experience significant chronic medical complications.[20] Late effects may occur in a variety of domains, including physical, medical, social, emotional, behavioral, and neurocognitive functioning. Children should undergo neuropsychologic evaluations and screening for learning disabilities.

Spinal Cord Tumors[22]

Listed in Table 12.1. Emergency management discussed below.

Emergency Management of Tumors[22,23]

Neurologic emergencies may occur as a result of a myriad of sources that include the underlying tumor itself (e.g., raised ICP, seizures, spinal cord

compression), treatment-related complications such as diabetes insipidus or SIADH from chemotherapeutic agents, systemic derangements leading to cerebrovascular events (hypoperfusion, thrombocytopenia), and central nervous system infections due to immunocompromised state.

Raised Intracranial Pressure

CNS tumors can cause raised ICP by obstructive hydrocephalus or by peritumoral edema. Raised ICP can manifest clinically as headache, vomiting, papilledema, and/or a decreased level of consciousness. Cushing's triad of hypertension, bradycardia, and respiratory depression is a late and preterminal sign of raised ICP.

Obstructive hydrocephalus is often treated surgically either through tumor resection or through shunting with a ventricular drain or endoscopic ventriculostomy if there is a risk of imminent herniation. Dexamethasone, a corticosteroid, is the mainstay of medical management for tumor-related edema. As reduction in edema is often not seen for 24 h after the initiation of corticosteroids, additional measures are often needed. In the acute setting of herniation related to increased ICP, measures such as mannitol and hyperventilation can be used.

Seizures

Children with a brain tumor are at increased risk to experience a seizure either at time of presentation or relapse or during treatment. Seizures generally result from focal irritation at the site of the tumor or neurosurgical resection. Seizure threshold may be lowered during time of treatment because of metabolic derangements, illness, or CNS infection. Generally, enzyme-inducing antiepileptic drugs (EIAEDs) that are metabolized through the cytochrome p450 enzymes (such as phenytoin and carbamazepine) should be avoided as they may alter the metabolism of chemotherapeutic agents. For patients on concurrent adjuvant therapy, first-line treatment is generally with non–enzyme-inducing AEDs, including levetiracetam, zonisamide, and lamotrigine. For patients in status epilepticus, benzodiazepines should be used as the first-line medication, followed by levetiracetam if loading with an antiepileptic medication is needed. There is no evidence to support the use of prophylactic antiepileptic medication in patients with CNS tumors after the 1st 7 d postoperatively. There should be a low threshold for electroencephalography and/or reimaging in a patient with first seizure or lumbar puncture if there is any concern for CNS infection. EEG may help direct the need for continued seizure prophylaxis.

Spinal Cord Compression

Compression of the spinal cord may occur with primary tumors of the spinal cord or with spinal metastases. Neurologic signs and symptoms may include back pain, constipation, change in urinary function/urinary retention, progressive focal motor or sensory symptoms, and gait changes. Neuroimaging using MRI with and without gadolinium must be considered in any child with a history of cancer and back pain. Early consultation with a neurosurgeon, radiation oncologist, and neurologist should be obtained. Although clear guidelines have not been established, especially in the pediatric population, high-dose corticosteroids should be considered. Recovery of function (e.g., urinary) depends in part on the duration of compression; so compression often presents a true emergency.

NEUROCUTANEOUS SYNDROMES

Introduction

Neurocutaneous syndromes (aka the phakomatoses) are a group of multisystem disorders involving the central nervous system that also have characteristic dermatologic and/or ophthalmologic manifestations. Common to the pathogenesis of most neurocutaneous syndromes are abnormalities in the formation, migration, or differentiation of the neural crest, although the extent of ectodermal involvement is sometimes not prominent. There are typically other systemic features specific to each syndrome. There is little consensus about which conditions should be included in this category, but the most commonly included conditions are neurofibromatosis (NF1, NF2), Sturge–Weber syndrome (SWS), tuberous sclerosis complex (TSC), ataxia telangiectasia (AT), von Hippel–Lindau disease (VHL), incontinentia pigmenti, hypomelanosis of Ito, and nevoid basal cell carcinoma syndrome (NBCCS). The accurate diagnosis and workup of these patients require coordination of care across multiple disciplines, including radiology, dermatology, neurology, and surgery among others. As a group, these disorders are summarized in Table 12.4. The most common disorders will be reviewed in more detail.

Neurofibromatosis Type 1

DEFINITION: NF1 is an autosomal dominant genetic disorder. The diagnosis has been established based on NIH consensus criteria (Table 12.5).[24]

PATHOPHYSIOLOGY: Approximately 50% of individuals inherit the affected gene from a parent and the other 50% are apparent de novo mutations. The *NF1* gene, located on chromosome 17q11.2, encodes the tumor suppressor gene encoding for neurofibromin, an inhibitor of GTPase-activating protein, which in turn regulates the functioning of the Ras protein. With neurofibromin dysfunction, and release of inhibitory control on the Ras protein, there is downstream cell proliferation and tumor development. In NF1, there is no clear genotype correlation with the broad phenotypic expression even among family members.

EPIDEMIOLOGY: Prevalence is ~1:3,500 individuals. No racial or gender predilection.

CLINICAL PRESENTATION: In addition to the clinical diagnostic features, other common features include macrocephaly, short stature, precocious puberty, scoliosis, hypertension, renal artery stenosis, and moyamoya syndrome.[25,26]

DIAGNOSTIC WORKUP: Clinical diagnosis should include slit-lamp examination. Neuroimaging is directed by clinical indication. Genetic testing is available for diagnosis and/or prenatal testing, but cannot predict severity of disease expression.

MANAGEMENT: Supportive and multidisciplinary, depending on the age of the individual and the signs, symptoms, and complications. While there is no specific cure for the condition, targeted therapies are underway to take advantage of what is known about the molecular biology and involvement of the Ras pathway.[27]

MONITORING: Depends on the age and clinical signs and symptoms. In children, yearly physical examination and ophthalmological assessment are recommended in addition to screening for learning and attention difficulties, and educational services as indicated.[28] Screening MRI is generally not recommended. Children should be evaluated for scoliosis and other bony

TABLE 12.4 Neurocutaneous Disorders: An Overview

Disorder (Incidence)	Cutaneous Findings	CNS Findings	Associated Findings	Imaging Features	Genetics	Prognosis
NF1 (1/30,000)	Café-au-lait macules Skin fold freckling Cutaneous neurofibromas Plexiform neurofibromas	Increased risk for CNS and PNS tumors 15% optic gliomas (3%–5% symptomatic) Other: Low-grade astrocytomas Malignant peripheral nerve sheath tumors (5%–10% lifetime risk of transformation) Learning disability (65%) AD(H)D (50%) Seizures Headaches	Hypertension Renal artery stenosis Lisch nodules Short stature Macrocephaly Precocious puberty Moyamoya Scoliosis Pheochromocytoma	CNS tumors MRI: T2 hyperintensity referred to as "NF spots" Controversial if they correlate with increased learning issues	AD Inherited/familial 50% 50% sporadic mutation *NF1 gene* (chrom. 17q11.2), encodes neurofibromin, which regulates Ras pathway	Variable
NF2 (1/60,000)	Bilateral vestibular schwannomas Schwannoma Ependymoma	Bilateral vestibular schwannomas Hearing loss Tinnitus Vertigo Focal weakness caused by spinal tumor or neuropathy Meningiomas Ependymomas Cutaneous schwannomas	Posterior capsular lens opacities		AD *NF2* (chrom. 22q12.2) encodes merlin, a tumor suppressor protein 50% inherited 50% de novo Complete penetrance with variable expressivity	Variable

Sturge–Weber (1/50,000)	Nevus flammeus (aka port-wine stain) Angiomatous lesion Usually distributed in the V1 region 5%–8% of newborns born with port-wine stain have risk of Sturge–Weber syndrome Size of lesion does not predict CNS involvement	Nonprogressive leptomeningeal and cortical angiomatosis Ipsilateral to cutaneous lesion Demonstrates atrophy, calcification, and sclerosis Mental retardation and seizures (75%–80%; typically in the 1st y of life) Spastic hemiparesis from chronic cerebral hypoxia Vascular headaches	Glaucoma (60%) Due to choroid vascular malformation of the eye ± hemangiomas involving the viscera	MRI: enlarged transmedullary veins and unilateral hypertrophy of the choroid CT: leptomeningeal angiomatosis in 1/more lobes and in 1/both hemispheres X-ray: tram-track signs secondary to gyral calcifications	Congenital Nonhereditary disorder Sporadic/unknown type of inheritance	Variably progressive Transient focal deficits may be prevented with prophylactic doses of aspirin Treatment is aimed at controlling seizure activity
Tuberous sclerosis (1/5,000–10,000)	Angiofibroma (adenoma sebaceum) Congenital hypopigmented macules (ash leaf spots 87%) Shagreen patch (usually lumbosacral) Less common: Periungual/subungual fibroma Café-au-lait spots	Cortical tubers Subependymal nodules SEGA Seizures Pervasive developmental delay Mental retardation	Retinal hamartomas Pulmonary lymphangiomyomatosis Renal angiomyolipomas	90% at least 1 supratentorial brain lesion White matter linear migration lines Corpus callosum agenesis/dysplasia Cortical dysplasia Infratentorial lesions present in $<2\%$	AD Variable penetrance *TSC1* (chrom. 9q34.3) encodes hamartin *TSC2* (chrom. 16p13.3) encodes tuberin Both are tumor suppressor genes	Major cause of death is status epilepticus, renal disease, brain tumors, and lung lymphangiomyomatosis (almost exclusive to women) Polycystic kidney disease (3%–5%)

(continued)

TABLE 12.4 Neurocutaneous Disorders: An Overview (Continued)

Disorder (incidence)	Cutaneous Findings	CNS Findings	Associated Findings	Imaging Features	Genetics	Prognosis
Ataxia telangiectasia (1/80,000–100,000)	Telangiectasias (bulbar conjunctivae, bridge of nose, ears, neck, and antecubital fossae) First seen at 3–6 yo Granulomas Graying hair Café-au-lait spots	Slowly progressive cerebellar ataxia Late: choreoathetosis (~85%) Oculomotor apraxia Nystagmus May have: Dysarthria Decreased reflexes Hypotonia Muscle weakness Cognitive impairment over time	Loss of skin elasticity and subcutaneous fat Recurrent sinopulmonary infections Increased risk of lymphoma, leukemia Labs: increased α-foetoprotein in up to 95%, increased CEA (carcinoembryonic antigen)	MRI: cerebellar atrophy	AR Chromosome 11q22 *ATM* gene	Neurological deterioration over time Usually unable to ambulate by start of 2nd decade Disease progression decelerates after adolescence Death results from bronchopulmonary infection or malignancy
Von Hippel–Lindau (1/36,000)	Vascular, broad, purpuric or even ecchymotic lesions (uncommon)	Cerebellar and spinal hemangioblastomas in ~60% Usually after the 3rd decade but may be found in children 50% develop unilateral or bilateral blindness from subretinal edema, hemorrhage, or retinal detachment	Multisystem tumors: Retinal hemangiomatosis (~3rd decade) Renal cell carcinoma Renal cysts Islet cell pancreatic tumors	Tumors are usually well circumscribed and solid/cystic Usually found in the paramedian aspect of the cerebellum	AD Variable penetrance *H1F1* (3p25-26) encodes for 2 different tumor suppressor proteins involved in cellular response to hypoxia Arise de novo in 70%–80%	Juvenile renal carcinoma Malignant hypernephroma (affects 25%, leading cause of death)

Incontinentia pigmenti	Staged skin lesions are erythematous and bullous at birth Later crust with residual pigmentation Follows lines of Blashko	In >30%: Seizures Cerebral ischemia/edema Spasticity Cortical blindness >10% developmental delay	Skeletal changes Alopecia Hypodontia Dystrophic nails Cataracts Strabismus Vitreous hemorrhage Retinal changes/detachment	MRI: hypoplasia of the corpus callosum, heterotopias, and small/large vessel occlusions	X-linked dominant Chromosome Xq28 Mutations in *IKBKG/NEMO*	Usually lethal in males Males may be affected with Klinefelter syndrome
Hypomelanosis of Ito	Uni/bilateral hypomelanotic, whorled, streaked, reticulated macules Trunk, head, or extremities Follow the lines of Blashko	Mental retardation 60% Seizures 50% Autism 10% Less common: hemimegalencephaly Hypotonia Arthrogryposis	Dysmorphisms Hemihypertrophy Dental Heart Renal	MRI: may show cortical dysplasia, heterotopias, hamartomas	Chromosomal variability	Variable

TABLE 12.5 NIH Diagnostic Criteria for NF1

Two or More of the Following Clinical Features Must Be Present
Six or more café-au-lait macules (>5 mm in prepubertal individuals; >15 mm in postpubertal individuals)
Two or more neurofibromas of any type, or one plexiform neurofibroma
Freckling in axillary or inguinal regions
Optic glioma
Two or more Lisch nodules (iris hamartoma) on slit-lamp examination
Distinctive osseus lesion, such as sphenoid dysplasia or thinning of the long bone cortex, with or without pseudoarthrosis
First-degree relative (parent, sibling, offspring) with NF1 based on above criteria

defects. Routine clinical cardiovascular assessment is essential. There is an increased risk of hypertension, cardiovascular disease, renal artery stenosis, and pheochromocytoma.

PROGNOSIS: Morbidity and mortality are often the result of plexiform neurofibromas, optic gliomas, or malignant peripheral nerve sheath tumors, for which there is an 8% to 12% lifetime risk. More than half the individuals with NF1 have evidence of learning disabilities, and attention deficit disorder is common. Life expectancy is reduced overall.

Neurofibromatosis Type 2

DEFINITION: Diagnostic criteria (Table 12.6). The most common feature is bilateral vestibular schwannomas, often associated with hearing loss.

PATHOPHYSIOLOGY: Genetic mutation of the *NF2* gene on chromosome 22q12, encoding for merlin (schwannomin). Merlin is a cytoskeletal protein, but also a tumor suppressor protein thought to control cell shape, cell movement, and intercellular communication. In NF2, clinical manifestations are more similar among family members than for NF1.

TABLE 12.6 Diagnostic Criteria for NF2

Definite NF2
Bilateral vestibular schwannomas[1]
Probable NF2
A first-degree relative with NF2 *and*
Unilateral vestibular schwannoma *or* any two of the following: meningioma, schwannoma, glioma, neurofibroma, juvenile posterior subcapsular lenticular opacities/juvenile cortical cataract
Possible NF2
Unilateral vestibular schwannoma *and* any two of the following: meningioma, schwannoma, glioma, neurofibroma, posterior subcapsular lenticular opacities/juvenile cortical cataract
Multiple meningiomas (≥2) *and* unilateral vestibular schwannoma *or* any two of the following: meningioma, schwannoma, glioma, neurofibroma, posterior subcapsular lenticular opacities/juvenile cortical cataract

[1]Usually do not develop before adolescence, occur in 95% of NF2 patients, and unlike neurofibromas, malignant change is rare.

EPIDEMIOLOGY: Prevalence is ~1:60,000 individuals.[29] No racial or gender predilection.

CLINCAL PRESENTATION: Typically signs and symptoms appear during late adolescence or in the early twenties (see Table 12.6).

DIAGNOSTIC WORKUP: Clinical evaluation, including ophthalmologic and audiologic assessment, and high-resolution MRI of the brain and spinal cord.[30] Other studies are obtained as indicated by the clinical findings.

MANAGEMENT: Primarily by treatment of disease manifestations.[31] Hearing loss is often identified as the 1st symptom secondary to vestibular schwannomas. Treatment is primarily surgical, although stereotactic radiosurgery can be an alternative to surgery. Hearing preservation and augmentation are important goals. Associated complications include headaches, balance problems, vertigo, facial weakness or paralysis. Patients are at risk for other brain and spinal cord tumors, such as meningiomas and ependymomas. A search for medical therapies continues.

MONITORING: For individuals with known diagnosis or risk, annual MRI is recommended, until at least the 4th decade of life. Close monitoring of hearing, including BAERs, is also recommended. Radiation may put patients at risk to develop new tumors or secondary transformation of existing tumors.

PROGNOSIS: Life expectancy is reduced, and the main cause of early death is expansion of a CNS neoplasm.

Sturge–Weber Syndrome (SWS)

DEFINITION: SWS is a rare, congenital disorder associated with facial port-wine cutaneous lesions in the distribution of the branches of the trigeminal nerve, ipsilateral glaucoma, seizures, mental retardation, and ipsilateral leptomeningeal vascular lesions.[32]

PATHOPHYSIOLOGY: The majority of patients with SWS have sporadic, nonfamilial disease. Only a few familial clusters have been reported.

EPIDEMIOLOGY: The frequency is unknown. No known racial or sex predilection.

CLINICAL PRESENTATION: Signs are manifest at birth with appearance of a unilateral port-wine stain on forehead and upper eye lid, in the distribution of the trigeminal nerve, with an accompanying ipsilateral vascular malformation of the pial blood. This vascular malformation ultimately leads to cortical calcification. Neurologic symptoms such as seizures may worsen over time and may be accompanied by weakness on the contralateral side. 50% of children have glaucoma present at birth or shortly thereafter.

DIAGNOSTIC WORKUP: Cranial CT and MRI are used to identify the intracranial abnormalities and are recommended in all patients with facial capillary malformations involving the trigeminal dermatome.[33] CT may demonstrate brain calcification.

MANAGEMENT: Treatment is symptomatic. Laser therapy may lighten or remove the birthmark. Antiepileptic drugs are traditionally used to treat the seizures, which can be difficult to control.[34] Neurosurgical procedures such as hemispherectomy may be effective to control seizures when medical therapy is ineffective. Educational services should focus on areas of learning delays.

MONITORING: Early monitoring for glaucoma is recommended, and initial assessment should be performed in the neonatal period because of risk for congenital glaucoma.

PROGNOSIS: Most children will develop seizures in the 1st y of life. There is a greater degree of intellectual impairment if seizures start before the age of 2 and/or are treatment-resistant. Life expectancy is reduced, but most deaths occur in individuals with profound intellectual impairment and intractable seizures.

Tuberous Sclerosis Complex

DEFINITION: TSC is a multisystem disorder that results in nonmalignant tumors of the brain and other vital organs, such as the kidneys, heart, eyes, lungs, and skin. Diagnostic criteria are described in Table 12.7.[35]

PATHOPHYSIOLOGY: TSC results from a familial (⅓) or sporadic (⅔) autosomal dominant mutation of either of two genes, *TSC1* and *TSC2*. *TSC1* is located on chromosome 9q34 and encodes the protein hamartin, and *TSC2* is located on chromosome 16p13.3 and encodes the protein tuberin. Both of these proteins act as tumor suppressor proteins, but *TSC2* has been associated with a more severe form of the disease. Current genetic testing identifies the mutation in ~80% of individuals diagnosed with the disorder.

EPIDEMIOLOGY: TSC occurs in all races and ethnic groups and in both genders. The prevalence is ~1:5,000–10,000 individuals. No racial or sex predilection.

CLINICAL PRESENTATION: Cardiac rhabdomyomas may be detected in prenatal period. In others, presentation is typically before the age of 6 y. The classic triad of symptoms includes seizures, mental retardation, and facial angiofibromas.[36] Individuals with TSC can experience none or all of the clinical signs discussed below, with a broad clinical spectrum of disease. The dermatologic manifestations of TSC are present in the majority of individuals

TABLE 12.7 Revised Diagnostic Criteria for Tuberous Sclerosis

Definite tuberous sclerosis complex: either two major features or one major feature plus two minor features

Probable tuberous sclerosis complex: one major plus one minor feature

Possible tuberous sclerosis complex: either one major feature or two or more minor features

Major Features	Minor Features
Facial anglofibromas or forehead plaque	Multiple, randomly distributed pits in dental enamel
Nontraumatic ungual or periungual fibroma	Hamartomatous rectal polyps
Hypomelanotic macules (three or more)	Bone cysts
Shagreen patch (connective tissue nevus)	Cerebral white matter radial migration lines
Multiple retinal nodular hamartomas	Gingival fibromas
Cortical tuber	Nonrenal hamartoma
Subependymal nodule	Retinal achromic patch
Subependymal giant cell atrocytoma	"Confetti" skin lesions
Cardiac rhabdomyoma, single or multiple	Multiple renal cyst
Lymphangiomyomatosis	
Renal angiomyolipoma	

(96%). These include facial angiofibromas (adenoma sebaceum) along the nose and cheeks, periungual fibromas, hypomelanotic macules (ash leaf spots), forehead plaques, shagreen patches (areas of dimpled skin often on the lower back or nape of the neck) and, variably, skin tabs, café-au-lait macules and poliosis (a tuft or patch of white hair on the scalp or eyelids). Retinal lesions (astrocytic hamartomas) can be appreciated by ophthalmologic examination. About half of all individuals have learning disabilities, ranging from mild to very significant, such that approximately half the persons meet diagnostic criteria for autism. Three distinctive CNS lesions include subependymal nodules (SEN) along the walls of the ventricles, (sub-)cortical tubers, and subependymal giant cell astrocytoma (SEGA), a low-grade glial tumor with a predilection for the foramen of Monro. Approximately 60% to 80% of patients with TSC have angiomyolipomas of the kidney and may present with hematuria. Another 20% to 30% will have renal cysts. The risk of renal cell cancer is around 2% to 5%, and occurs around 2nd or 3rd decade. Patients with TSC can also develop lymphangioleiomyomatosis (LAM), with progressive cystic changes in the lung and pulmonary failure or risk of pulmonary hemorrhage. Cardiac rhabdomyomas are seen in ~50% of persons with TSC and often regress after birth.

DIAGNOSTIC WORKUP: Family history, skin examination with Wood's lamp (to evaluate for hypomelanotic macules), as well as search for ungual fibromas, facial angiofibromas, dental pits, or other skin manifestations. MRI is done to evaluate for cortical tubers and SEN, and fundoscopic examination to evaluate for retinal nodular hamartomas. Renal ultrasound is used to evaluate for angiomyolipoma or renal cysts, and echocardiography, in infants, to evaluate for rhabdomyoma. Prenatal ultrasound and in utero MRI can identify cardiac rhabdomyomas and at times cerebral lesions, and can allow for early diagnosis in utero. Clinical examination of family members is recommended as clinical penetrance is variable. Molecular genetic testing in family members at risk is clinically available for genetic risk assessment, including prenatal diagnosis in those in whom a familial mutation is identified. Phenotypic variation is great.

MANAGEMENT: Multidisciplinary management and treatment strategies are typically focused toward specific symptoms, e.g., antiepileptic drugs to control seizures and surgical approach to renal lesions. Targeted drug therapy is currently in development. In 2010, the mTOR inhibitor everolimus was FDA approved for treatment of SEGA tumors.[37]

MONITORING: Periodic physical examination, including skin examination, ophthalmologic assessment, and developmental assessment. Imaging of the central nervous system by CT or MRI is recommended every 1 to 3 y, mainly to screen for SEGA tumors.[38] Renal and pulmonary imaging as indicated.

PROGNOSIS: Prognosis depends on the severity of symptoms. Those individuals with mild symptoms generally do well and have a long life span, while those with more severe form, involving various degrees of learning disability and autism, uncontrollable seizures, or kidney failure, may experience significant disabilities. Overall life expectancy is reduced, with death due to renal failure (secondary to angiomyolipomas, cysts, or both), LAM, brain tumors, or status epilepticus.

Ataxia Telangiectasia

DEFINITION: AT is a rare genetic, multisystemic disorder that is characterized by progressive ataxia, choreoathetosis, oculocutaneous telangiectatic lesions of the skin, frequent infections, increased sensitivity to ionizing radiation, and predisposition to malignancies.

PATHOPHYSIOLOGY: This autosomal recessive inherited disorder results from defective DNA damage repair secondary to a mutation of the gene *ATM* on chromosome 11q22.3. *ATM* activates a key regulator of multiple signaling cascades and activates cell cycle checkpoints, DNA repair, and apoptosis. When defective, p53 activation is delayed, thereby increasing the risk of cancer.[39] Cells are at increased risk to damage by ionizing radiation.

EPIDEMIOLOGY: Incidence is ~1:40,000 live births. No gender or ethnic predilection.

CLINICAL PRESENTATION: Children demonstrate normal early development until gait and truncal ataxia become apparent. This is followed by polyneuropathy, progressive ataxia, and signs of premature aging (graying of the hair). Motor skills continue to deteriorate, accompanied by progressive oromotor difficulties. Telangiectasias typically occur on exposed portions of skin or conjunctiva. Immunodeficiencies occur in 60% to 80% of individuals with AT and result in recurrent sinopulmonary infections. Overall risk of cancer is 10% to 20%, of which 85% are leukemia and lymphoma.

DIAGNOSTIC WORKUP: Diagnosis relies on clinical findings, as well as family history and neuroimaging studies. Patients should be evaluated for decreased serum immunoglobulin levels and elevated alpha-fetoprotein. MRI scans can demonstrate cerebellar atrophy.

MANAGEMENT: Supportive, no proven disease-specific treatment to delay the progressive ataxia and other complications. Individuals should avoid radiation exposure, even with diagnostic X-rays, as this might lead to increased chromosomal breakages. Antioxidants have been given empirically, but have not been formally tested. IVIG for those with frequent infections or abnormal immune function and decreased IgG. Aggressive pulmonary hygiene.

MONITORING: Surveillance for infections and neoplasms is recommended.

PROGNOSIS: Most now live beyond 25 y of age and some into the 4th and 5th decades.[40]

Von Hippel–Lindau Disease

DEFINITION: VHL is a rare, AD disorder involving hemangioblastomas of the cerebellum, spinal cord, kidney, and retina.[41]

PATHOPHYSIOLOGY: The *VHL* gene (chromosome 3p25.3) encodes for a cytoplasmic protein that functions as a tumor suppressor gene.[42] Approximately 80% of cases are familial and 20% involve a sporadic mutation. Penetrance is high, and virtually all people with *VHL* mutations will have disease-related symptoms by 65 y of age.

EPIDEMIOLOGY: Estimated at ~1:36,000 live births. Median age at first clinical symptom is 20 to 25 y. VHL affects all racial groups and both sexes equally.

CLINICAL PRESENTATION: Wide variation in age of onset, organ systems affected, and severity. Signs and symptoms include angiomatosis, hemangioblastomas (particularly of cerebellum and brainstem), pheochromocytoma, renal cell carcinoma, pancreatic cysts, and café-au-lait macules.

DIAGNOSTIC WORKUP: A clinical diagnosis is established by a positive family history with a single CNS hemangioblastoma or visceral lesion. If there is no clear family history, two or more hemangioblastomas or one hemangioblastoma and one visceral lesion are required. Genetic screening is up to 100% sensitive and specific. Clinical and molecular screening of family members is essential for early risk detection.

MANAGEMENT: There is no curative treatment currently, but early recognition and treatment of specific disease manifestations can reduce medical complications and improve quality of life.

MONITORING: A comprehensive protocol has been developed for periodic (re)examination of affected patients to monitor for the various multiorgan lesions. This includes annual physical examination, annual fundus examination, MRI of the brain every 3 y up to age 50, annual renal ultrasound with renal CT every 3 y, and annual 24-h urine collection for vanillylmandelic acid (VMA).[43] First- and second-degree relatives of patients with VHL are at risk and should be monitored for clinical manifestations.

PROGNOSIS: Life expectancy is shortened. The most common cause of death is renal cell carcinoma.

Nevoid Basal Cell Carcinoma Syndrome

DEFINITION: NBCCS is known as basal cell nevous syndrome or Gorlin syndrome. This is a hereditary disorder with characteristic facial appearance and predisposition for basal cell carcinoma.[44]

PATHOPHYSIOLOGY: NBCCS is an AD disorder caused by mutations in the *PTCH1* gene on chromosome 9q, which functions as a tumor suppressor gene.[45] Approximately 70% to 80% of individuals are thought to have familial form, while 20% to 30% have an apparent de novo mutation.

EPIDEMIOLOGY: Prevalence is ~1:56,000–164,000 (wide range of estimates).

CLINICAL PRESENTATION: Included are multiple basal cell carcinomas of the skin, odontogenic keratocyst (75%), palmar pits, rib and vertebral anomalies, intracranial calcification, distinct facies (hypertelorism, macrocephaly with or without hydrocephalus, milia on the cheeks and around the eyes and lips), and increased risk of medulloblastoma in childhood (5%).

DIAGNOSTIC WORKUP: Diagnostic criteria are listed in Evans et al.[29] and on www.genetests.org. Calcification of the falx cerebri is the most common radiologic finding in skull radiographs. The finding of bifid ribs or other vertebral abnormalities can aid in the diagnosis. Evaluation of chest, cervical and thoracic spine, and hand or foot radiographs is recommended. Baseline echocardiography to evaluate for cardiac fibromas and then if clinical suspicion arises. Annual MRI is recommended up to age 7 to screen for medulloblastoma. Genetic testing can confirm the diagnosis in patients with atypical findings or for familial genetic risk assessment, including prenatal diagnosis.

MANAGEMENT: Treatment is supportive and aimed at reduction of symptoms.[46] There is no specific cure for the disease. Individuals should reduce exposure to UV light and avoid radiation therapy. There are targeted therapies against the PTCH receptor in early phase clinical trials. Topical therapies have been used for basal cell carcinomas.

MONITORING: Monitoring for basal cell carcinomas is crucial. During childhood, developmental and physical assessments are recommended. X-rays are used to evaluate for rib and vertebral anomalies. Evaluation by an orthodontist familiar with NBCCS is recommended, with an orthopantogram every 12 to 18 mo in individuals older than age 8 to identify jaw keratocysts. Clarification of the genetic status of at-risk individuals is indicated because of risk of complications and need for surveillance of basal cell carcinomas.

PROGNOSIS: The basal cell carcinomas can be the most challenging feature, which determines the prognosis for most patients. Most have a normal life span.

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ONLINE RESOUCES (NEURO-ONCOLOGY)

Pediatric Brain Tumor Foundation (PBTF) – www.pbtfus.org

American Brain Tumor Foundation (ABTA) – www.abta.org

Pediatric Low-Grade Astrocytoma Foundation (PLGA) – www.fightplga.org
www.cancer.org/Cancer/BrainCNSTumorsinChildren/DetailedGuide/

ONLINE RESOURCES (NEUROCUTANEOUS SYNDROMES)

AT: Ataxia – Telangiectasia Children's Project – www.atcp.org

NF:
Advocure – www.advocurenf2.org
Children's Tumor Foundation – www.ctf.org
Crew – www.nf2crew.org
Neurofibromatosis Network – www.nfnetwork.org

SWS: Sturge–Weber Foundation – www.sturge-weber.org

TSC: Tuberous Sclerosis Alliance – www.tsalliance.org

VHL: Von Hippel–Lindau Family Alliance – www.vhl.org

13 Neurologic Critical Care

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INTRODUCTION

The acute neurologic care of critically ill patients and a critical care approach to acute neurologic conditions are emerging interests within the field of pediatric neurology. The medical conditions discussed in this chapter are neurologic emergencies.

AN APPROACH TO THE NEUROLOGICALLY CRITICALLY ILL CHILD

To approach a patient with a disorder of consciousness requires rapid directed review of the history and a focused neurologic exam.[1]

HISTORY: Should be acquired from relatives and witnesses and should include:

- Onset: acute, subacute, and insidious
- Preceding symptoms: headache, vertigo, vision or hearing complaints, focal neurologic findings, fever, and signs of systemic illness
- Environment: recent trauma, access to toxins or medications
- Medical history: medical problems (epilepsy), medications

GENERAL PHYSICAL EXAM: Focused on vital signs, respiratory pattern, and hemodynamics; also observe for evidence of trauma, infection, nuchal rigidity.

NEUROLOGIC EXAM: Should focus on mental status, level of brainstem dysfunction, and focal neurologic findings. Coma scales may be useful, but a descriptive exam is generally preferred.

- Mental Status: Eyes open or closed? Responds or regards? Follows any commands?
- Cranial Nerves: Blink to threat (CN II). Reactivity of pupils (CN III). Spontaneous eye movements or tracking (CN III, IV, VI). Corneal reflexes (CN V, VII). Oculocephalic reflex, assuming no cervical trauma (CN VIII, III, VI). Gag (CN IX, X, XII).
- Motor: Asymmetries in tone or spontaneous movements. Response to noxious stimuli with localizing, withdrawal, or posturing. Asymmetries in reflexes.

DIFFERENTIAL DIAGNOSIS: The differential diagnosis for altered consciousness is broad. Many of the possible diagnoses, including trauma, anoxia, seizures, infection, and metabolic encephalopathy, are covered in this chapter.

ICU MONITORING: There are various neuroimaging techniques, as well as invasive monitoring, that may be useful. See Table 13.1.

ACUTE INTRACRANIAL HYPERTENSION

Assessing the degree of brain oxygenation is a fundamental step in the care of neurologic emergencies. In this section we will first address the normal

TABLE 13.1 Neuromonitoring in the ICU

Technique	Benefits/Utility	Clinical Scenario
Computed tomography (CT)	Quick, low cost. Negative = radiation exposure	Hemorrhage, infarction, mass lesion, bony lesion
Head ultrasound (HUS)	Noninvasive, lower cost, no radiation. Requires an open fontanel	IVH, larger hemorrhages, and mass effect, serial monitoring
MRI		
Conventional imaging (T1, T2)	Structure, CSF	Structural lesion, edema
Diffusion-weighted imaging (DWI) and apparent diffusion coefficient (ADC)	Areas of restricted diffusion	Hypoxic and/or ischemic injury, abscess
T1 with gadolinium contrast	Identifies areas of blood–brain barrier breakdown	Tumor, abscess
Magnetic resonance angiography (MRA)	Vessel integrity and path	Thrombosis, dissection, vascular malformations
Magnetic resonance venography (MRV)	Venous integrity and path	Thrombosis, vascular malformations
Arterial spin labeling	Perfusion study without radiation	Areas of decreased (or increased) perfusion
Susceptibility-weighted imaging (SWI) or gradient echo (GRE)	Assessing venous blood and iron	Microhemorrhages, contusion, thrombosis
Magenetic resonance spectroscopy (MRS)	Assesses for metabolic abnormalities	Metabolic encephalopathy, trauma, hypoxic-ischemic injury
Bedside monitoring		
EEG	Continuous, real-time assessment of cortical activity	Seizure detection, burst suppression, encephalopathy
Near infrared spectroscopy (NIRS)	Continuous, real-time brain oxygenation assessment (Arterial - Venous O_2)	Coma, encephalopathy, trauma
Transcranial Doppler	Noninvasive	Vasospasm, perfusion
Intracranial pressure (ICP) monitoring	Direct measurement of ICP. Negative = invasive	Any condition with concerns for increased ICP

Note: See Chapter 3 for more details.

physiology of cerebral perfusion and brain oxygenation, followed by general pathophysiology.

NORMAL PHYSIOLOGY: The brain requires oxygen and glucose for its metabolic needs, which requires maintaining cerebral blood flow (CBF).

- Cerebral blood flow (CBF) $= \dfrac{\text{Carotid arterial pressure} - \text{Jugular venous pressure}}{\text{Cerebrovascular resistance (CVR)}}$
- CBF $= \dfrac{\text{Cerebral perfusion pressure (CPP)}}{\text{CVR}}$
- CPP = Mean arterial pressure (MAP) − Intracranial pressure (ICP)
  - MAP = 2/3 Diastolic pressure (DP) + 1/3 Systolic pressure (SP)
  - MAP = DP + 1/3 (SP – DP)

  Therefore, increases in blood pressure lead to increases in CPP *and* increases in ICP lead to decreases in CPP
- Normal range for CPP is age dependent since MAP increases with age while ICP remains mostly unchanged (Table 13.2; note that these values vary slightly based on gender and height)
- Cerebral vasculature mechanisms to maintain CPP (Fig. 13.1)
  - Metabolic mechanisms based on plasma osmolality
  - Neural mechanisms can be intrinsic and extrinsic
    - Intrinsic: Autoregulation (A, Fig. 13.1)
    - Extrinsic: $PaCO_2$: 35–45 mm Hg, increased $PaCO_2$ (B) leads to vasodilation, which increases CBF and indirectly the ICP (C). Conversely, decreasing the $PaCO_2$ with hyperventilation will acutely lower the ICP. Finally, when the pO_2 is low (<50 mmHg), CBF increases, as can the ICP (D).

ETIOLOGY: Brain edema from traumatic brain injury (TBI), hypoxic-ischemic encephalopathy (HIE), or ischemic stroke as well as bleeding or expanding lesion are common causes. In infants and children this may also

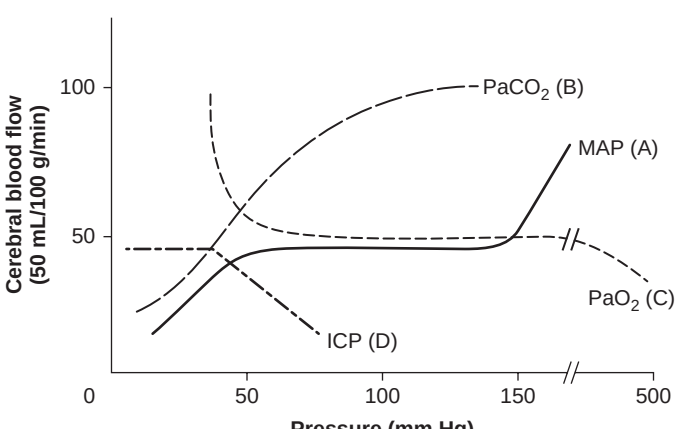


FIGURE 13.1 Cerebral Vasculature Mechanisms to Maintain Cerebral Perfusion Pressure (CPP). Cerebral blood flow (CBF) = CPP over cerebral vascular resistance (CVR). With a MAP 50 to 150 mm Hg in older children and adults (lower range in infants and younger children). **Autoregulation** maintains stable CBF with changes in CVR. (Adapted with permission from Westover MB, Choi E, Awad KM, et al., eds. *Pocket Neurology*. Philadelphia, PA: Lippincott, Williams and Wilkins; 2010:46–47.)

occur with dysfunctions of ventricular shunts and their valves (ventriculosubgaleal, ventriculoperitoneal, ventriculoatrial, and ventriculopleural shunts).

General Pathophysiology:

- The cranial vault contains:
  - Brain parenchyma, 80%; blood, 10%; CSF, 10%.
  - The amount of CSF ~150 mL, with 500 mL made daily (about 20 mL/h).
- In adults and older children the ICP is generally between 11 and 28 cm H_2O or 8 to 20 mm Hg, although this range decreases with age[2] (see Table 13.2).
- Any increase in brain parenchyma, blood, or CSF can produce changes in mechanical forces and may lead to herniation (Fig. 13.2).
- Both cytotoxic and vasogenic mechanisms can lead to cerebral edema.
  - Cytotoxic edema is caused by cellular injury that leads to excitatory amino acid release, leading to cell depolarization and sodium traveling into the cell, causing swelling.
  - Vasogenic edema is the result of dysfunctional vessels, such as those of a tumor, which allow passage of intravascular fluid into the interstitial space.

CLINICAL FEATURES: Symptoms include headache, vomiting, vision changes, and gaze palsies. Impending herniation may be heralded by *Cushing's triad*, which includes hypertension, bradycardia, and irregular respirations.

TRAUMATIC BRAIN INJURY

DEFINITION: TBI is one of the leading causes of trauma-related hospitalizations and mortality in children. It occurs when an external mechanical force causes brain dysfunction.

ETIOLOGY: In children the causes vary by age, with falls being the leading cause in children 0 to 4 yo and motor vehicle accidents being by far the leading cause in adolescence, ages 15 to 19. Nonaccidental head trauma in young children is an important cause of TBI and should always be assessed for. It is the leading cause of abuse-related deaths in the United States.[3]

EPIDEMIOLOGY: Recent estimates by the CDC reveal that from 2002 to 2006 there were 511,257 traumatic brain injuries in children 0 to 14 yo that led to 473,947 ED visits, 35,136 hospitalizations, and 2,174 deaths annually.[3]

PATHOPHYSIOLOGY: The biomechanics of TBI involve both linear and/or rotation forces. Linear forces, such as those resulting from a fall, tend

TABLE 13.2 Normal Heart and Respiratory Rates, Blood Pressure, Mean Arterial Pressure (MAP), Intracranial Pressure (ICP), and Cerebral Perfusion Pressure (CPP) for Different Ages[2,55,56,57]

Age	Heart Rate (beats/min)	Resp. Rate (breaths/min)	Blood Pressure (mm Hg)	MAP (mm Hg)	ICP (mm Hg)	CPP (mm Hg)
0–3 mo	100–150	35–55	65–85/45–55	35–65	2–5 (3–7 cm H_2O)	>30
3–12 mo	80–120	25–45	70–100/50–65	55–75		
1–6 y	65–110	20–30	85–110/45–75	65–85	3–7 (4–10 cm H_2O)	>40
6–12 y	60–95	14–22	95–120/55-80	70–90		>50
>12 y	60–100	12–18	100–130/60–80	70–95	< 20 (11–28 cm H_2O)	>60

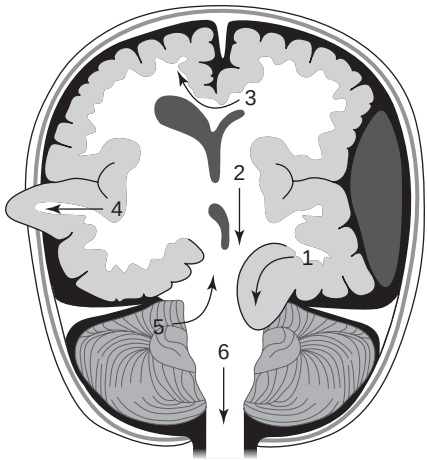


FIGURE 13.2 Types of Brain Herniation. *1.* Uncal: ipsilateral CN III palsy and contralateral hemiplegia or posturing. *2.* Central transtentorial: coma with bilateral small pupils and progression of posturing from decorticate to decerebrate with loss of brainstem reflexes. *3.* Subfalcine: coma and contralateral weakness to posturing. *4.* Extracranial (when craniectomy is present): deficits from herniated territory. *5.* Upward cerebellar: cerebellar symptoms to coma and bilateral posturing. *6.* Tonsillar (downward cerebellar): decreased arousal, pyramidal signs, respiratory insufficiency, coma. (Adapted with permission from Westover MB, Choi E, Awad KM, et al., eds. *Pocket Neurology.* Philadelphia, PA: Lippincott Williams and Wilkins; 2010:46–47.)

to cause brain contusions, focal injuries, and coup–contrecoup injuries. Rotational injuries occur in motor vehicle accidents and sports injuries, and nonaccidental trauma leads to shearing forces causing traumatic axonal injury occurring in white matter fiber tracts. All of these injuries lead to increased excitatory neurotransmission and neurometabolic cascades, leading to axonal injury and cell death.[4] Furthermore, children's brains seem to be more susceptible to cerebral swelling following head injury as compared with those of adults.[5]

CLINICAL FEATURES: The history and exam should be focused as discussed earlier. Mechanism of injury and the environment in which the injury occurred (e.g., seat belt, fall from height, drugs or alcohol involved) will guide diagnosis and treatment. One should assess for fractures by periorbital or retroauricular ecchymoses ("raccoon eyes" or "Battle's sign"), an asymmetric fixed pupil, neck trauma, or other signs suggesting the need for emergent neurosurgical intervention.

DIAGNOSTIC WORKUP:

1. Noncontrast head CT remains the best neuroimaging modality for quickly assessing for bony abnormalities, hemorrhage, and swelling.
2. MRI will be more sensitive for ischemia and subtler structural abnormalities.
3. Lab testing should be focused on assessing for cause of the injury (urine toxicology) and systemic injury (e.g., liver and renal function).

MANAGEMENT: Includes both medical and neurosurgical interventions aimed at addressing cerebral swelling and neuroprotection (2012, updated guidelines).[6]

- Osm 300–360
- Measure BP (MAP). Goals: Maintain CPP (see Table 13.2)
- $PaCO_2$ 35–40

MONITORING: ICP monitoring or EEG may be indicated when neurologic examination is limited by impaired consciousness or paralysis. Dysautonomia occurs in 10% of children following TBI and should also be carefully monitored for.[7]

TREATMENTS: Includes osmotherapy, sedation, and supportive measures[8] (Table 13.3).

PROGNOSIS: Mortality from severe traumatic brain injuries in patients admitted to the PICU ranges from 9% to 22%.[9,10] About a 3rd of patients will have severe disability, and 40% to 50% will have moderate disability, with only 11% to 17% having good recovery. All of these numbers appear to be improved when a pediatric neurocritical care program is instituted.[11] Patients with TBI may be left with cognitive and/or motor deficits. The degree of traumatic axonal injury and global white matter pathology is likely related to the degree of cognitive deficits.[12]

HYPOXIC-ISCHEMIC ENCEPHALOPATHY

HIE in the pediatric population most commonly happens in the perinatal period (see Chapter 19); however, a number of insults that lead to cardiac or respiratory arrest have implications in older pediatric patients as well.

DEFINITION: HIE is the loss of oxygen or blood flow to the brain, leading to brain damage and neurologic sequelae.

ETIOLOGY: The etiology of HIE differs significantly between infant, children, and adult patient populations. In newborn infants HIE occurs in the perinatal period and may be related to hypotension, respiratory failure, infection, and can be related to metabolic or genetic factors. In adults hypoxic-ischemic injury is typically related to cardiac arrhythmia, including ventricular fibrillation or tachycardia. In the pediatric population, asphyxia, such as caused by drowning, upper or lower airway obstruction, sudden infant death syndrome (SIDS), trauma, and other causes leading to asystole or bradyarrhythmias are much more common.[13]

EPIDEMIOLOGY: 16,000 children die annually from cardiopulmonary arrest.[14] The most common causes of noncardiac arrest include drowning, SIDS, trauma, intoxications, respiratory causes, such as asthma, aspiration, or other acute airway obstruction, and sepsis[15]; however, the rates of death from SIDS have been cut in half in the last 15 y.[16] Cardiac etiologies are the most common cause of cardiopulmonary arrest in infants beyond the perinatal period.[17] The most common causes of cardiac causes of arrest in patients 0 to 13 yo are congenital abnormalities, while primary arrhythmias were the most common in children 14 to 24 yo.[18]

PATHOPHYSIOLOGY: The brain requires large amounts of oxygen and glucose for cellular metabolic demands. When decreased blood oxygenation (hypoxia) or blood flow (ischemia) occurs, this leads to loss of energy reserves in the form of adenosine 5-triphosphate (ATP). ATP depletion maintains membrane gradients,[19] and disruption of these begins a cascade of detrimental events, including cell depolarization, glutamate release, and

TABLE 13.3 Treatment of Increased Intracranial Pressure (ICP)

Goal	Treatment/Medication	Mechanism/Benefits/Risk
Osm therapies: • Osm 300–360 • Maintain CPP • CPP = MAP − ICP • ICP < 20 • CPP > 40	20% mannitol Bolus: 1 g/kg Maint: 0.25–0.5 g/kg q2–6h	1. Decreases blood viscosity increasing CPP (rapid, transient) 2. Osmotic effect (water from parenchyma drawn into vessel). *Note:* requires intact blood–brain barrier (BBB) Risk: accumulation in areas of BBB breakdown
	Hypertonic saline 3% acute use: 6.5–10 mL/kg 3% maintenance: 0.1–1 mL/kg/h 23% rarely used because of safety in small patients	1. Osmotic benefit (sodium does not cross the BBB well) 2. Theoretical: improved resting membrane potentials; decreased inflammation Risk: rebound in ICP
$PaCO_2$ 35–40	Hyperventilation	Induces hypocarbia → vasoconstriction Mild: $PaCO_2$ 30–35 mm Hg Aggressive: can be considered as a temporizing measure with $PaCO_2$ <30 mm Hg in the first 48 h Risk: iatrogenic ischemia
Decrease brain metabolism	Anesthetics e.g., barbiturates	1. Reduce oxygen demand 2. Decreased electrical activity 3. Decreased neurotransmitter synthesis
	Quiet, normothermia (preventing hyperthermia)	Decreases brain excitation/activity, thereby decreasing oxygen demand
General measures	Pressors Head of bed 30°	Maintain MAP Reduces ICP, maintains CPP, prevents aspiration

ultimately Ca^{2+} influx into the cells, leading to cell necrosis and apoptosis. Additionally, creation of free radicals, accumulation of toxic by-products, and local inflammatory response, as well as reperfusion injury contribute to cell necrosis and death.[20]

CLINICAL FEATURES: The clinical presentation depends on the etiology of the accident and the success of acute onsite CPR and EMS response. Clinical features are likely to include altered consciousness, and may include coma, seizures, myoclonus, movement disorders, as well as posthypoxic encephalopathy occurring 24 to 48 h after regaining consciousness.

DIAGNOSTIC WORKUP AND MONITORING:

- Systemic labs to assess injury to other organs (e.g., liver, kidneys) and degree of injury (lactate).
- EEG may provide prognostic information with a discontinuous tracing or the presence of epileptiform discharges indicating a poor prognosis.[21]
- Somatosensory and auditory evoked potentials have both been shown to correlate with neurologic recovery in pediatric patients following a variety of neurologic injuries, including trauma and drowning.[22–24]
- CT scans may be useful for identifying cerebral edema, and early abnormalities are associated with poor prognosis, but may also be normal following an anoxic injury and do not correlate with outcome.
- MRI (T2, DWI sequences) correlates better with clinical outcome. MR spectroscopy (MRS) can demonstrate reduced NAA peaks and NAA/creatine ratio in pediatric patients following severe head injury as a marker of poor neurologic outcome.[25]

MANAGEMENT AND TREATMENT: Initial management should address the ABCs, as well as maintain normal glucose and electrolyte balance. Cerebrovascular management may be complicated by dysautonomia, which occurs in 31% of children following cardiac arrest.[7] Addressing and managing increased ICP and metabolic rate as discussed above is also appropriate. Hypothermia following cardiac arrest has been shown to be beneficial in adults[26] and neonates (see Chapter 19), and there is currently an ongoing randomized clinical trial to evaluate its effect in the pediatric population. In addition to hypothermia, there are a number of neuroprotective therapies that are receiving research attention.

PROGNOSIS: Predicting the outcome from hypoxic-ischemic coma is difficult in children. The *Levy criteria* is a valuable tool used to assess neurologic outcome in adults on the basis of exam findings during the first week of coma.[27] This criteria has not been validated in children, but may be referred to as a guide. Mortality rates are at least 75% to 90%, with the highest rate in out-of-hospital arrests.[28] Long-term cognitive impairments in memory, executive function, and behavior may also be seen.[29,30] In cardiac arrest, short-term memory impairments may be transient or persistent depending on the duration of arrest time and comorbid anxiety.[29]

VASCULAR EVENTS

Stroke and hemorrhage are discussed in Chapter 18.

BRAIN DEATH

Unfortunately, understanding brain death and the exam required is an important aspect of pediatric ICU care.

DEFINITION: The Uniform Determination of Death Act, accepted by the American Medical Association published in 1980 and recently updated,[31] states that "brain death in term of newborns, infants, and children is a clinical diagnosis based on the absence of neurologic function with a known irreversible cause of coma." Preterm infants $<$37 wk are specifically excluded from the guidelines. These recently revised guidelines emphasize that "coma and apnea must coexist" and reinforce the importance of age-appropriate hemodynamic parameters.

ETIOLOGY: Of the nearly 25,000 deaths leading to organ donation from 1994 to 2012, the causes of death included TBI 46%, anoxia 19%, and hemorrhage or stroke 5% (Unos.org).

CLINICAL FEATURES: The necessary criteria for initiating a brain death exam were recently updated from the 1987 task force. The following physiologic parameters must be addressed[31]:

- Hypotension: systolic blood pressure or MAP should be in an acceptable range, typically within 2 standard deviations of the mean.
- Hypothermia must be corrected, with a core body temperature of >35°C (95°F).
- Severe metabolic disturbances, which may cause coma, must be corrected.
- Drug toxicities, particularly those medications known to cause coma, including benzodiazepines and barbiturates.

NEUROLOGIC EXAM: See Table 13.4.

SUPPORTIVE DIAGNOSTIC TESTS: EEG, radionucleotide imaging.

TABLE 13.4 Checklist for Determination of Brain Death

Date and time of exam:

Supervising attending physician:

Cause of coma
- ❑ Injury is sufficient to explain neurologic findings.
- ❑ Findings not explained by pharmacologic agents or intoxication.
- ❑ Findings not explained by reversible metabolic abnormalities.
- ❑ Findings not explained by reversible alteration in oxygenation, BP, temperature.

Neurologic exam
- ❑ No evidence of hypotension, hypothermia, or metabolic disturbance.
- ❑ Patient is comatose (unresponsive) without sedative medications.

Absent brainstem reflexes
- ❑ Pupillary light
- ❑ Corneal
- ❑ Oculocephalic
- ❑ Oculovestibular
- ❑ Oropharyngeal

Apnea testing
- ❑ $PaCO_2$ 20 mm Hg above baseline $PaCO_2$ and ≥60 mm Hg with no respiratory effort.

Observation period
- ❑ Two exams performed to document brain death, separated by 24 h in neonates and 12 h in infants and children.
- ❑ Based on absence of cerebral perfusion on SPECT scan no observational period is necessary.

Other tests: EEG and/or radionuclide CBF if apnea testing cannot be performed.

Patient declared dead on _____ (date) at _____ (time).

Signature of Attending Physician: _____

Adapted from Boston Children's Hospital checklist and recent recommendations. Please refer to your institution's guidelines for a specific protocol.

STATUS EPILEPTICUS

Status epilepticus (SE) is one of the most common pediatric neurologic emergencies.

DEFINITION: A self-sustaining seizure or repeated seizures without a return to baseline that lasts longer than 5 min.

EPIDEMIOLOGY: SE occurs annually at a frequency of 50 episodes per 100,000 people aged 1 mo and older[32] with as many as 30 to 41 episodes per 100,000 people per year in children 1 mo to 15 y.[33] The children with the highest incidence in both studies were under 1 yo. The recurrence risk in children <4 y is 38%.[32]

ETIOLOGY: These differ somewhat by age. Systemic infection and low antiepileptic levels account for over 70% of cases of SE. Remote causes, such as previous brain injuries, account for 30% to 40% of cases.[32] Stroke, drugs and toxins, metabolic causes, CNS infections, hypoxia, and trauma account for other causes. Two other distinct entities affecting children are febrile infection-related epilepsy syndrome (also known as fever-induced refractory epileptic encephalopathy in school-aged children), or FIRES, and idiopathic hemiconvulsion–hemiplegia syndrome (IHHS). These both occur in the setting of a febrile illness without evidence for a causal microorganism or an autoimmune phenomenon. FIRES begins with SE lasting several weeks, involves perisylvian areas, including mesial temporal structures. In a series of 77 patients with FIRES outcomes were poor, with nearly 12% mortality in the acute phase, 93% having subsequent refractory epilepsy, and only 18% retaining normal cognitive function.[34] IHHS begins in infancy with unilateral clonic SE and is followed by hemiplegia with pharmacoresistant epilepsy. The etiologies of FIRES and IHHS remain unknown.[35]

PATHOPHYSIOLOGY: The pathophysiology of SE is not well understood. It is known that the efficacy of benzodiazepine therapy, which acts by binding to GABAA receptors, decreases with seizure duration. This may be due to postsynaptic GABAA receptors being actively transported into the cell[36] and emphasizes the importance of early treatment of SE.

CLINICAL FEATURES: SE may be generalized, focal, or nonconvulsive.

DIAGNOSTIC WORKUP AND MONITORING: Testing and labs should be directed at the potential etiologies of SE mentioned above.

- Lab: CBC with differential, Chem7, calcium, magnesium, phosphorus
- Neuroimaging: CT may help rule out ischemia, hemorrhage, or trauma. MRI, particularly with a higher-resolution 3T scanner, is preferred to identify more subtle seizure foci.
- EEG has many roles in the diagnosis and facilitating the treatment of SE.

MANAGEMENT AND TREATMENT (Fig. 13.3): ABCs, ensuring an adequate airway and managing circulation are extremely important and can prevent early respiratory failure and cardiovascular arrest. Respiratory and hemodynamic monitoring, as well as the management of temperature and metabolic factors (hypoglycemia and hyponatremia) should be continued throughout the treatment of SE.[37]

PROGNOSIS: According to a large prospective database compiled through the Greater Richmond Metropolitan Area Status Epilepticus Project (GRMASE), by using the 30-min definition, the 30-d mortality rate for subjects with seizures lasting 10 to 29 min was only 2.6% compared with a 19% rate in patients diagnosed with SE but who otherwise had comparable clinical features.[38] The extent of aggressive treatment measures for focal SE or patients with subclinical sustained epileptiform discharges is somewhat controversial.

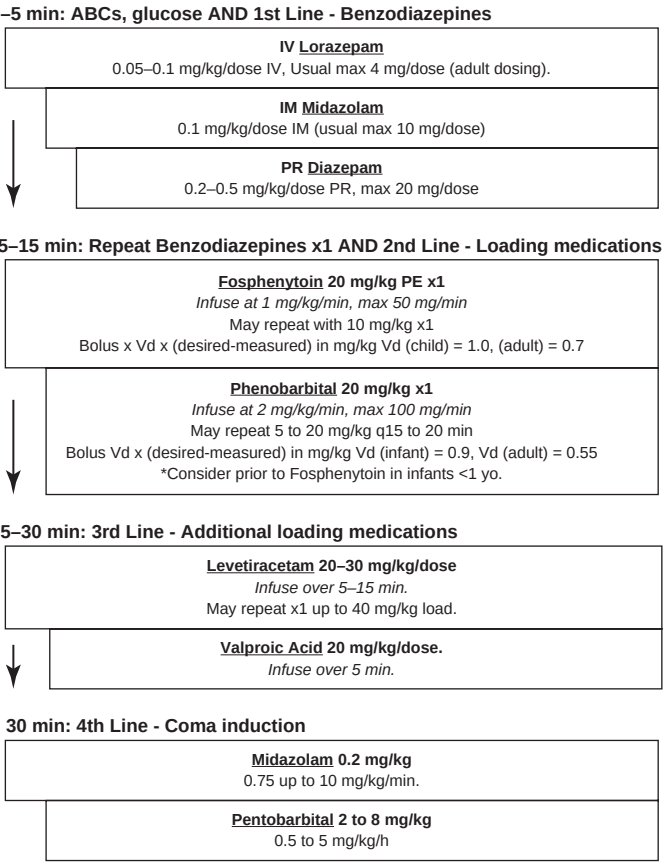


FIGURE 13.3 A General Approach to the Management of Status Epilepticus. Attention should always be given to the patient's airway and hemodynamics, as well as reversible causes of status (e.g., hypoglycemia).

METABOLIC ENCEPHALOPATHY

Metabolic encephalopathies are common in the ICU. As in adult patients, these are often from toxic etiologies, sepsis, or organ failure (e.g., liver, kidney). In addition to these, inborn errors of metabolism also must be considered in the pediatric population (particularly if encephalopathy develops over a few days to weeks after the initiation of breast feeding).

DEFINITION: Altered mental status attributable to underlying metabolic or toxic etiology. Comprehensive algorithms (hyperammonemia, anion gap metabolic acidosis, and metabolic coma) and specifics about each metabolic disorder can be found in Chapter 7.

ETIOLOGY: See Table 13.5 for a differential of pediatric metabolic encephalopathies.

TABLE 13.5 Etiology of Metabolic Encephalopathy in the ICU

Inborn Errors of Metabolism and Examples	Electrolyte Abnormalities	Toxins	Organ failure	Infection/ Immuno
Gluconeogenesis and carbohydrate Glycogen storage diseases Pyruvate Fructose Fatty acid oxidation MCAD Amino acids Phenylketonuria Nonketotic hyperglycinemia Glutaric aciduria	Hyper/hyponatremia Hyper/hypocalcemia Hyper/hypomagnesemia Hypophosphatemia Hyper/hypoglycemia	Sedatives Anticholinergics Salicylates Arsenic Lead Carbon monoxide Organophosphates Ethylene glycol Methanol	Hepatic encephalopathy Renal failure/uremia Pulmonary failure with hypoxemia or hypercapnea	Sepsis ADEM
Organic acids Propionic acidemia Methylmalonic aciduria				
Urea cycle				
Mitochondrial Leigh's syndrome MELAS Respiratory chain disorders				
Peroxisomal Zellweger syndrome				
Lysosomal Mucopolysaccharidoses Gaucher Nieman–Pick				
Metal metabolism Wilson's Copper				
Purine and pyrimidine Lesch–Nyhan syndrome				

Adapted from Frontera JA. Metabolic encephalopathies in the critical care unit. *Continuum.* 2012;18(3):611–639.

EPIDEMIOLOGY: The incidence is unknown, but presumed to be quite common. In adult patients, delirium occurs in 70% of ICU patients.[39] In pediatrics, an estimated 2.2% of PICU admissions have inborn errors of metabolism, with more than half requiring mechanical ventilation.[40]

CLINICAL FEATURES AND PRESENTATION: Metabolic encephalopathies may present with mental status changes, including altered consciousness, confusion, agitation, fluctuating attention (delirium), or coma. Other signs and symptoms may include seizures, metabolic acidosis, hepatomegaly, vision or hearing deficits, hyper- or hypotonia.

DIFFERENTIAL DIAGNOSIS: Is very broad and depends on age, history and onset of symptoms, and neurologic exam; see Table 13.5.

DIAGNOSTIC WORKUP: Toxic screen, chemistries to assess electrolytes, glucose, renal function, LFTs, ammonia, metabolic studies, including lactate and pyruvate. If inborn error is suspected, serum amino acids, urine organic acids, urine acylglycines, and acylcarnitine profile may be indicated. See Chapter 7 for more details.

MANAGEMENT AND TREATMENT: Supportive ICU care and treatments directed at underlying etiology.

PROGNOSIS: There is a 28% mortality in patients admitted to the PICU with an inborn error in metabolism.[40]

HYPONATREMIA

Hyponatremia is a complication of a variety of brain injuries and medications in the PICU.

DEFINITION: Sodium (Na) $<$130 mEq/L. It is considered acute when it develops in $<$48 h and chronic when its onset is unknown or $>$48 h.

ETIOLOGY: Can arise from a number of causes, generally divided into euvolemic (with increased total body water), hypervolemic (with a greater increase in water than sodium), and hypovolemic (with sodium greater than water loss). In the ICU distinguishing between the syndrome of inappropriate antidiuretic hormone (SIADH) and cerebral salt wasting (CSW) is important.

EPIDEMIOLOGY: Following subarachnoid hemorrhage in adults, hyponatremia was due to SIADH and CSW 70% and 6.5% of the time, respectively.[41] SIADH can not only be associated with intracranial pathology (tumor, hemorrhage, hypoxia, TBI) but may originate from peripheral sources such as neuroendocrine tumors, small cell cancer, and pulmonary and pleural lesions.

Physiology of Fluid Balance:

- Plasma osmolality = Sum of all solutes (osmoles per kg of water)
- POsm = $2(Na^+)$ + Glucose/18 + *BUN*/2.8
- POsm = $2(Na^+)$
  - When there is no increase of other solutes (hyperprotenemia, hyperlipidemia, hyperglycemia)
- Normal pOsm = 280–295 mOsm/kg; urine Osm = 50–1,200 mOsm/kg

CLINICAL FEATURES AND PRESENTATION: Ranges from confusion to coma, and can include seizures, irritability, muscle pain or weakness, vomiting, as well as classic herniation syndrome due to malignant cerebral edema.

DIAGNOSTIC WORKUP: In addition to studies geared at the underlying cause, assessing volume status, testing electrolytes, plasma osmolality,

urine sodium, and urine osmolality may all be useful. See Figure 13.4 for a diagnostic approach to hyponatremia.

MANAGEMENT AND TREATMENT: In general:

- **Hypovolemic hyponatremia:** requires normal saline replacement (most commonly secondary to dehydration).
- **Hypervolemic hyponatremia:** managed with water and sodium restriction.
- **Euvolemic hyponatremia:** treated with water restriction only.

More specifically:

- **SIADH** is treated with water restriction and normal to hypertonic saline.
- **CSW** is treated with salt loading volume replacement and fludrocortisone.
- If Na has fallen rapidly (<48 h), there are symptoms, or Na is <110 mEq/L, then it should be corrected rapidly.
  - The goal of treatment is to increase the serum sodium level by 1.5 to 2 mEq/L/h until symptoms subside or until the sodium concentration is >118 to 120 mEq/L, with the primary focus to minimize the risk of seizure. Even in symptomatic patients, the sodium level should not be increased by >12 mEq/L in the first 24 h, or by >18 mEq/L in the first 48 h, to avoid osmotic demyelination syndrome.
  - When patients become asymptomatic and sodium levels rise above 118 mEq/L, correction should be slowed to no >8 mEq/L in 24 h to achieve the target sodium concentration.
- Chronic hyponatremia should be corrected at a slower rate, not exceeding 0.5 mmol/L/h or 10 to 12 mEq/L over the first 24 h.

Use of hypertonic 23% Na solution is controversial in the PICU and reserved only for acute management when imminent herniation or seizures are present.

COMPLICATIONS: Overcorrection of sodium may lead to seizures or central pontine myelinolysis (although osmotic demyelination has not been described in prepubertal children to date).

HYPERNATREMIA

Most common causes of hypernatremia are iatrogenic (due to infusion of hypertonic solutions during fluid resuscitation), free water deficit [calculated by $dosing\ factor \times weight\ (kg) \times ((serum\ Na/140) - 1)$, where dosing factor = 0.6 if male and 0.5 if female], and diabetes insipidus (DI).

Diabetes Insipidus

DEFINITION: Disorder characterized by excessive thirst and excretion of large amounts of severely diluted urine, leading to dehydration. Two types of DI: *Central DI* is the most common type caused by a deficiency of circulating vasopressin, also known as antidiuretic hormone (ADH). *Nephrogenic DI* is caused by an insensitivity of the kidneys to ADH. It can also be an iatrogenic artifact of drug use.

ETIOLOGY: *Nongenetic causes:* Injury to the hypothalamus or pituitary gland from head trauma, tumor, neurosurgical procedures, basilar tuberculosis meningitis, encephalitis, meningitis, or sarcoidosis. At all ages, destructive lesions of the pituitary, the hypothalamus, or both are the most common cause of DI. *Genetic causes:* Central DI with an autosomal

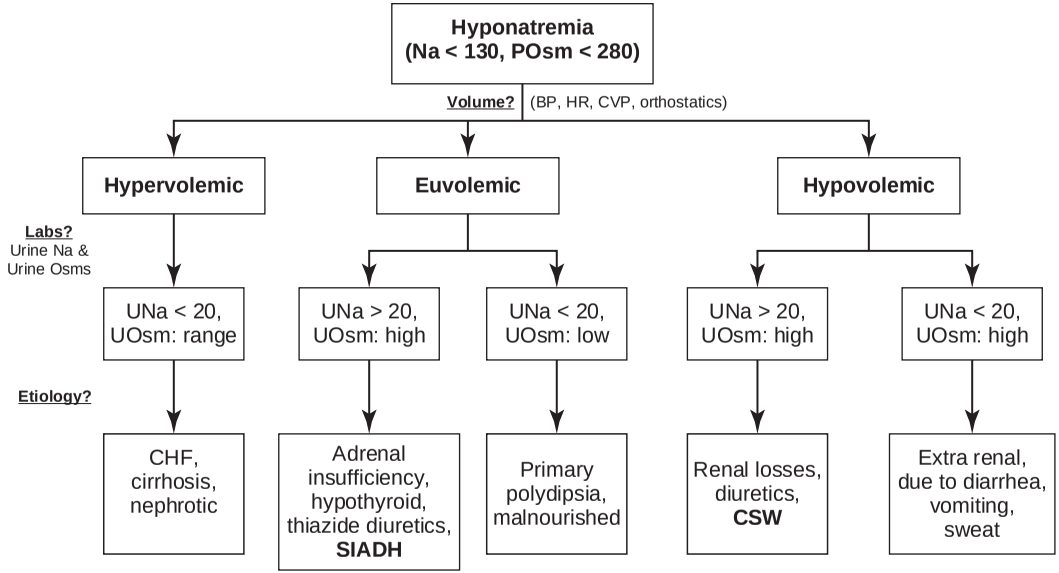


FIGURE 13.4 A General Approach to Hyponatremia. CHF, congestive heart failure; CSW, cerebral salt wasting; Na, sodium; POsm, plasma osmolality; SIADH, syndrome of inappropriate antidiuretic hormone; UNa, urine sodium; UOsm, urine osmolality.

dominant pattern inheritance is due to a mutation in the pre-pro-arginine vasopressin (*prepro-AVP2*) gene, mapped to locus 20p13. Central DI with diabetes mellitus, optic atrophy, and mental retardation (Wolfram syndrome) may be inherited in an autosomal recessive pattern (locus 4p16) or may be due to mitochondrial deletions. X-linked nephrogenic DI occurs from mutations in the antidiuretic arginine vasopressin V_2 receptor (*AVPR2*) gene, mapped to Xq28. Nephrogenic DI with an autosomal dominant or recessive pattern is due to mutations in the gene designated *AQP2* (water channel formation in the distal tubule).

EPIDEMIOLOGY: 1 in 30,000 children (98% central variety, 2% nephrogenic type).

CLINICAL FEATURES AND PRESENTATION: In the critically ill child or infant the most common initial sign is increased urine output with hypernatremia and hyperosmolarity. In the ambulatory setting children symptoms commonly include excessive thirst, excessive urine production, and dehydration. Infants with DI may also exhibit irritability, poor feeding, failure to grow, and high fevers. If severe hypernatremia or dehydration occurs, altered mental status and seizures can occur.

Diagnostic Workup:

- *Lab:* Urine specific gravity of the 1st morning urine. Serum Na and osmolarity. Dilute urine with a relatively high serum sodium and osmolarity effectively establishes the diagnosis. The serum Na may be as high as 170 mEq/L, while the serum osmolarity is >300 mOsm/kg. An accurate 24-h urine collection is important. The total urine output is high, and the number of osmoles excreted per day is small. Serum K and Ca are important to exclude the possibility of polyuria secondary to hypokalemia or hypercalcemia.
- Water deprivation test: A normal response should be observed in central DI and psychogenic DI, but not in nephrogenic DI.
- MRI brain: Can detect pituitary cysts, hypoplasia, and destruction secondary to mass or inflammatory lesions.

MANAGEMENT: Treating underlying tumor, inflammatory, infectious, or high ICP cause can reverse central DI in some cases.

Fluid Resuscitation: It is vital to replace the free water losses in the urine in the acute setting by matching urine output with IV fluids.

Pharmacological tx: For central DI the treatment of choice is desmopressin (a synthetic vasopressin analog). Aqueous vasopressin (Pitressin) and desmopressin (DDAVP) preparations are available for intravenous (IV) or intranasal use in emergency circumstances. Other useful medications include chlorpropamide and thiazide diuretics (25%–75% reduction in urine volume). Nephrogenic DI cannot be effectively treated with desmopressin because the receptor sites are defective and the kidney is prevented from responding. Thiazide diuretics, amiloride, and indomethacin or aspirin are useful when coupled with a low-solute diet. Overtreatment with desmopressin can result in hyponatremia and seizures.

Diet: Provide affected infants with a breast milk diet to decrease solute load. Protein should account for 6% of caloric intake, and sodium should be reduced to 0.7 mEq/kg/d. Young children should have 8% of their caloric

intake in the form of protein to enable normal growth. Sodium intake must be maintained at 0.7 mEq/kg/d.

PROGNOSIS: Long-term survival in cases of central DI depends on the precipitating cause. In primary central DI, the prognosis is excellent with early recognition and appropriate desmopressin therapy. The earlier onset of nephrogenic DI and the reduced ability to treat this type of the disease render the child more prone to attention deficit, hyperactivity, learning disorders, and psychomotor delay. As long as water remains available at all times to replace the massive losses, long-term survival is not in question.

BACTERIAL MENINGITIS AND ENCEPHALITIS

This section deals with emergencies related to bacterial CNS infections.[42,43] More details can be found in Chapter 22.

DEFINITION: Inflammation of the leptomeninges (meningitis) or brain parenchyma (encephalitis) secondary to infection.

ETIOLOGY: Bacterial pathogens by age (Table 13.6). Signs and symptoms of infections by intracellular bacteria such as *Mycoplasma, Ehrlichia sp., Rickettsia rickettsii* resemble the signs and symptoms of viral encephalitis more than those of bacterial meningitis (see below). *Mycobacterium tuberculosis*, although less common in the United States, remains an important cause of meningitis across the globe. In one recent study, nearly 40% of children admitted to Beijing Children's Hospital with tuberculosis had meningitis.[44]

EPIDEMIOLOGY: Remains a worldwide health issue with a mortality in untreated cases that approaches 100%. In children, 90% of cases are reported in patients 1 mo to 5 y.

TABLE 13.6 Bacterial Pathogens by Age and Recommended Treatments

Age	Pathogen	Treatment
0–1 mo	Group B *Streptococcus* *E. coli* *Listeria monocytogenes* *Strep. pneumo*	Ampicillin 50–100 mg/kg q6-8h *and* Cefotaxime 100 mg/kg q8h *or* Gentamicin 2.5 mg/kg q8h
1–3 mo	*Strep. pneumo* *E. coli* *Neisseria meningitides* Group B *Streptococ-cusL. monocytogenes* *Haemophilus influenzae*	Ampicillin 50–100 mg/kg q6-8h *and* Cefotaxime 100 mg/kg q8h *or* Ceftriaxone 100 mg/kg q24h
3 mo–18	*N. meningitides* *Strep. pneumo* *H. influenzae*	Cefotaxime 100 mg/kg q8h *or* Ceftriaxone 100 mg/kg q24h *and* Vancomycin

Stechenberg B. Bacterial meningitis. In: Barton LL, Friedman NR, eds. *The Neurologic Manifestations of Pediatric Infectious Diseases and Immunodeficiency Syndromes.* Human Press; 2008. Tauber MG, Schaad UB. Bacterial infections of the nervous system. In: Swaiman KF, Ashwal S, Ferriero DM, et al. eds. *Swaiman's Pediatric Neurology: Principles and Practice.* 5th ed. Philadelphia, PA: Saunders; 2012.

PATHOPHYSIOLOGY: Bacterial meningitis begins typically with hematogenous spread and less commonly by direct transmission from sinuses or mastoid.

CLINICAL FEATURES AND PRESENTATION: Fever (94%), vomiting (82%), meningismus (77%) in younger children, while older children will also report headache and neck pain or stiffness (60%–80%). Other presentations include seizures (20%–30%) and less commonly coma (10%). *Kernig sign*: stretching of the hamstring with knee extension causes back pain, and *Brudzinski sign*: passive neck flexion causes involuntary hip and knee flexion. CNS manifestations of Tb include meningitis, intracranial tuberculoma, and spinal tuberculous arachnoiditis.

DIFFERENTIAL DIAGNOSIS: Focal neurologic signs or increased ICP may indicate a brain abscess. Viral meningitis, as well as trauma and neoplastic processes, should also be considered.

DIAGNOSTIC WORKUP: A lumbar puncture is the crucial diagnostic test but should not be performed before brain imaging when there is evidence of increased ICP or mass (focal seizure, focal neurologic deficit on exam or papilledema). Neuroimaging should be performed in comatose patients or those with focal neurologic findings prior to LP (see Table 13.7 for CSF findings).

MANAGEMENT AND TREATMENT: Treatment (see Table 13.6). Additionally, the administration of dexamethasone has been demonstrated to reduce the incidence of hearing loss in children with bacterial meningitis, particularly those with Haemophilus influenzae (Hib) meningitis, as well as reduce mortality in Streptococcus pneumoniae meningitis.[45] The recommended dose is 0.15 mg/kg (up to 10 mg in adults) q6h for 2 to 4 d, initiated 10 to 20 min before or at least concomitant with the first antimicrobial dose.[46]

PROGNOSIS: Neurologic sequelae occur in 10% to 36% of patients, including hearing loss (15%–30%), parenchymal damage (5%–30%), focal neurologic findings (10%–15%), and intellectual or learning disabilities (5%–20%). In tuberculosis meningitis, the clinical outcome is poor even when treated with conventional antituberculous drugs. Corticosteroids are commonly used in addition and may help reduce swelling and congestion

TABLE 13.7 CSF Findings in Healthy Children and Bacterial and Viral Meningitis

	WBC (per µL)	Glucose (mg/dL)	Protein (mg/dL)	Differential
Healthy newborn	<9 (typically 1–5)	30–120	45–75	No PMNs
Healthy child	<6 (typically 0)	40–80	15–45	No PMNs
Bacterial meningitis	>1,000	<1/2 serum Often <40	>250	>50% PMNs Often >90%
Viral meningitis	5–100	>1/2 serum	50–250	Typically lymphocytic

Adapted from Bale JF. Viral infections of the nervous system. In: Swaiman KF, Ashwal S, Ferriero DM, et al., eds. *Swaiman's Pediatric Neurology: Principles and Practice*. 5th ed. Philadelphia, PA: Saunders; 2012. Mann K, Jackson MA. Meningitis. *Pediatr Rev.* 2008;29(12):417–430.

of the meninges and thus decrease ICP, thereby lowering the risk of death or disabling neurologic deficit among survivors. A Cochrane review evaluating either dexamethasone or prednisolone given in addition to antituberculous drugs demonstrated that corticosteroids help reduce the risk of death or disabling residual neurologic deficit, particularly in HIV-negative people.[47]

COMPLICATIONS: Seizures, stroke, and increased ICP are all potential complications of bacterial meningitis.

VIRAL MENINGITIS AND ENCEPHALITIS

This section deals with emergencies related to viral CNS infections.[48] More details can be found in Chapter 22.

DEFINITION: Infection of the leptomeninges (meningitis) or brain parenchyma (encephalitis).

ETIOLOGY: Viral pathogens associated with more dramatic CNS presentations include HSV, Eastern and Western equine viruses, West Nile, Epstein–Barr virus, rabies, human herpesvirus-6, and varicella.

EPIDEMIOLOGY: Rates of viral encephalitis range from 3 to 33 cases per 100,000 people, depending on endemic areas and inclusion of aseptic meningitis.

PATHOPHYSIOLOGY: Viral meningitis typically is acquired via hematogenous spread of the virus, after initially finding entry via the skin and mucosal surfaces of conjunctiva, respiratory, genital, and GI tracts. The rabies and herpes viruses gain entry to the CNS via nerves.

CLINICAL FEATURES AND PRESENTATION: In general, viral meningitis tends to be less severe than bacterial infections; however, the entities covered in this section may have dramatic clinical presentations. E.g., in HSV altered consciousness and fever occur in >90% of cases and seizures in >40%, as well as focal neurologic findings. Varicella may present similarly and often includes cerebellar ataxia.

DIAGNOSTIC WORKUP: As above, a lumbar puncture is the crucial diagnostic test (see Table 13.7 for CSF findings). Testing should include CSF PCR for suspected viruses (most commonly found HSV, VSV and CMV, *Enterococcus*). Consider sending viral encephalitis panel for arboviruses (Eastern Equine, Japanese, West Nile, La Crosse, Western Equine, and St. Louis encephalitis) depending on the geographical region and prevalence. Consult CDC website for maps of reported cases and laboratory referrals.

MANAGEMENT AND TREATMENT: Standard of care includes Acyclovir treatment until a negative result for HSV PCR is obtained. Acyclovir is also the appropriate treatment for varicella. Other antivirals may be considered depending on the viral pathogen. Supportive care with antipyretics, IV fluids (particularly with Acyclovir treatment, to prevent acute kidney injury), and hemodynamic monitoring is appropriate.

PROGNOSIS: Depends on the etiology. Untreated HSV has 50% mortality, while varicella encephalitis results in 5% to 10% mortality regardless of treatment.[49]

COMPLICATIONS: Varicella meningitis in particular is a risk factor for stroke since it can lead to leukocytoclastic vasculitis of the proximal medial cerebral and basilar arteries.[50] Seizures as well as immunologic complications (e.g., Guillain–Barré) should be treated as they occur.

IMMUNOLOGICALLY MEDIATED CONDITIONS

A broad range of autoimmune and inflammatory diseases, including antibody-medicated encephalitis (e.g., anti-NMDA receptor, anti-Hu), CNS vasculitis (primary and secondary), cerebellitis, demyelinating conditions (acute disseminated encephalomyelitis [ADEM], acute inflammatory demyelinating polyneuropathy [AIDP]), and myasthenia gravis (MG), may be seen in the ICU setting during their initial presentation, flares or aggressive immunosuppressant therapies. They often occur following viral infections or vaccine administration. The acute management issues will be briefly reviewed here, but for more details, see Chapter 17 for antibody-mediated encephalitis, ADEM, and vasculitis, and Chapter 6 for AIDP and MG.

Acute Demyelinating Conditions

DEFINITIONS: ADEM is a demyelinating condition affecting the central nervous system. AIDP is a demyelinating polyneuropathy associated with ascending weakness and hyporeflexia, commonly referred to as Guillain–Barré syndrome. Variants include Miller Fisher syndrome, which consists of ophthalmoplegia, hyporeflexia, and ataxia. These can progress to include respiratory compromise.

ETIOLOGY: Triggers are often undetermined, are commonly associated with a preceding viral infection or vaccine administration.

DIAGNOSTIC CRITERIA: ADEM requires acute or subacute onset with frequently multiple symptoms at presentation due to its multifocal nature in the CNS and must include encephalopathy.[51] AIDP must include progressive motor weakness of more than one limb and areflexia.[52]

Diagnostic Workup:

- ADEM: MRI with and without contrast and CSF studies, looking for WBCs, protein, and oligoclonal bands, which can be normal or nonspecific with mild elevations in WBCs and protein.
- AIDP: CSF reveals elevated protein and generally normal WBCs (albuminocytologic dissociation). EMG will demonstrate a demyelinating neuropathy, with 80% having evidence of nerve conduction slowing or block at some point during the illness.[52] Spinal MRI may show nerve root enhancement.

TREATMENT: IV steroids, such as high-dose methylprednisolone 15 mg/kg every 24 h (up to 1,000 mg per dose) for 3 to 5 d, and/or IV immunoglobulin (IVIG), typically at 1 g/kg/day for two days, or 400 mg/kg/day for 4 days; or plasma exchange.

PROGNOSIS: Typically have good recoveries.

COMPLICATIONS: Respiratory compromise requiring mechanical ventilation can occur in either, more commonly AIDP. The degree of phrenic nerve involvement (C3, C4) may predict the need for mechanical ventilation better than negative inspiratory force (NIFs).

Cerebellitis

DEFINITION: Cerebellitis consists of inflammation and swelling of the cerebellum visible on MRI. It often requires intensive care-level monitoring given a risk for swelling and herniation. It can be distinguished from acute cerebellar ataxia as there are no MRI findings in the latter.

ETIOLOGY: Viral infections, as well as autoantibodies such as anti-Yo, anti-Hu, and anti-Purkinje have been implicated in the etiology and

pathophysiology of acute cerebellar ataxia, but there is less evidence for particular pathogens in cerebellitis.

EPIDEMIOLOGY: No data available.

CLINICAL FEATURES AND PRESENTATION: Headache, vomiting, and fever at presentation vs. the prodromal illness that occurs with acute cerebellar ataxia.

DIFFERENTIAL DIAGNOSIS: Other causes of ataxia, including intoxication, metabolic disorders, meningitis, neoplasm, familial ataxic syndromes, or degenerative disorders.

DIAGNOSTIC WORKUP: Peripheral blood often demonstrates a leukocytosis. CSF may reveal a pleocytosis and in some cases oligoclonal bands. Given the low yield of CSF studies, LP should be done with caution given the high risk of herniation. MRI reveals signal change in the cerebellum with increased T2 signal and enhancement with gadolinium contrast.

MANAGEMENT AND TREATMENT: Recognizing and treating any progressive swelling is crucial. Steroids have been recommended without any notable adverse effects. Surgical decompression of the posterior fossa can relieve dramatic swelling and herniation. Antibacterial and/or viral therapy is likely also indicated early on in presentation.

PROGNOSIS: Variable and can potentially be poor. Residual motor and/or cognitive deficits are possible and likely related to permanent cerebellar injury.[53]

Myasthenia Gravis

DEFINITION: MG is an autoimmune neuromuscular disease characterized by early fatigue and weakness of skeletal muscles resulting from decreased availability of acetylcholine receptors in the postsynaptic membrane.

ETIOLOGY: Antiacetylcholine receptor (AchR) antibodies are found in majority of patients.

CLINICAL FEATURES: Muscles become progressively weaker during periods of activity and improve after periods of rest. Symptoms can occur suddenly and/or be intermittent. The most serious complication of MG is myasthenic crisis, which is acute weakness of the respiratory and bulbar muscles, requiring ventilatory assistance. As vital capacity falls and cough and sigh mechanisms deteriorate, atelectasis develops, resulting in hypoxemia. Ultimately, fatigue, hypercarbia, and ventilatory insufficiency occur. Superimposed pulmonary infections lead to increased morbidity and mortality.

DIAGNOSTIC WORKUP: Serology testing for anti-AchR antibodies is positive in 85% of patients with generalized MG; the percentage falls to 50% in patients with ocular myasthenia.[54] Other tests include single fiber electromyography (SFEMG), and the ice pack and edrophonium tests both may temporarily relieve symptoms. A CXR can reveal widening of the mediastinum, suggestive of thymoma.

MANAGEMENT: In the ICU pulmonary function tests are poorly predictive of the need for mechanical ventilation in MG. Therefore, all efforts are aimed at employing the least invasive means for respiratory care, such as BiPAP via nasal mask or negative pressure ventilation, before severe hypoventilation occurs.

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14 Headache and Pain Syndromes

Lauren Doyle Strauss and Anna Minster

OVERVIEW OF HEADACHES

Introduction

Headache is the most common manifestation of pain in childhood and is the most frequent reason for referral to a child neurologist. Although migraine tends to be most studied and better recognized by parents, tension-type headache is the most common. It is important to recognize, diagnose, and treat the pain of headaches which can often first present in childhood, as recurrent or unremitting headaches can lead to significant disability that can persist into adulthood.

EPIDEMIOLOGY: (1) The prevalence of all types of headache increases with age. According to Bille's landmark epidemiologic survey conducted in the 1950s in Sweden of 6,000 school children, the prevalence of "headache" ranged from 37% to 51% in 7 yo, rising to 57% to 82% by age 15. Frequent headaches occurred in 2.5% of 7 yo, which increased to 15% with 15 yo.[1] **(2) With migraines, prevalence increased with age; however, gender predilection changes.** In children (3–7 yo), migraine prevalence is 1.2% to 3.2% and is more common in boys. By 7 to 11 y of age, 4% to 11% have migraines, but is now seen equally in boys and girls. Around the age of puberty (studied at 15 y of age), the prevalence increases to 8% to 23%, with girls more frequently affected than boys.[2,3] **(3) Tension-type headache has the highest lifetime prevalence.** Prevalence ranges in different studies from 30% to 78%, which would make it the most common headache type. **(4) Chronic daily headache accounts for significant proportion of referrals to headache clinics.** Chronic daily headaches of various types have a prevalence of about 1% in adolescents, which increases in adulthood.[4] It accounts for 15% to 20% of referrals to headache clinics. **(5) Headache is a leading cause of disability.** According to the World Health Organization (WHO), migraine alone is 19th among all causes of years lived with disability (YLDs).[5] Headache disorders can cause personal suffering, which can lead to impairment of family and social life, and performance in school.

PATHOPHYSIOLOGY: (1) Vascular Theory: First theory proposed by Harold Wolff in 1940. Intracranial vasoconstriction is responsible for the aura of migraine and the rebound vasodilation activates perivascular nociceptive nerves, resulting in headache. **(2) Neurovascular Theory:** More widely accepted. ***Cortical spreading depression*** explains the aura; consists of rapid and nearly complete depolarization of neurons, with massive efflux of K^+ ions extracellularly. It originates in the visual cortex and propagates like a wave throughout brain tissue at a rate 2 to 6 mm/min. It can also be a/w **relative decrease in blood flow**, leading to plasma protein extravasation through the dural vessels, causing activation of the meningeal afferents. Thought to centrally activate the trigeminal nucleus within the brainstem, leading to ***sensitization*** **of the trigeminal afferents**.

Clinical Approach to Headache Patients

HISTORY: Involve both the children and their parents in history taking as often parents are unaware of associated symptoms. Most headaches in childhood are benign, but be cognizant of parents' anxiety as there may be concerns about malignant causes. A detail-oriented history is crucial for an appropriate diagnosis and to eliminate unnecessary tests (Table 14.1).

TABLE 14.1 Important Details in History Taking

Headache patterns	Acute vs. chronic vs. recurrent, progressive vs. non-progressive, or mixed pattern
Headache description	Onset, location, severity of pain on pain scale, quality (dull, pressure, twisting, sharp, pounding, throbbing, stabbing), frequency, duration, temporal association (time of day or menses cycle)
Aura	Timing, length, type (visual, sensory, language, or motor disturbances)
Associated symptoms	Tinnitus, numbness, paresthesias, weakness, dysarthria, nausea, vomiting, dizziness (light-headedness or vertigo), blurred vision, diplopia, photophobia, phonophobia, fatigue, scotoma, scintillations, transient visual obscurations, eye pain, neck pain, osmophobia
Severity of morbidity	Missed days of school/work, ED visits
Headache triggers	Food triggers (commonly include food dyes, MSG, chocolate), caffeine use, odors, noisy environment, dehydration, catamenial or hormone association, weather change, certain odors, physical activity, sleep (delayed sleep onset, frequent night awakening, snoring, apnea, periodic limb movements in sleep, excessive sleep), anxiety, mood, history of social stressors, illicit drug use, dental concerns (dental infection/abscess, teeth grinding, emerging wisdom teeth, TMJ pain), history of concussion, history of carsickness
Alleviating factors	Sleep, medications, position (standing vs. supine), cold/warm compress/shower, distraction by a different activity
Medication Hx	Current/failed abortive or prophylactic medications, ask if abortive medications taken at the onset of headache, dosing (important to document maximum doses of failed medications), frequency, specifically ask about OCP
Other treatment Hx	Therapy, acupuncture, massage therapy, exercise, music, yoga, meditation
Family history	History of headaches, migraines, anxiety, depression, sleep apnea, seizures
Previous evaluations	Imaging (CT, MRI), formal ophthalmologic exam, EEG, sleep study, dental evaluation, LP with opening pressure
Parental concerns	What are you concerned about? What do you think is causing the headaches?
Patient concerns	Conduct interview separately

CLASSIFICATION OF HEADACHES: (1) International Headache Society (IHS) developed the *International Classification of Headache Disorders*, 2nd edition (ICHD-II), which can guide approach (Table 14.2).[6] (2) First

TABLE 14.2 ICHD-II: Primary and Secondary Headaches

Primary headaches	• Migraine – Migraine without aura – Migraine with aura • Familial hemiplegic migraine (FHM) • Sporadic hemiplegic migraine • Basilar-type migraine – Periodic syndromes that are commonly precursors of migraine • Cyclical vomiting • Abdominal migraine • Benign paroxysmal vertigo of childhood • Status migrainosus • Tension-type headache • Cluster headache and other trigeminal autonomic cephalalgias • Other primary headaches
Secondary headaches	Headache attributed to • Head or neck trauma – Acute posttraumatic headache – Chronic posttraumatic headache • Cranial or cervical vascular disorder • Nonvascular intracranial disorder • Headache attributed to idiopathic intracranial hypertension – Headache attributed to low cerebrospinal fluid pressure – Headache attributed to intracranial neoplasm • Substance or withdrawal from substances • Alcohol-induced headache • Headache induced by food components and additives • Ergotamine-overuse headache • Triptan-overuse headache • Opioid-overuse headache • Caffeine withdrawal headache • Infection – Headache attributed to intracranial infection – Headache attributed to systemic infection • Disorders of homeostasis • Sleep apnea headache – Headache attributed to arterial hypertension – Headache attributed to hypothyroidism • Disorders of cranium, neck, eyes, ears, nose, sinuses, teeth, or other facial or cranial structures • Psychiatric disorders
Cranial neuralgias	• Cranial neuralgia and central causes of facial pain
Other headaches	• Other headache, cranial neuralgia, central or primary facial pain

Note: Full listing available on International Headache Society's Web site www.ihs.org.
The International Classification of Headache Disorders: 2nd edition. *Cephalalgia.* 2004;24 (suppl 1):9–160. New version of classification (ICHD-III) is expected in late 2013.

determine whether the headache is primary or secondary (consider when onset or worsening is associated with a disorder known to cause headaches, as in underlying medical or neurologic conditions).

EVALUATION OF HEADACHE: (1) Focused Exam: Vital signs can reveal hypotension, hypertension, or fever. General exam can reveal infectious signs such as sinus tenderness, erythematous tympanic membranes or throat, lymphadenopathy, and nuchal rigidity. Neurologic exam should focus on papilledema, visual acuity, eye movements, visual field testing, and weakness. **(2) Need for Imaging:** Consider for patients with **red flags**: waking up from sleep, change in headache quality or intensity, or associated neurologic symptoms or exam findings. **(3) Appropriate Brain Imaging:** MRI: preferred due to absence of radiation, level of detail, and evaluation of posterior fossa. CT: consider for acute increase of ICP (e.g., hemorrhage, mass lesion, or hydrocephalus), focal neurologic exam, unstable patient, or lack of MRI availability. **(4) Vessel Imaging:** CTA or MRA should be obtained for the evaluation of arterial dissection, cerebral hemorrhage, or cerebral infarction. If there is concern about a sinus venous, then CTV or MRV should be included. See Neuroimaging chapter for details. **(5) Laboratory:** CBC, ESR, serum or urine toxicology screens, thyroid function tests, and pregnancy screen. **(6) Headache Diary:** Extremely helpful in establishing a diagnosis and monitoring improvement. Advise patient to mark intensity on a pain scale, quality, location, timing of menses, triggers, and associated symptoms such as an aura, neurologic symptoms, photophobia, phonophobia, nausea, or vomiting. Teenagers should be encouraged to keep their own diaries. Many sample headache calendars are available on the Internet. Examples include *www.childrenshospital.org/az/Site986/Documents/CHBMy_Headache_Diary.pdf* (quite detailed), and the American Headache Society's Committee for Headache Education has daily, weekly, and monthly versions of diaries on their website *www.achenet.org/resources/headache_diaries*. Many smart phone applications are available to create digital calendars, tables, and graphs, all of which can be electronically included in the medical record. **(7) Other Evaluations:** If there are signs of meningitis with acute presentation of headache with fever, neck pain, or nuchal rigidity; emergent LP should be done. In idiopathic intracranial hypertension (IIH), therapeutic LP may also need to be done urgently if there are concerns about vision loss; otherwise, it can be done as an outpatient. EEG is not usually recommended unless symptoms overlap with possibly ictal phenomenon such as paresthesias or weakness in one limb, stereotyped simple visual phenomenon, dysarthria, confusion, or decreased responsiveness. Headache can be an aura, ictal or postictal symptom.

PRIMARY HEADACHES

Migraine without Aura

Migraine without aura is the most frequently seen type of migraine.

SYMPTOMS: Often children notice a prodrome of symptoms different from what is considered an aura and can include mood changes, lethargy, yawning, cravings (often chocolate), increased thirst, diarrhea, and constipation prior to the onset of headache.[7]

DEFINITION: Table 14.3 includes the ICHD-II for children with migraine without aura.[6] Migraines can occur frequently, but if >2×/wk, reconsider secondary headache.

Migraine with Aura

DEFINITION: Similar to migraine without aura; however, has preceding "typical aura": an attack of a reversible focal neurologic symptom that

TABLE 14.3 ICHD-II Criteria for Migraine without Aura

A. At least five attacks fulfilling criteria B through D
B. Headache attacks lasting 1–72 h
C. Headache has at least two of the following characteristics:
   1. Unilateral location, which may be bilateral or frontotemporal (not occipital) in young children
   2. Pulsating or throbbing quality or varying with heartbeat
   3. Moderate or severe pain intensity
   4. Aggravation with, or needing to avoid routine physical activity (e.g., walking, climbing stairs)
D. During the headache, at least one of the following:
   1. Nausea or vomiting
   2. Photophobia and phonophobia, which may be inferred from behavior in young children
E. Not attributed to another disorder

usually develops gradually over 5 to 20 min and lasts <1 h.[6] It is possible to have auras without headache.

AURA: Approximately 14% to 30% of children who have migraine report visual disturbances, distortions, or obscurations before or as the headache begins.[8] Visual phenomena are the most common, but there are other types (Table 14.4).

OTHER CONSIDERATIONS: (1) Complicated visual perceptions or spreading paresthesias can also be seen in epilepsy, which should be considered. (2) Alice-in-Wonderland syndrome is rare and usually only seen in children. It includes bizarre visual hallucinations where objects can appear larger (macropsia), smaller (micropsia), distorted (metamorphopsia), or distant (teleopsia). (3) Retinal migraine, also called ocular or ophthalmic migraine, is seen more often in adolescents than in children. Sudden onset of monocular visual disturbances last <1 h and are associated with ipsilateral retro-orbital pain. Fundoscopic exam at the time of the headache can show constriction of retinal veins and arteries and retinal pallor. Evaluation of hypercoaguable states or embolic sources should be considered.

TABLE 14.4 Typical Auras Seen in Migraine with Aura

Visual	Negative scotoma (area of absent vision)
	Scintillating scotoma (aka fortification scotoma, teichopsia)
	Photopsia (flashing lights)
	Visual field deficits—hemi- or quadrantanopsia
	Alice-in-Wonderland syndrome: macropsia, micropsia, metamorphopsia, teleopsia
	prosopagnosia (inability to recognize faces)
Sensory	Paresthesias
	Dysesthesias (unpleasant sensation, including burning, wetness, itching, electric shock)
	Perioral $\pm$ hand numbness (chiro-oral)
Motor	Hemiparesis, monoparesis
Language	Aphasia, dysphasia
Psychiatric	Confusion, amnesia
Auditory	Tinnitus, hypacusia (impaired hearing)

Basilar-Type Migraine

CLINICAL FEATURES: Complicated migraine with aura where the headache is usually occipital and preceded by brainstem-related symptoms with pallor, visual disturbances, vomiting, ataxia, vertigo, and clumsiness. Mean age of onset is 7 y. Motor weakness is not an associated symptom, and if present, consider hemiplegic migraine.

DIAGNOSIS: See Table 14.5 for ICHD-II diagnostic criteria.

DIFFERENTIAL DIAGNOSIS: Drug ingestion, arteriovenous malformations, congenital brain malformations such as Chiari and Dandy–Walker, or vertebral dissection or thrombosis.

Familial Hemiplegic Migraine (FHM)

DEFINITION: An AD genetic form of migraine with an aura that includes some degree of hemiparesis.

DIAGNOSIS: Hemiplegic migraine is characterized by aura of visual field deficits, hemisensory changes, hemiplegia, and aphasia that precedes the headache by 30 to 60 min, but can persist after headache resolution. Some FHM patients can have atypical severe attacks with signs of diffuse encephalopathy that can lead to coma.

FOUR SUBTYPES: Recent genetic discoveries have subdivided FHM into four subtypes. (1) FHM1 accounts for about 50% of cases and is caused by mutations in a gene coding for the P/Q-type calcium channel α subunit, *CACNA1A*. (2) FHM2 is the second most common caused by mutations in the Na^+/K^+-ATPase gene *ATP1A2*. (3) FHM3 is a rare subtype of FHM caused by mutations in a sodium channel α-subunit coding gene, *SCNA1*. (4) There are many sporadic and FHMs that do not fit into FHM 1–3 subtypes and are considered to be FHM4. It is suspected that new mutations will be found on chromosome 1q.

DIFFERENTIAL DIAGNOSIS: (1) **FHM** often first presents in adolescence, and intracranial hemorrhage, stroke, tumor, atriovenous malformation, acute disseminated encephalomyelitis (ADEM), and CNS infection must be excluded with urgent brain imaging. A hypercoagulable workup should be done. (2) **Seizures** are a possibility, and an EEG should also be considered. (3) **Alternating hemiplegia of childhood**, which is currently in the

TABLE 14.5 ICHD-II Criteria for Basilar-Type Migraine

A. >2 attacks fulfilling criteria B–D
B. Aura consisting of >2 of the following fully reversible symptoms, but no motor weakness:
   Dysarthria, vertigo, tinnitus, hypacusia, diplopia, ataxia, visual symptoms simultaneously in both temporal and nasal fields of both eyes, decreased level of consciousness, simultaneously bilateral paresthesias
C. At least one of the following:
   1. At least one aura symptom develops gradually over ≥5 min and/or different aura symptoms occur in succession over ≥5 min
   2. Each aura symptom lasts ≥5 and ≤60 min
D. Headache must fulfill criteria for migraine without aura (see Table 14-3) and begin during the aura or follow aura within 60 min
E. Not attributed to another disorder

appendix of the ICHD-II, has been debated as a variant of hemiplegic migraine, a periodic syndrome in childhood, or a form of epilepsy. Some cases have been associated with an *ATP1A2* gene mutation, which is also seen in FHM2. It presents <18 mo of age, with a hemiparesis that alternates with each attack and is a/w nystagmus, tonic spells, dystonic posturing, choreoathetoid movements, and autonomic disturbances.[6] Acute attacks are usually aborted with sleep.

Childhood Periodic Syndromes

There are several syndromes felt to be precursors to migraines which in the past used to be referred to "migraine variants." Often there will be a strong family history of migraines, motion sickness, or periodic syndromes. The ICHD-II includes three conditions: benign paroxysmal vertigo, cyclic vomiting syndrome (CVS), and abdominal migraine (AM). A fourth syndrome, paroxysmal torticollis, has recently been linked to migraine with molecular genetic testing and is included in the appendix of ICHD-II. With the associated symptoms related to these syndromes, it is important to exclude other pathologic diagnoses (Table 14.6).

Tension-Type Headaches (TTH)

DEFINITION: The most prevalent type of primary headache. Dx can be made after >10 headaches with associated symptoms occurring over at least 3 mo. (1) It is differentiated by the ICHD-II as infrequent (<1 d/mo on average), frequent (1 to 15×/mo), and chronic (≥15×/mo). (2) The headache pain usually has a bilateral location, pressing or tightening quality, and mild to moderate intensity. (3) No associated aura, nausea, or vomiting, but occasionally photophobia or phonophobia. (4) New daily persistent headache is a TTH where patients with no prior headache history often identify exactly when their headache started and headaches continue daily for >3 mo. No underlying secondary cause should be identified.

Chronic Daily Headache

Chronic daily headache is not a diagnosis but rather a collective term and includes chronic TTH, new daily persistent headache, chronic migraine, and hemicrania continua. (1) Chronic migraine must be present for ≥15 d/mo for 3 mo to meet criteria. (2) Hemicrania continua is characterized by daily continuous unilateral pain with conjunctival injection and/or lacrimation, nasal congestion and/or rhinorrhea, or ptosis and/or miosis which persists for >3 mo. Treatment with indomethacin always leads to resolution.

OTHER CONSIDERATIONS: In all types of chronic headaches, it is important to rule out secondary causes and, in particular, medication or analgesic overuse.

SECONDARY HEADACHES

Idiopathic Intracranial Hypertension

Idiopathic intracranial hypertension, formerly known as pseudotumor cerebri, is an important entity to diagnose in the setting of chronic headache. The etiology is not well understood, but is thought to be an impaired reabsorption of CSF.

CLINICAL FEATURES: The headache pain is usually of diffuse and pounding quality that worsens with Valsalva or recumbent position and can be

TABLE 14.6 Periodic Syndromes in Childhood

	Cyclic Vomiting	Abdominal Migraine	Benign Paroxysmal Vertigo of Childhood	Benign Paroxysmal Torticollis
Description	Episodic attacks of N/V, more common at night or early morning, usually triggered by stress or illness, usually lasting 24–48 h, occurring every 2–4 wk	Episodic attacks of acute midline, moderate to severe intensity abdominal pain assoc. with pallor, flushing, N/V without diarrhea or constipation, lasting 1–72 h	Brief episodes of sudden-onset unsteadiness ± fear, nystagmus, dizziness, clumsiness, nausea, or unilateral throbbing H/A	Episodes of sudden-onset head tilt secondary to cervical dystonia ± vomiting and ataxia that can last hours to days
Age	Mean age of onset 5 y, diagnosis often made later, resolves usually by age 10[39]	Mean age of onset 7 y. Resolves by adolescence or adulthood[40]	Age of onset 2–4 y, resolves by 5 y[41]	Onset in infancy (2–8 mo), improves by 2 y, and end by 3 y[42]
Gender	Girls = Boys	Girls > Boys (3:2)	Girls = Boys	Girls >> Boys
ICHD-II Diagnostic Criteria[6]	1) >5 attacks of N/V lasting 1 h to >4 times/h 2) Symptom-free between attacks 3) Not attributed to another disorder—may require GI investigation	1) >5 attacks where abd. pain lasts 1–72 h: A. midline location, B. dull or "just sore" quality, C. moderate or severe intensity 2) During the pain, has >2 other symptoms: anorexia, N/V, pallor 3) Not attributed to another disorder—may require GI and renal investigations	1) >5 attacks of severe vertigo occurring without warning and resolve spontaneously after minutes to hours 2) Must have normal neurologic exam, including audiometric and vestibular functions between attacks 3) Consider epilepsy—should have EEG	1) No minimum number of attacks required of head tilt (can switch sides with each attack), ± rotation that resolves spontaneously within minutes to days, can occur monthly 2) Must have ≥1 assoc. symptom: pallor, irritability, malaise, vomiting, ataxia 3) Normal neurologic examination between attacks 4) Not attributed to another disorder

(continued)

TABLE 14.6 Periodic Syndromes in Childhood (Continued)

	Cyclic Vomiting	Abdominal Migraine	Benign Paroxysmal Vertigo of Childhood	Benign Paroxysmal Torticollis
Differential diagnosis	Bilious vomiting or severe abd. pain raises concern for malrotation with volvulus, gallbladder disease, choledochal cysts, hepatitis, pancreatitis, or a ureteropelvic junction obstruction. If focal neuro exam, consider increased ICP. Metabolic disorders. Münchausen by proxy	GERD, IBS, IBD, cholecystitis, gastric ulcer, nephrolithiasis, UTI	Benign positional paroxysmal vertigo and episodic ataxia, epilepsy, neurinomas, and tumors of the pontocerebellarangle or posterior fossa, Ménière disease, and vestibular neuronitis	GERD (Sandifer syndrome), complex partial seizure, posterior fossa tumors, and idiopathic torsional dystonia
Treatment: acute	Supportive measures with hydration, antiemetics (more effective in 1st h), sedative (benzodiazepine, diphenhydramine), triptans (sumatriptan)	Oral analgesics ± metoclopramide, sumatriptan	Antiemetics, sleep aborts most attacks	No treatment
Treatment: prophylactic	1) Avoid triggers (sometimes cheese or chocolate), 2) antimigraine (cyproheptadine, propranolol, amitriptyline),[43] 3) prokinetic (erythromycin)[44]	1) Avoid triggers such as fasting, irregular sleep, stressors, identified food triggers, foods rich in amines or xanthine. 2) Cognitive therapy, relaxation programs. 3) Migraine treatments	Reserved for frequent attacks, cyproheptadine	Reserved for painful attacks, cyproheptadine
Prognosis	Estimated that 75% develop migraines by 18 y[39]	Resolves in 60% of children. 70% had H/A either prior, during, or after diagnosis[45]		Can resolve or evolve into migraine with aura, especially basilar-type migraine Possible genetic link to CACNA1A mutation[46]

progressive in severity. Symptoms can include diplopia, transient visual obscurations, and pulsatile tinnitus.

RISK FACTORS: Obesity, endocrinopathies (hypothyroidism, Addison disease), medication use (tetracyclines, hormones, lithium, vitamin A, and steroids), polycystic ovarian syndrome, anemia, systemic lupus erythematosus, chronic kidney disease, and sleep apnea. It is more often seen in females.

EXAM: Can reveal findings secondary to increased ICP, including 6th nerve palsies, peripheral visual field deficits, papilledema, or change in visual acuity.

DIAGNOSTIC CRITERIA: (1) There are established criteria called the Modified Dandy Criteria (Table 14.7).[9] (2) Brain imaging is often unrevealing, but can show subtle findings of slit-like ventricles or "empty sella sign" (flattening of the pituitary gland). (3) LP shows elevated pressure on lumbar puncture of >25 cm H_2O obtained in the lateral decubitus position with legs extended. For patients who require sedation, propofol is recommended over ketamine. Propofol is known to decrease ICP and hence is considered safer, but can cause a falsely lower opening pressure. Ketamine is known to increase ICP.[10,11] In fluoroscopically guided LPs, the prone position used can increase opening pressure by a mean of 2.7 cm H_2O.[12]

TREATMENT: Focused on preventing or stabilizing vision loss from optic nerve damage as a result of the increased ICP. The diagnostic tap can also be therapeutic, and sometimes, repeated lumbar punctures are needed. First-line medical treatment is acetazolamide. Furosemide and topiramate are considered second line. In severe cases where vision loss is rapidly progressing, placement of a lumbar shunt or optic nerve sheath fenestration may be indicated.

Cerebral Sinus Venous Thrombosis (CSVT)

More commonly CVST is seen in neonates; however, when it occurs in older children and adolescents (Table 14.8), the symptoms and exam findings are the same as in patients with IIH. The presence of seizures and/or hemiparesis is suggestive of the venous infarction. Rule out a hypercoagulable state, including elevated hematocrit.[13]

Chiari I Malformation

DEFINITION: Downward herniation of cerebellar tonsils through foramen magnum >5 mm often with "peglike aspect" of the tonsils or complete effacement of the subarachnoid space at the foramen magnum.[14]

TABLE 14.7 Modified Dandy–Walker Criteria

Symptoms of raised ICP (headache, nausea, vomiting, transient visual obscurations, or papilledema)
No localizing signs with the exception of abducens (6th) nerve palsy
Patient is awake and alert
Normal CT/MRI findings without evidence of thrombosis
LP opening pressure of >25 cm H_2O and normal biochemical and cytological composition of CSF
No other explanation for the raised intracranial pressure

TABLE 14.8 Sinus Venous Thrombosis in Children and Adolescents

Headache	Worsening over several days, thunderclap headache (sudden onset, high severity)
Other symptoms	Visual obscurations, seizures, lethargy, hemiplegia, seizures
Risk factors	Dehydration, thrombophilia, hypercoagulable state, elevated Hct, nephrotic syndrome chronic inflammatory diseases (IBD, SLE) Medication: estrogen-containing contraception, L-asparaginase Infection: meningitis, mastoiditis, and sinusitis Injury: direct injury, line placement within veins (ECMO)
Exam findings	Papilledema, 6th nerve palsy, encephalopathy
Diagnosis	CT scan w/wo contrast can miss the diagnosis in 10%–40% of cases and underestimate involvement and presence of infarcts. CTV more sensitive, but MRI with MRV is preferred because no radiation and can show possible related venous infarcts. MRV done with contrast eliminates flow gap artifacts and superior to time-of-flight venography. Conventional angiography done to confirm or prior to intravascular intervention
Treatment	If related to infection, appropriate antibiotic and possible surgical drainage. Anticoagulation is controversial—LMWH for 1 wk, then Coumadin for 3–6 mo. If hemorrhage present, hold off on treatment, and start anticoagulants or thrombolytics if imaging in 5 d shows propagation. May need to treat increased ICP with LP
Outcome	If presenting with seizures or venous infarcts, higher likelihood or neurologic deficits or death. In one large Canadian study at 1–2-y follow-up, 65% normal, 35% neurologic deficit, 20% seizures, 9% died[13]

CLINICAL FEATURES: Patients present in their 20s or 30s with headache features relating to intermittently elevated ICP such as nocturnal occurrence, exacerbation by the Valsalva maneuver (Table 14.9). In childhood, this is often an incidental finding.

TABLE 14.9 Chiari I Malformation

Presenting symptoms	
Headache	Pressure-like (not pounding) suboccipital pain, radiates to vertex, retro-orbitally, or neck; worsens with exertion, Valsalva and head position
Ocular	Scotoma
Otoneurologic	Dizziness, nystagmus, oscillopsia, tinnitus, and dizziness
Brainstem/cerebellar	Dysphagia, sleep apnea, dysarthria
Imaging	MRI with sagittal views will show downward deviation of tonsils >5 mm below foramen magnum ± compression of cerebellar cisterns, syringomyelia
Treatment	Surgery is indicated if symptomatic and >5-mm decompression and duraplasty. If between 3 and 5 mm, can consider surgery if symptomatic. Additional shunting of syrinx is sometimes necessary

Concussion

DEFINITION: Concussion was defined by the American Academy of Neurology (AAN) as a "trauma-induced alteration in mental status that may or may not involve loss of consciousness."[15] It can be a result of indirect or direct head trauma occurring from a collision or fall leading to an alteration in mental status that may or may not involve loss of consciousness. The confusional episode and amnesia may occur immediately after the blow to the head[16] or several minutes later.[17]

Characteristic symptoms and cognitive impairment seen with concussion are outlined in Table 14.10.[15] The term *concussion* is often used interchangeably with mild traumatic brain injury (mTBI); however, mTBI is defined by the Centers for Disease Control and Prevention (CDC) and the American Congress of Rehabilitation Medicine as the "loss of consciousness for no more than 30 min or amnesia as a result of a mechanical force to the head, and a Glasgow Coma Scale (GCS) score of 13 to 15."[18] Generally, clinicians reserve mTBI to describe patients with a more severe GCS than generally thought with concussion. Concussive symptoms usually resolve without treatment in a short time; however, concussions can lead to persistent symptoms and morbidity referred to as postconcussive syndrome (PCS). PCS is not well-defined, and may include symptoms like chronic headaches, concentration problems, photophobia, fatigue, irritability, sleep problems, personality and mood changes. The exact causal relation of these (remote or long-lasting) symptoms to the original event is often unclear. Similar to that of the posttraumatic headaches (below), treatment is symptomatic and supportive, and includes counseling (e.g., cognitive behavioral therapy), temporary educational modifications, and reactivation (e.g., physical therapy and gradual increase of activity). It is a frequent complaint in both headache and concussion specialty clinics. Note that PCS should not be confused with chronic traumatic encephalopathy (CTE), a progressive degenerative disease diagnosed postmortem in individuals with a history of multiple concussions sustained in professional athletics.

EPIDEMIOLOGY: Estimated occurrence is 1.6 to 3.8 million sporting concussions/year in the United States.[19] Sports-related injury and motor vehicle accidents are the most common causes in children. Sports-related injuries in the high school population are estimated to account for 9% of all athletic injuries.[20] Football and girls' soccer contribute the most to the total number of concussions in high school sports.[21]

DIAGNOSIS: Symptom onset may be delayed due to factors such as continued physical exertion or repeat concussion and can make diagnosis difficult.

TABLE 14.10 Definition of Concussion

Symptoms typically begin immediately or within minutes of impact
Symptoms can be worse at onset or with time
Loss of consciousness is not required for diagnosis
Common acute signs (min–h): headache, nausea or vomiting, disorientation, confusion, amnesia, dizziness or vertigo, and incoordination
Common late signs (d–wk): persistent headache, light-headedness, poor attention and concentration, memory dysfunction, easy fatigability, irritability and low frustration tolerance, photophobia, difficulty focusing, phonophobia, tinnitus, anxiety, depressed mood, sleep disturbance

Practice parameter: the management of concussion in sports (summary statement). Report of the Quality Standards Subcommittee. *Neurology.* 1997;48:581–585.

There are several helpful diagnostic tools available that can be used in initial assessment. One example is Sport Concussion Assessment Tool 2 (SCAT-2), which is a standardized module to assess physical and neurologic exam features and symptoms to calculate a Standardized Assessment of Concussion Score (SAC). This can be compared to baseline SAC scores if available to determine severity of concussion.[22] Differences in baseline scores have been evaluated based on age and gender.[23]

TREATMENT: All athletes with suspected concussion should be removed from play, medically assessed, and then monitored for resolution or evolution of symptoms. Based on the AAN's practice parameters in 1997, concussions were graded into three categories mostly based on the duration of symptoms and the presence or absence of loss of consciousness, and recommendations on return to play were made based on each category[15]; however, it is generally felt that a more individualized approach is warranted. A plan for a graduated return to academic and athletic responsibilities should be adjusted based on return of symptoms.

Posttraumatic Headaches

Headaches may occur and persist in both mild and severe head injuries and can be similar to a migraine, tension-type, or a mixed-type headache (Table 14.11). If headaches were present prior to the injury, they tend to become more frequent or severe following a concussion. The ICHD-II diagnostic criteria divide posttraumatic headaches into acute and chronic headaches, which begin within 2 wk following injury. Acute headache resolves within 3 mo, while chronic headaches continue for longer.[6] Prevalence ~3.2% in children with a mild to moderate head injury, but not well established. Etiology is poorly understood. Course is benign and usually resolves within 6 mo.[24] Treatment is targeted toward symptoms.

Medication Overuse Headache

Medication overuse headache (MOH) is a chronic daily headache that develops with the overuse of certain abortive medications in a susceptible patient. Headaches typically occur in the morning following awakening, and are associated with neck pain. ICHD-IIR further defines MOH as a new or worsening headache occurring $\geq$15 d/mo from regular overuse of one or more acute/symptomatic medications for $>$3 mo (e.g., ergotamine, triptans, barbiturates, opioids, analgesics, or combination analgesic medications).[25] Patients take rebound headaches often as evidence for an ongoing presence

TABLE 14.11 Posttraumatic Headache

Symptom	Medical Treatment	Nonmedical Treatment
Tension-type	Analgesics, NSAIDs (limit to twice weekly to avoid rebound)	Physical therapy
Migraine	Triptans, antiemetics	Counseling, biofeedback, stress management
Persistent (wk)	TCAs	Important to stress return to prior daily activities

of an underlying headache. The concept can be explained to patients by drawing a parallel to caffeine withdrawal headaches, which many people are familiar with. Abortive medications have shown different thresholds of use for headache chronification (butalbital only 5 d/mo, opioids 8 d/mo, and NSAIDs 10 to 15 d/mo)[26]; hence patients who take mixed preparations (acetaminophen, ibuprofen, aspirin, caffeine, butalbital, diphenhydramine) may be more prone to getting MOH. Treatment consists of weaning the overused medications, with appropriate anticipatory guidance of possible rebound headaches, starting a preventative medication, consideration of a treatment bridge with steroids, and providing limits on future use of abortive medications to only ≤2 d/wk (even when various medications are alternated).[27] In patients who are overusing butalbital, abrupt withdrawal can be life-threatening, and a wean can be accomplished with a 100-mg butalbital to 30-mg phenobarbital conversion.[28]

HEADACHE TREATMENTS

First-Line Headache Treatments

The most important part of treatment in headaches would be to provide realistic expectations for the parents and child that headaches will gradually improve in frequency and severity and in more refractory cases may take months of therapy. There are many approaches to consider prior to starting medical treatments.

LIFESTYLE CHANGES: Important to address, may be difficult for patients and families to adopt, but in many cases can be the most successful intervention in reduction or even elimination of headaches. Avoidance of food triggers, elimination of caffeine use, appropriate sleep and meal schedule, improvement of hydration, starting daily exercise, encouragement to maintain daily functioning can all be very effective (Table 14.12).

SLEEP HYGIENE: Fatigue due to lack of sleep is often a major trigger. Sleep hygiene should be discussed to improve sleep schedule. Eliminate naps and excessive sleeping on the weekends. Minimum number of hours of sleep for children is 9 to 10 (not the usual 8 h for adults). Although some children may be up late in the night, they should be encouraged to return to school on a daily basis. Missed school only adds to stress with missed academic work, time away from friends, and, in some cases, missed days of work for parents.

TABLE 14.12 Nonpharmacological Therapies

Lifestyle changes	
Avoidance of food triggers	Hydration exercise
Elimination of caffeine	Improving sleep hygiene and meal schedule, weight loss
Nonmedical treatments	
Physical therapy	Guided imagery, cognitive behavioral therapy
Massage therapy	Meditation, acupuncture
Yoga	Osteopathic manipulation
Evaluations by other services	
Psychiatry	ENT (OSAS), nutrition, dental (TMJ, bruxism)

OTHER EVALUATIONS: (1) Dental referral if there are concerns about dental infection or abscess, bruxism, emerging wisdom teeth, or TMJ pain. (2) Otolaryngology evaluation if concerned about obstructive sleep apnea. (3) Weight loss has been shown in some adult studies to be effective with treatment of idiopathic intracranial hypertension, and therefore, for overweight children referral to a nutritionist may be beneficial.[29] (4) Counseling, cognitive behavioral therapy, meditation or guided imagery are especially important in patients with known social stressors or with comorbid psychiatric conditions such as anxiety or depression. (5) Many therapies focus on muscle relaxation and stretching but can also help with stress relief such as physical therapy, massage therapy, osteopathic manipulative therapy, and acupuncture. Yoga has become more popular recently and incorporates meditation, music therapy, stretching, and exercise.

Pharmacologic Treatments

Classification guides evidence-based decisions of medication regimen. Some patients can be treated with only **abortive medications** if headaches are infrequent and immediate effect is required. However, if headaches are more frequent, disabling, and interfering with daily life, **preventative medications**, which take longer to work, should be considered. Table 14.13

TABLE 14.13 Preventative Headache Medications

	Dosing	Considerations/ Side Effects
	Antidepressants	
Amitriptyline	0.25 mg/kg/d qhs; increase 0.25 mg/kg/d q2wk to max 1 mg/kg/d	Do not use within 14 d of MAOi. Can induce mania in Bipolar patients. Side effects: anticholinergic effects, arrhythmia, sedation, narrow angle glaucoma.
Nortriptyline	Dosing not established in children or migraines. PO: Adult: 10–25 mg qhs, inc. 25 mg qwk, max 75 mg qhs or div b.i.d.	Similar to amitriptyline but less sedation and anticholinergic effects.
	Carbonic anhydrase inhibitor	
Acetazolamide	25 mg/kg/d with a max dose 100 mg/kg or 2 g/d. Adult dosing: start 500 mg b.i.d, max 2–4 g/d	Sulfa allergy is relative contraindication. S/E: digital and oral paresthesias, anorexia, malaise, metallic taste, fatigue, N/V, mild metabolic acidosis, and kidney stones. Need to monitor serum bicarb during treatment initiation

TABLE 14.13 Preventative Headache Medications (Continued)

	Dosing	Considerations/ Side Effects
	Beta-blockers	
Atenolol	2–6 mg/kg/d	Avoid in asthmatics
Metoprolol	2–6 mg/kg/d	Avoid in asthmatics
Propanolol	2–4 mg/kg/d	Avoid in asthmatics
	Calcium channel blockers	
Verapamil	1–5 y: 40–80 mg q8h>5 y: 80 mg q6–8h	Do not use in patients with poor LV function or heart block. Avoid grapefruit as can increase serum levels
	Antihistamine	
Cyproheptadine	2–8 mg/kg/d qhs or div. b.i.d.	Appetite stimulant, drowsiness, impaired coordination, photosensitivity reactions. Can lower effectiveness of SSRI
Furosemide	2 mg/kg once daily; inc. 2 mg/kg/dose to max dosing 6 mg/kg/dose t.i.d.	Can lead to dehydration, hypokalemia
	Antiepileptic drugs	
Valproic acid	10–15 mg/kg/d div. q.d.–t.i.d, titrate to effect 5 mg/kg/d q1wk, max 30–60 mg/kg/d	Liver failure, hyperammonemia, pancreatitis, dose-related thrombocytopenia
Gabapentin	Day 1: 5 mg/kg qhs; Day 2: 5 mg/kg b.i.d; Day 3: 5 mg/kg t.i.d, Goal: 8–35 mg/kg/d div. t.i.d.	Emotional lability, aggressive behaviors, difficulties with concentration, hyperactivity, and restlessness. Caution and decrease the dose in patients with renal dysfunction
Topiramate	Children: 1–10 mg/kg/d div. q12h Adults: start 25 mg/d; increase by 25 mg/d qwk to total dosing 200 mg div. q12h	Nephrolithiasis, acute-angle glaucoma, anorexia, weight loss. Slower uptitration can reduce effects of cognitive dysfunction, psychiatric disturbances, sedation, paresthesias, light-headedness, and ataxia. Caution in patients with renal dysfunction

(continued)

TABLE 14.13 Preventative Headache Medications (Continued)

	Dosing	Considerations/ Side Effects
Zonisamide	1–2 mg/kg/d div q12h; increase by 0.5–1 mg/kg/d q2wk; usual dose: 5–8 mg/kg/d	Agitation, anxiety, ataxia, and behavior disorders. Caution in patients with renal or hepatic dysfunction. Potential for sulfonamide reactions
	Herbal supplements	
Magnesium	In mg of elemental magnesium/d: 1–3 y: 80 mg, 4–8 y: 130 mg, 9–13 y: 240 mg, 14–18 y: females 360 mg, males 410 mg	Several preparations available: magnesium oxide has lower bioavailability than other preparations magnesium chloride and magnesium lacatate Avoid in neuromuscular or renal disease. May alter glucose regulation or cause diarrhea
Coenzyme Q_{10}	100 mg t.i.d.	Abdominal discomfort, N/V. May increase bleeding risk
Vitamin B_2 (riboflavin)	200–400 mg b.i.d.	Orange discoloration of urine
Vitamin B complex ($B_{1-7,9,12}$)	1 tab q.d.	Product contains iron, be wary of iron toxicity
Melatonin	0.5–10 mg qhs	Avoid in patients with platelet or bleeding abnormalities
Butterbur (*Pestasites hybridus*)	Recommended dosing not established. 25–75 mg b.i.d.	Be sure to use preparation that is free of liver-damaging chemicals pyrrolizidine alkaloids and minimum of 15% active ingredient pestasins. Avoid with allergy to ragweed, marigolds, and daisies
Feverfew (*Tanacetum parthenium*)	100–250 mg q.d.	Avoid in patients with platelet or bleeding abnormalities. Avoid in pregnancy. There is a withdrawal syndrome with rebound headaches, nervousness, and joint stiffness

outlines common preventative headache medications available, including commonly prescribed supplements. Table 14.14 lists abortive medications given acutely at the time of a headache.

TABLE 14.14 Abortive Headache Medications

Acute Medications	Dosing	Considerations/Side Effects
	Antiemetics	
Ondansetron	PO: 4–11 y: 4 mg q8h; >11 y: 8 mg q8h IV: 0.15 mg/kg/dose q8h, max 16 mg/dose	Can prolong QT interval
Metoclopramide	PO: 0.4–0.8 mg/kg/d q6h	Possible extrapyramidal symptoms, including dystonic reaction, seizures
Prochlorperazine	PO, rectal: 0.4 mg/kg/d q8h IV: 0.15 mg/kg as a single dose	High incidence of extrapyramidal reactions, especially in children. Avoid in patients with narrow-angle glaucoma, severe liver or cardiac disease. Lowers seizure threshold
Dimenhydrinate	PO: 2–5 y: 12.5–25 mg q6–8h; 6–12 y: 25–50 mg q6–8h; >12 y: 50–100 mg q4–6h	Lowers seizure threshold
	Analgesic/NSAIDs	
Acetaminophen	15 mg/kg q4h	Max 4 g/d of acetaminophen, avoid in children due to risk of Reyes
Ibuprofen	7.5–10 mg/kg q6h	*Acute use:* inhibits platelet aggregation and may prolong bleeding time, N/V, abdominal discomfort Avoid use in renal or hepatic dysfunction. *Chronic use:* peptic ulcers, increased risk of GI bleeding or perforation, and renal injury
Ketorolac	IV: age 2–16 y, <50 kg: 0.5 mg/kg q6h >16 y, >50 kg: 30 mg q6h PO: 20 mg, then 10 mg q4–6h; max dose: 40 mg/d	Similar cautions as NSAIDs (see ibuprofen). Duration of therapy should not exceed 5 d
Naproxen sodium	<12 y: 5–7 mg/kg q12h, >12 y: 220 mg q8h	Similar cautions as NSAIDs (see ibuprofen)
	Mixtures	
Excedrin migraine (acetaminophen 200 mg, aspirin 250 mg, caffeine 65 mg)	1–2 tabs q6h	Max 4 g/d of acetaminophen, avoid in children due to risk of Reyes

(continued)

TABLE 14.14 Abortive Headache Medications (Continued)

Acute Medications	Dosing	Considerations/Side Effects
Mixtures		
Fioricet (acetaminophen 325 mg, butalbital 50 mg and caffeine 40 mg)	1–2 tabs q6h	Max 4 g/d of acetaminophen. Increased risk of medication overuse headache
Fiorinal (aspirin 325 mg, butalbital 50 mg, caffeine 40 mg)	1–2 tabs q6h	Avoid in children due to risk of Reyes. Increased risk of medication overuse headache
Steroids		
Medrol Dose Pak (methyprednisolone)	PO: 4-mg tabs. Day 1: 8 mg/4 mg/4 mg/8 mg. Day 2: 4 mg/4 mg/4 mg/8 mg. Day 3: 4 mg q.i.d. Day 4: 4 mg t.i.d. Day 5: 4 mg b.i.d. Day 6: 4 mg q.a.m.	Avoid in diabetics

Triptans

MECHANISM OF ACTION: Triptans are **abortive migraine-specific medications** (Table 14.15). They are selective serotonin 5-HT1B/1D agonists that act by constricting the dilated meningeal vessels through stimulation of 5-HT1B on the blood vessel wall. They inhibit neurotransmitter release and nociceptive transmission by stimulating 5-HT1D receptors on central and peripheral trigeminal sensory nerves. Best given at the *onset of aura or headache* because less effective in blocking ongoing sensitization in the second-order trigeminovascular neurons.

DIFFERENT OPTIONS: Frovatriptan and naratriptan have slower onset of action and a longer half-life and thus are often used in the treatment of menstrual migraine. Rizatriptan and eletriptan have the highest pain-free rate at 2 h, shortest time to peak plasma concentration. Failure to respond to one triptan does not predict failure to respond to any of the other triptans. The initial dose may be repeated in 2 h. Triptans should never be combined, and there should at least be a 24-h interval between 2 different triptans. Best efficacy if given at onset of the symptoms, but can still be considered later in the course. All triptans can be used in younger children provided (1) no contraindications and (2) both parents and physician agree.

COMMON SIDE EFFECTS: Hot flashes, chest or jaw discomfort.

CONTRAINDICATIONS: Cardiovascular disease, uncontrolled hypertension, central and peripheral vascular disorders, atypical/hemiplegic migraine because of potential increased risk of a cerebrovascular event.

CHRONIC PAIN AND PAIN SYNDROMES

INTRODUCTION: It is important to define pain in respect to quality, location, and severity as this can significantly affect diagnostic workup and treatment. For this reason, pain has been often referred to as the "5th vital sign."

TABLE 14.15 Triptans

	Time to Onset (h)	Half-Life (h)	Bioavailability (%)	Available Preparations	Dosing
Fast-acting triptans					
Sumatriptan[1]	1.5	2–2.5	14	Oral	1 mg/kg/dose, 25 mg (<50 mg), 50 mg (>50 mg)
				Nasal spray	5 mg (<50 mg, <9 y), 10 mg (>10–11 y), 20 mg (>50 kg, >12 y)
Zolmitriptan	2	2.5–3	40–48	Regular/ZMT	2.5 mg (<12 y), 5 mg (>12 y)
				Nasal spray	5 mg (>12 y)
Rizatriptriptan	1.2–2.5	2–3	45	Regular ODT	5 mg (<40 kg), 10 mg (>40 kg)
Almotriptan[2]	1.4–3.8	3.2–3.7	70–80	Oral	6.25 mg or 12.5 mg or 25 mg (>50 kg)[1]
Eletriptan	1–2	4–7	50	Oral	20 mg or 40 mg (>50 kg)
Slow-acting triptans					
Naratriptan	2–3	5–6	63 (men), 74 (women)	Oral	1 mg, 2.5 mg
Frovatriptan	2–4	24–30	24–30	Oral	2.5 mg

[1]Preparation available with naproxen.
[2]FDA approved for children >12 y.

TABLE 14.16 FLACC Scale[30]

	Score 0	Score 1	Score 2
Face	No particular expression or smile	Occasional grimace or frown, withdrawn, uninterested	Frequent to constant quivering chin, clenched jaw
Legs	Normal position or relaxed	Uneasy, restless, tense	Kicking or legs drawn up
Activity	Lying quietly, normal position, moves easily	Squirming, shifting back and forth, tense	Arched, rigid, or jerking
Cry	No cry (awake or asleep)	Moans or whimpers, occasional complaint	Crying steadily, screams or sobs, frequent complaints
Consolability	Content, relaxed	Reassured by occasional touching, hugging, or being talked to, distractible	Difficult to console or comfort

Note: The scale is scored for each criterion a score of 0, 1, or 2 to obtain a total score in the range 0–10.

DETERMINING SEVERITY: Determining severity in children can be challenging, which has led to the creation of several scales to assign a pain score. The FLACC scale (Face Legs Arms Cry Consolability) is commonly used to assess pain in children between the ages of 2 and 7 y (Table 14.16).[30] In the Wong–Baker FACES Pain Rating scale a child <3 yo is asked to choose between cartoon faces ranging from happy to sad, representing how they feel.[31] Others include visual analog, numerical analog, and verbal descriptive scales.

DETERMINING QUALITY: There are several different pain qualities or types. Pain is divided into nociceptive and neuropathic pain, with

TABLE 14.17 Types of Pain

Type of Pain	Cause	Quality
Nociceptive	Stimulation of intact nociceptors from tissue injury and inflammation	
Somatic type	Receptors in skin, soft tissue, skeletal muscle, and bone	Localized, sharp, aching, squeezing, stabbing, or throbbing pain
Visceral type	Receptors in internal organs, such as the kidney and gastrointestinal tract	Poorly localized, dull, crampy, or achy pain
Neuropathic	Stimulation or abnormal functioning of damaged sensory nerves by compression, transection, infiltration	Burning, shooting, electric, or tingling pain

TABLE 14.18 Sensory Nerve Fiber Types

Type	Conduction (m/s)	Function
A-β fibers	Rapidly conducting (40–50)	Vibration, proprioception, touch
A-β fibers	Slowly conducting (10–30)	Initial pain and temperature
C fibers	Very slowly conducting (0.7–2.3)	Delayed pain and temperature

nociceptive further categorized as somatic and visceral (Table 14.17). There are different sensory nerve fiber types (Table 14.18), and it is felt that the injury of these nerve fiber types can lower their activation threshold, leading to innocuous stimuli causing pain. From repeated firing, the sensory pathway can become sensitized by the release of glutamate, which can feed back to presynaptic membranes, causing central sensitization.

TREATMENT: As with headache, treatment of chronic pain should be multidisciplinary. Please refer to Table 14.19 for stepwise approach to pharmacologic agents.[32]

Complex Regional Pain Syndrome

CLINICAL FEATURES: Continued pain disproportionate to the inciting injury or event accompanied by edema, hyperhidrosis, cyanosis, or changes in the skin temperature. It often affects an arm or a leg and may spread to another part of the body. Average age of presentation is 13 yo; in girls ~2× more common than in boys. Children are less likely to have a history of an inciting noxious insult and the leg is more often involved.

TWO TYPES: (1) Type I is reflex sympathetic dystrophy with no associated demonstrable nerve damage. (2) Type II, formally known as causalgia, does have nerve damage. Patients will describe or experience sensory changes such as hyperesthesia, allodynia, asymmetry in skin coloration or temperature.

TREATMENT: Focuses on neuropathic pain treatments and physical and occupational therapies.[33] Psychological support often plays a more prominent role, and children tend to have a better outcome as compared to adults.

Fibromyalgia

DIAGNOSIS: American College of Rheumatology first established criteria in 1990[34]; diagnosis requires 3 mo of widespread musculoskeletal pain in absence of other underlying causes for the symptoms, and the presence of 5 to 11 of the 18 tender points. Tender points are detected by light pressure at specified locations in the neck, shoulder, chest, hip, knee, and elbow regions. New criteria proposed in May 2010[35] eliminate tender points as part of the criteria, and instead focus on a widespread pain index and a symptom severity scale. The widespread pain index score is determined by counting the number of areas on the body where the patient has felt pain in the last week, and then each area is rated on a severity scale from 0 to 3 and added up for a total score. To meet the new criteria, a patient must have $\geq$7 pain areas and a symptom severity score $\geq$5 or, alternatively, 3 to 6 pain areas with a symptom severity score of $\geq$9. Fibromyalgia has been recently recognized in children and has been referred to as juvenile fibromyalgia but does not have separate criteria.

TABLE 14.19 Medical Treatments for Neuropathic Pain

Name	Starting Dose	Maintenance Dose	Side Effects	Considerations
First-line agents				
Tricyclic antidepressants (TCAs)				
Amitriptyline	0.1 mg/kg qhs, may inc. over 2–3 wk	0.5–2 mg/kg qhs	Anticholinergic side effects, arrhythmia, sedation, narrow-angle glaucoma	Do not use within 14 d of MAOi. Can induce mania in bipolar patients
Nortriptyline	Not established in children. Adult: 10–25 mg qhs, inc. 25 mg qwk	75 mg qhs or div. b.i.d.	similar to amitriptyline	Lower anticholinergic and sedation effects compared to amitriptyline
Serotonin norepinephrine uptake inhibitors (SNRIs)				
Duloxetine	Not established in children. Adult: 30 mg q.d. for 1 wk, then inc. to 60 mg q.d.	60 mg q.d.	Uncontrolled narrow-angle glaucoma. May inc. risk of suicidality	FDA-approved treatment for fibromyalgia. Do not give with MAOi.
Venlafaxine	Week 1: 12.5 mg/d. Titration: If $<$40 kg, inc. by 12.5 mg q wk to max 50 mg/d div. b.i.d; if $\geq$40 kg, inc. by 25 mg q wk to max 75 mg/d div. t.i.d.	mean dose: 60 mg/d (1.4 mg/kg/d) div. b.i.d. or t.i.d.	HTN	Can induce mania in bipolar patients
Calcium channel alpha-2-delta ligands				
Gabapentin	Day 1: 5 mg/kg qhs; Day 2: 5 mg/kg b.i.d; Day 3: 5 mg/kg t.i.d.	8–35 mg/kg/d div. t.i.d.	Emotional lability, aggressive behaviors, difficulties with concentration, hyperactivity, and restlessness	Caution and dec. the dose in renal dysfunction

Pregabalin	Not established in children. Adult: 75 mg b.i.d, inc. dosing over 1 wk	450 mg/d	Dizziness, drowsiness	FDA-approved treatment for fibromyalgia
		Adjunctive topical agents		
Capsaicin		Lotion: >2 y, apply t.i.d.–q.i.d; patch: ≥12 y, apply t.i.d.–q.i.d. ×7d; cream/gel/liquid: adult, apply t.i.d. ×2–4 wk		Do not apply to areas of skin breakdown
Lidocaine patch		Lotion, jelly, gel ointment, topical solution, cream: apply thin film t.i.d.; patch: adult, 1–3 patches b.i.d.	If used in high doses: arrhythmias, methemoglobinemia, seizures, coma, respiratory depression, death	Do not use overlying bandage or apply on areas of skin breakdown
		Second-line agents		
		Other antiepileptic drugs		
Carbamazepine	Not established in children. Adult: ER tabs, 100 mg b.i.d; liquid 50mg q.i.d.	400–800 mg/d	Drowsiness, headaches, motor discoordination, GI upset. Can exacerbate hypothyroidism, lower blood counts, cause aplastic anemia, and cause SIADH.	First-line treatment of trigeminal neuralgia. Liquid preparation available
Lamotrigine	Not well established in pain but in epilepsy. Week 1+2: 0.3 mg/kg/d div. q.d. or b.i.d; Week 3+4: 0.6 mg/kg/d div. b.i.d; Week 5+: inc. by 0.6 mg/kg/d q1–2wk	4.5–7.5 mg/kg/d (max: 300 mg/d) div. b.i.d.	Skin rash, including Steven–Johnson syndrome. With *in utero* exposure: inc. chance of cleft lip/palate	Orally disintegrating tablet available. Estrogen-containing OCPs may dec. serum concentration

(continued)

TABLE 14.19 Medical Treatments for Neuropathic Pain (Continued)

Name	Starting Dose	Maintenance Dose	Side Effects	Considerations
Oxcarbazepine	Not well established in pain but in epilepsy. 8–10 mg/kg/d div. b.i.d; increase dose q3d by 5 mg/kg/d	Max dosing: 20 kg, 900 mg/d div. b.i.d. to 70 kg, 2,100 mg/d div. b.i.d.	Hyponatremia usually within 1st 3 mo	There is an oral suspension available
Topiramate	See Table 14.13			
Valproic acid	See Table 14.13			
		Opioid or opioid-like		
Methadone	0.1 mg/kg/dose q4h ×2–3 doses, then q6–12h or 0.7 mg/kg/24 h div. q4–6h	Max dose: 10 mg	May cause QTc prolongation or cardiac arrhythmias	Half-life is long at 5 d
Tramadol	1–2 mg/kg/dose q4–6h	Max single dose: 100 mg; Max total daily dose is less than both 8 mg/kg/d or 400 mg/d	Can lower seizure threshold at higher doses	Acts on Mu receptors and also inhibits serotonin and norepinephrine. Lower risk of opioid dependence than traditional opioids
		Nonopioid analgesics		
Acetaminophen	See Table 14.14			
NSAIDs	See Table 14.14			

TREATMENT: Pregabalin was the first FDA-approved medication. Also treat with analgesics, antidepressants, and antiepileptics. Should use integrated treatment plan that also incorporates aerobic exercise and cognitive behavioral therapy.

Phantom Limb Pain

CLINICAL FEATURES: Following limb amputation, patients can report limb awareness, phantom sensations, pain located at the stump; and in 50% to 80% of cases, people also report phantom limb pain.[36] Amputees often report that the phantom limb feels shorter and can have burning-quality pain. Pain may have central component as it is not relieved by local anesthesia injected at the stump site.

TREATMENT: Not well studied but typically geared toward same treatments for neuropathic pain, e.g., antidepressant medication and calcium-channel blockers, including carbamazepine.[37] Opioids, calcitonin, ketamine, and sensory discrimination training can also be used. Antidepressants and spinal cord stimulation have shown effect, and there is also a more novel therapy that uses a mirror box to create artificial visual feedback so patients can "move" the phantom limb from uncomfortable positions to relieve pain.[38]

Spasticity-Related Pain

DEFINITION: Spasticity is often found in children with cerebral palsy, traumatic brain or spinal cord injury, multiple sclerosis, and strokes. It is characterized by tight muscles and decreased muscle control and, in more severe cases, contractures, joint deformities, and abnormal postures. This can be associated with pain described as a feeling of tightness in muscles, muscle spasms, or painful tightness around joints.

TREATMENT: The first-line treatment includes occupational and physical therapies. When spasticity is more severe, medications such as benzodiazepines or $GABA_B$ agonists (baclofen) can be effective. Botulinum toxin or phenol can be injected to target specific muscles. Surgical options include tendon release or implantation of an intrathecal baclofen pump.

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ONLINE RESOURCES

The National Headache Foundation – www.headaches.org

The American Committee for Headache Education – www.achenet.org

The International Headache Society – www.ihs.org

15 Behavioral Pediatric Neurology

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PSYCHIATRIC MANIFESTATIONS OF NEUROLOGIC DISEASE

Psychiatric symptoms may be the first/early symptom of neurologic disease, can assist in localization and diagnosis. Disorders with diverse presentations (i.e., psychosis and mood disorder) are listed by most common manifestations. Virtually all neurodegenerative disorders may have cognitive/executive/mood disorders at some time during disease course, but typically not at presentation except as follows.

Presenting with Psychosis or Executive Dysfunction

Progressing Over Hours to Weeks

Acute Confusional Migraine

Disorientation ±agitation, children > adolescents.

Sydenham Chorea

Inattention, behavioral outbursts, obsessive–compulsive features.

CNS Vasculitis

Often small vessel, not visualized on conventional angiogram or MRA, often with headache, fever, and focal neurologic signs.

CNS Lupus[5]

Psychosis, loss of acumen, bizarre behavior, headache.

Porphyria

Hallucinations, paranoia, confusion coincide with systemic symptoms.

Epilepsy

Especially originating from temporal, orbitofrontal, and cingulate cortices, often (but not always) associated with preceding visceral or olfactory aura, sudden onset/termination. **Infection:** Diverse in timing and anatomical tropism, almost always with systemic symptoms.

Antibody-Mediated Encephalopathies

Often respond to IVIG, treatment of primary malignancy if paraneoplastic.[6]

NMDA Receptor Encephalitis

Speech regression or loss, bizarre behavior, incontinence, dyskinesias, and seizures.

Anti-GAD Encephalitis

Classic limbic encephalitis, with disorientation, mood disturbance, and seizures.

Ophelia Syndrome

Rapid-onset, dense amnesia, associated with Hodgkin lymphoma.

Opsoclonus–Myoclonus–Ataxia Syndrome

Inattention, impulsivity, mood disturbance coincide with onset of movement disorders.

Hashimoto Encephalopathy

Unclear relationship between CNS symptoms and antithyroid antibodies, often steroid-responsive (diagnostic).

Metabolic Disorders

Mitochondrial and substrate dysmetabolism disorders with triggered exacerbations often have acute cognitive/executive decline on backdrop of slowly progressive dementia.

Progressing Over Months to Years

Huntington disease: Attention deficits, belligerence, substance addiction, parkinsonism/gait disturbance > chorea before age 20 y, all HD-mimics have same psychiatric profile. **Chorea-acanthocytosis:** Disinhibition, executive function deficits. **Wilson disease:** Frank psychosis, inattention, disinhibition, insomnia.

Presenting with Personality Change Early in Course

Rapid Evolution

Typically with focal deficits and/or systemic signs.

Infection, Ischemia

Both stepwise, progressive changes possible. Embolic, hemorrhagic, moyamoya-related infarcts may all present with change in attention/cognition/executive function. **CNS vasculitis** (including lupus): Diffuse, waxing and waning deficits. May also be slowly progressive.

Slowly Progressive

Storage Disorders

Juvenile neuronal ceroid lipofuscinosis (Batten disease); Gaucher disease type 3 (general cognitive decline, no psychosis); Niemann–Pick type C (psychosis, hallucinations, progressive dementia—always with other diffuse neurological symptoms).

Leukodystrophies (esp. X-ALD, MLD)

Behavioral changes, attention deficits, and school failure dominate early presentation; rare cases may present acutely; later-onset vanishing white matter disease often has behavioral or psychiatric disturbance present at onset, with motor features coincident or following rapidly.

Presenting with Mood Disorders

Sydenham chorea: Depression, anxiety, and obsessive–compulsive symptoms common, develop early, and may persist for many months. **SCA17**

(likely other degenerative ataxias too): Depression may precede ataxia; **Early-onset parkinsonism** (PARK7). **Epilepsy:** More commonly comorbid than as a presenting symptom. **NBIA disorders** (neurodegeneration with brain iron accumulation): Mood disorders and personality change common in late adolescent-onset.

NEUROLOGIC PRESENTATIONS OF PSYCHIATRIC DISEASES

Psychiatric disorders commonly present in neurologic practice, both as complications of neurologic diseases and as mimics of distinct neuropathology. 15% to 30% of all neurology outpatient visits remain medically unexplained.[7,8] Failing to recognize/aid this large patient group is simply not an option. Fortunately, such disorders are often readily distinguished from neurologic diseases and many are responsive to treatment.

Depression

Common features of depression may be mistaken for neurological disease; psychomotor slowing or retardation, parkinsonism, abulia, insomnia and poor attention, ADHD, memory disturbance, insomnia, delusions and hallucinations, fragments of many neurological diagnoses.

Catatonia

A clinically defined disorder of motor immobility, often with waxy tone alternating with excessive, repetitive, and purposeless actions; social withdrawal, mutism, refusal of interaction or nutrition/hydration; fever and autonomic dysregulation. May be misdiagnosed as status epilepticus (convulsive or nonconvulsive), dystonic storm, encephalitis, malingering.

Etiology

Unknown. Linked with schizophrenia and autism, but occurs in many disorders: lesions of medial prefrontal cortex, anterior nuc. thalamus; antiphospholipid antibody syndrome; Lupus cerebritis; Trisomy 21; Anti-NMDA receptor encephalitis; Prader–Willi syndrome; global developmental delay; temporal lobe epilepsy; depression, anxiety, or mania; cocaine, ecstasy abuse; hyponatremia; Wilson disease.

Demographics

F = M, adult = child, 5% in psychiatric outpatients, ~15% among autism spectrum disorders, higher in children receiving acute psychiatric care.[9] Catatonia in children does not differ substantially from catatonia in adults: signs, symptoms, treatments, many causes are identical.

Treatment

High-dose benzodiazepines and electroconvulsive therapy lead to improvement in 80% to 100% of patients.[10] Treatment is independent of causative disorder. Poorly diagnosed in children; only 11% are diagnosed early in course and only 6% receive therapeutic standard of care. Delayed treatment limits efficacy of therapy. Most severe form (malignant catatonia) is fatal in 10% to 20%, but responds if recognized early.

Somatoform Disorders

Symptoms that suggest a medical diagnosis but are caused by psychiatric disturbance, usually referred to neurology. Linked to heightened sensitivity to normal body fluctuations, increased basal autonomic arousal.

Definitions

Somatization: Pattern of multiple chronic complaints, shifting frequently, lasting years. **Conversion:** (25% of somatoform disorders in adults, ~50% in children), acute onset of discrete neurological symptoms, persists months/years with limited change in symptom. **Pain disorder:** Distress out of proportion to or without preceding injury, headache, abdominal, pelvic sites common, but any area can be affected. **Hypochondriasis:** Fear and preoccupation with specific disease.

Demographics

Symptoms poorly explained by a medical diagnosis are very common—⅓ of all neurology outpatient visits.[7] Linked to anxious/depressive personality types, mood disorder, (+) family history of mood, or somatoform diagnoses is common.

Conversion Disorder

Somatoform diagnosis most likely to involve neurology, and most common in children.

Demographics

Psychogenic disorders are common in children, ≈ to adult frequency: 2 to 5/100,000 children/y, as common as all-cause encephalitis; 6% to 15% of neurology outpatient visits; 5% of new-onset seizures; 3% of movement disorders clinic visits, and 25% of inpatient movement disorders consultations.[11,12] Gender: F = M, prepuberty, in adolescents/adults conversion disorder females 2 to 10× > males. ~25% cases are <10 y, but in reported cases/personal experience may be as young as 4 y.

Etiology

Though historically linked to psychological distress (hysteria), now demonstrated to have abnormal brain activity correlating with location and type of symptoms.[13] Sense of agency (ownership of thought/action) is abnormal,[14,15] pattern of fMRI/PET activity with movement is abnormal. These "functional" derangements normalize with treatment. Thus the symptoms are not consciously generated and are not under patient control.

Diagnosis

Trust your exam; if you are uncertain, refer. Functional disorders have patterns of presentation distinct from their organic counterparts. See Table 15.1.

"Diagnosis of exclusion" is inaccurate, undermines trust in one's assessment, and forces unnecessary testing/anxiety/cost/delay in treatment. Sharing affirmative findings on exam with patients demonstrates your cautious evaluation, gives time for news to sink in (e.g., "This downgoing toe is reassuring; your weakness is not from a spinal cord injury.") Misdiagnosis for conversion disorder is rare (5%), identical to rate for other neurological diagnoses.[16] Style of presentation is critical—physician says: nonorganic, factitious, psychogenic, pseudo; patient hears: "all in your head," "faking it," or "not worthy of my time and energy." This perception is based on: (1) the view in society that psychiatric disorders are less serious than "real" diseases; (2) that they are the patient's fault; (3) the way providers frame and discuss the symptoms. Conversion symptoms are beyond the patient's control, are as debilitating and distressing as organic symptoms—approaching patient with sympathy and respect is essential for successful treatment. **Note:** DSM-IV criteria require identification of psychological

TABLE 15.1 Essential Elements in the Assessment of Functional Disorders in Children

Begin with compassion, honesty, and respect. Acknowledge patient's fear and disability. Build trust.

Historical elements that suggest a functional diagnosis:

Acute onset, rapid rise to plateau of severity

Spontaneous remission

Physical exam features supporting a functional diagnosis:

Distractibility, severity increases with attention to symptom

Symptom adaptation (e.g., entrainment of tremor, change in seizure semiology, suggestibility)

Relieved by placebo or when patient believes he or she is unobserved

Disability or pain is selective and/or out of proportion to limitations found on exam

Presence of functional signs: give-way weakness; Krohn, double-crossed arms tests, or dropped-hand (arm weakness); Hoover or Raimiste tests (leg weakness); near–far tubular vision test (visual defect); dissociation of paired sensory modalities (vibration and position sense), splitting midline, nondermatomal distribution (sensory loss)

Indications for testing, even when a functional diagnosis is likely:

Objective focality on neurological exam

A prior neurologic diagnosis of a similar symptom (e.g., new non-epileptiform seizures in a patient with established epilepsy)

If trust is undermined by lack of studies, limit scope, build case with data

After diagnosis is made, assess for triggers, foci for therapy:

Academic stressors (e.g., transitions, bullying, high-demand schools, many extracurricular activities)

Social disruption, presence of friendships, peer conflict, online interactions

Family transitions (move, job loss/change, new spouse/partner, new sibling), financial hardships, intrafamily conflict

Identify persons who are sources of symptom modeling

cause—not required in DSM-5, not currently required to dx specific manifestations (e.g., psychogenic movement disorders, nonepileptic seizures).

Treatment

In children, 80% to 90% make full recovery, far better response than in adults.[11,17] Of those who recover completely, 96% do so within 4 wk. Factors that predict better outcome: shorter disease duration; stated trust in physician; belief in the diagnosis; patient and physician's expectation of recovery. Therapy begins with careful exam, affirming the positive findings that led to the dx. Unpacking stressors is often therapeutic, may resolve, and often reduces symptoms. Early referral to and ongoing care by psychologist/psychiatrist experienced with functional disorders. Minimize testing and demedicalize where possible. CBT shown to be effective in clinical trials. Very helpful to maintain relationship with neurologist—provides affirmation in diagnosis, ready evaluation if new sx develop, "backup" if psych relationship is difficult. Cost and duration of care are similar to that for patients with similar organic diagnoses.[18] **Caveat:** 10% to 15% of patients with psychogenic disorders have coexisting organic disorder—must address both.

TIC DISORDERS

Definition

Tics are rapid, arrhythmic, repetitive movements or sounds that wax and wane over weeks/months to involve other body parts, actions.

Simple Tic

Brief, single body area involved, though multiple simple tics often coexist.

Complex Tic

More purposeful appearing movements/sounds, often in rigid coordinated patterns of action, may be compulsive (touching/tapping), aggressive (hitting/punching self), involve mimicry of self (palilalia) or the words (echolalia) or actions (echopraxia) of others, use of socially inappropriate words/phrases (coprolalia) or gestures (copropraxia).

Presentation

1st tics onset commonly between 3 and 8 y, usually motor (head, neck, shoulders most common), followed 1 to 2 y later by vocalizations. Symptoms typically peak in early adolescence, then taper off and remit/recede in ~80% of patients. **Triggers:** Stress, fatigue, excitement, infections, beginning/end of school year, holidays, others noticing tics. **Premonitory urge:** (building sense of pressure/itch/"wrongness") that can be briefly resisted, nondistractable, relieved by performing tic is near-universal. Urge and ability to suppress may not be evident in young or developmentally delayed patients. Single tics emerge, flourish over weeks to months, and eventually migrate to other body parts/actions. In this constant pattern of waxing/waning, several tics often overlap, with multiple tics seen within a day. Coprolalia/copropraxia occur in only 10% to 20% of TS patients, are rare in non-TS tic disorders. **Unusual tic types:** Tonic (abdominal or pelvic tensing, breath-holding); dystonic (writhing, twisting, distorting movements); negative tic (vocal or movement block); forced laughter. Tics are an uncommon psychogenic movement disorder, though occasional patients with tics can have superimposed elaborative tics. Distinguish from **stereotypies** (stereotypy distractible, start <3 y, even in infancy) and **myoclonus** (myoclonus less complex, typically rapid "lightning-like" jerks, not suppressible)-for both, no evolution to other body parts, no internal drive/premonitory urge.

Transient Tic Disorder of Childhood

Regardless of number/severity; duration >1 mo and <1 y; best used in retrospect for brief tics that have abated; proposed DSM-5 change name to "Provisional Tic Disorder."

Chronic Motor or Vocal Tic Disorder

Restricted to one class (either motor or vocal tics, not both), duration at least 1 y.

Tourette Syndrome (TS)

"Gilles de la Tourette" is the full last name of the 19th century French physician who described this disorder. Multiple motor & $\geq$ one vocal tic, duration >1 y; must exclude other causes (e.g., drugs, basal ganglia injury) & general medical conditions. Severe tics seen in 5%, often refractory to treatment (self-injurious, or violent behaviors such as punching, pinching, eye poking), termed malignant TS. TS and chronic tics exist on a clinical spectrum, are not clearly separate disorders, and segregate together in families. DSM-5 removed previous requirement for all tic disorders regarding no tic-free interval >3 mo.

Demographics

Most common movement disorder in childhood: transient tic disorder, 20% to 30%; chronic motor or vocal tic disorder, 2% to 3%; TS, worldwide

prevalence ~1%, male predominance (~4:1). Of chronic tic disorders, by the age of 20 y: ⅓ resolve, ⅓ continue at low intensity, ⅓ are symptomatic. Comorbidities with TS are frequent (88%): ADHD, 60%; OCD, ~30%; learning disability, ~25%; mood disorders, 20%; conduct/oppositional defiant disorder, 15%.[1] Family hx often (+) for tic, ADHD, and/or OCD (TS triad).

Pathophysiology

Genetic mechanism undetermined, but strong heritability: in TS, 55% concordance between monozygotic twins, 8% in dizygotic. Tics are a developmental disorder: ⅔ "outgrow" or markedly lessen. Hypothesized mechanisms: reduced integrity of somatosensory cortex–basal ganglia connections leading to motor disinhibition; dopaminergic hyperinnervation of the striatum; impaired top-down cortical control from frontal lobe networks; numerous other neurotransmitter abnormalities of unclear significance.[2]

Treatment

Most patients have mild tics, need only education and reassurance. Disability is better predicted by comorbidities, individual/family factors than by tic classification.

Medications

Indicated only if tics cause self-injury/pain, social/academic/functional impairment.

1st Tier

α2 agonists (clonidine, guanfacine), multiday dosing is required (not just q.h.s.); less evidence for topiramate

2nd tier

Atypical antipsychotics (risperidone, ziprasidone, aripiprazole); quetiapine, olanzapine generally less effective

3rd tier

Typical antipsychotics (haloperidol, pimozide, fluphenazine); highest efficacy but many short- & long-term side effects; efficacy proportional to D2R potency; pimozide NOT necessarily better than haloperidol or fluphenazine and has many drug–drug interactions, ↑ QTc

Other

Tetrabenazine (depletes neuronal dopamine, as effective as 2nd + 3rd tier with less tardive dyskinesia risk; for some patients 1st tier, but limited by 25% emergent depression and cognitive blunting); botulinum toxin (consider for single-site bothersome tic).

Habit Reversal Training (HRT)

Teaches pts to recognize premonitory urges & perform voluntary behavior that is incompatible w/ tics. Randomized controlled trial showed modest improvement in tic severity.[3]

Deep Brain Stimulation (DBS)

For severely disabling, medication-refractory tics; optimal location of electrode placement (CM thalamus, GPi, subthalamic nucleus) still unclear.

Education

Education of family & schools is often sufficient treatment. May need counseling, support services, classroom accommodations.

Comorbid Disorders

Important to treatment, often more impairing than tics.

OCD

Cognitive behavioral therapy (CBT), SSRIs, atypical antipsychotics, DBS for severe cases.

ADHD

Stimulants NOT contraindicated—no difference in tic exacerbation; methylphenidate vs. clonidine vs. placebo; combo clonidine/ methylphenidate best for combined ADHD/tics.[4] Amphetamine derivatives, atomoxetine (NE reuptake inhibitor), guanfacine also proven effective. In practice, can see transient tic worsening after stimulant initiation but often abates with time, reduced likelihood with low-dose initiation and slow up-titration.[2]

PANDAS

Pediatric **A**utoimmune **N**europsychiatric **D**isorders associated with Group **A** **S**treptococcal infection is a controversial diagnosis. Preadolescents show abrupt onset of OCD symptoms ± severe tics, often with behavioral regression, enuresis, attention deficits. Unclear whether it's a distinct disorder or a subset of TS or OCD sufferers, with an infectious trigger. Attempts to identify anti-neuronal antibodies (as seen in Sydenham chorea) have led to rare positive and numerous negative basic science studies. Difficult to link decisively with strep infections, given the high carrier rate and asymptomatic infections. Reported improvements following IVIG or plasmapheresis, but not steroids. IVIG not currently recommended outside of a clinical trial. Short-course antibiotics are generally accepted, while protracted/prophylactic antibiotics are likely of no benefit, though hotly debated. Recently proposed to also follow *Mycoplasma* or *Borrelia* infections; therefore renamed PANS (pediatric acute-onset neuropsychiatric syndrome).

ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD)

Definition and Diagnostic Criteria

Neurobiological/neurodevelopmental condition manifesting in early childhood, with core symptoms of hyperactivity, impulsivity, and/or inattention. Per AMA Council on Scientific Affairs, "One of the best-researched disorders in medicine, and the overall data on its validity are far more compelling than for many medical conditions."[19] **Subtypes:** Predominantly inattentive, predominantly hyperactive/impulsive, or combined type.

DSM-IV Criteria[20]

≥6 of 9 inattentive and/or ≥6 of 9 hyperactive/impulsive (H/I) symptoms. Symptoms must persist for ≥6 mo; be maladaptive & inconsistent w/ developmental level; present in ≥2 settings (school, home, etc); present before 7 yo (<12 yo in DSM-5 as below); cause significant impairment in social, academic, or occupational functions; not attributable to another physical, situational, or mental disorder. **Note:** Might not be recognized until after 7 yo, when school/work becomes more challenging (especially in inattentive subtype).[21] See Table 15.2.

TABLE 15.2 ADHD Symptoms (DSM-IV)[20]

Inattentive	Hyperactive/Impulsive (H/I)	
1. Inattentive to details/ careless mistakes 2. Difficulty sustaining attention 3. Does not listen when spoken to directly 4. Does not follow-through/ finish tasks 5. Difficulty organizing 6. Avoids/dislikes tasks requiring sustained attention	1. Fidgets w/ hands/feet, squirms in seat 2. Difficulty remaining seated 3. Runs about/climbs excessively (adolescents w/ subjective restlessness) 4. Difficulty playing/engaging in leisure activities quietly 5. "On the go," "driven by motor" 6. Talks excessively	Hyperactivity symptoms
7. Loses things 8. Easily distracted 9. Forgetful	7. Blurts answers before questions completed 8. Difficulty awaiting turn 9. Interrupts/intrudes on others	Impulsivity symptoms

DSM-5 Changes[22]

(1) Classification: ADHD moved to "Neurodevelopmental Disorders" group, clustered with learning disorders (LD), not "disruptive disorders" (oppositional defiant disorder [ODD] and conduct disorder [CD]) to reflect developmental brain correlates. **(2) Age criteria:** Symptoms were present by 12 yo (not 7 yo) but did not have to cause impairment by 12 yo. Multiple studies show no difference between child identified by 7 yo vs. later in regards to course, outcome, severity, or tx response. **(3) Subtypes:** Symptoms/pattern may change with age and context, classification may differ between informants, may have symptoms from both "subtypes"; similar response to meds across subtypes. Still need ≥6 to 9 symptoms over the past 6 mo from either/both inattentive or H/I list but no longer categorized as "subtypes," but described as "presentations": H/I presentation (with ≤5 inattentive symptoms), inattentive presentation (3–5 H/I symptoms), restricted inattentive presentation (≤2 H/I symptoms), combined presentation (≥6 inattentive and ≥6 H/I symptoms). Restricted inattention subtype needs further study. **(4) Adult/adolescent diagnosis:** Still require retrospective onset <12 yo, but DSM symptoms originally developed in children and symptoms/pattern may change with age and context; can see age-related "decline" in number of symptoms. Need ≥5 symptoms for adults (>17 yo) and there is description of symptoms more tailored to adults. **(5) ADHD in autism spectrum disorders:** ADHD can now be diagnosed in ASD patients; previously excluded by "cannot be attributed to another mental disorder" criterion.

Epidemiology

Prevalence and Gender

Most commonly diagnosed pediatric neurobehavioral disorder; affects 4% to 12% school-age children.[23] Children appear to have male predominance; likely due to decreased rates of aggression/disruptiveness in girls, so not referred until later. Adults M:F ratio equal suggesting underdiagnosis in females in childhood. Percent of children ever diagnosed with ADHD increased from 7% in 1998–2000 to 9% in 2007–2009 (using parental report).[24]

Underdiagnosed and Undertreated

Study using clinical assessment showed only 50% children meeting clinical criteria ever received diagnosis or medical treatment.[25] 3.5% of U.S. children received stimulants in 2008; majority of those with ADHD are NOT receiving stimulant treatment.[26]

Subtypes

Combined subtype 50% to 75%, inattentive subtype 20% to 30%, hyperactive/impulsive <15%. Combined subtype most common, most severe, greatest risk of comorbidities.[27]

Comorbidities

anxiety disorders, depression, bipolar, ODD, CD, learning disabilities, substance abuse.[27]

Pathophysiology[23]

Heterogenous disorder with multiple contributing factors: genetic, neuroanatomical, neurochemical, environmental.

Neurochemical

Catecholamine dysregulation; dopamine (DA) and norepinephrine (NE) in prefrontal cortex (PFC) & frontal–subcortical pathways. PFC impaired by too little or too much catecholamine—inverted U-shaped dose-response curve. **PFC function impaired:** Too little NE and DA (ADHD) or too much NE and DA (via stress or stimulant medication dose too high); excessive NE activates α-1 and β-1 adrenergic receptors and DA overstimulates D1 receptors → distracted, disorganized, forgetful, impulsive. **PFC function improved:** With treatment, moderate levels NE and DA activate postsynaptic α-2A receptors and D1 receptors respectively → focused, organized, responsible.[28]

Neuroimaging

Smaller anterior cingulate cortex (ACC) & dorsolateral prefrontal cortex (DLPFC); delay in development of cortical thickness (pattern of development between ADHD & controls similar, but delayed in ADHD); DLPFC, ACC, & parietal areas remain thinner in ADHD adults; increased disorganization of white matter tracts emanating from PFC; attenuated frontostriatal activity on go/no go test (needed for inhibitory control & attn); increased activation non-frontostriatal regions (ACC, parietal) vs. controls; stimulant treatment shown to improve ACC & DLPFC activation.

Genetics

Mean heritability 75% (100% indicates entirely genetically influenced, 0 is no genetic influence) vs. depression/anxiety/asthma <50% heritable; likely polygenic; some evidence for candidate genes. Numerous common DNA variants implicated but not yet confirmed; rare, large deletions/duplications (copy number variants [CNV]) reported, though same CNV seen in different developmental disorders.[29]

Environmental

Maternal smoking during pregnancy, *severe* early deprivation (ordinary variations in child-rearing do *not* contribute to ADHD).

Clinical Features

DSM symptom clusters required but are somewhat simplified description. Display variable executive function deficits: response inhibition, planning & organizing, working memory, self-regulation (including emotional self-regulation), frustration tolerance, complex problem solving, intrinsic motivation, goal-directed behavior ("procrastination"). **Poor attention regulation** gives the appearance that child can pay attn when he/she "wants to" (e.g., studies baseball cards for hours but can't focus on math homework). **Poor self-perception & difficulty w/self-external appraisal** can → positive & negative illusory bias (unrealistic optimism—ability to complete a project at the last minute—or pessimism—will always be blamed for problems). May develop **demoralization** and **low self-esteem** secondary to persistent impairments of untreated ADHD; often mistaken for depression.

Executive Functions (EF)[30–32]

Definition

Brain circuits that prioritize, integrate, and regulate other cognitive functions. Provide the mechanism for self-regulation: "Any action directed at the self that is used to modify behavior so as to alter the likelihood of a later consequence."[32]

Neuropsych Test Model

E.g., Stop-signal task, Tower of Hanoi, Wisconsin card sorting. Propose that only a percentage of ADHD patients have impaired EF.

"Real World" Model of Complex Interacting Deficits

Theories proposed by Russell Barkley and Thomas Brown—ADHD is by its nature an impairment in the development of EF or of brain's self-regulatory mechanisms; *all* pts with ADHD have EF impairments. **Russell Barkley theory of EF** involves self-directed activities seen overtly in childhood but eventually become covert/private; disrupted/delayed in ADHD: (1) *Self-directed attention* → self-awareness & monitoring. (2) *Self-directed inhibition* → impulse control, delay of gratification, inhibits pre-potent response, & interrupts ongoing response. (3) *Self-directed sensing* (especially imagery) → holding events in mind, sense of past & future, sense of time, cross-temporal organization of behavior, sustains nonverbal info mentally (nonverbal WM). (4) *Self-speech* (internalization of language) → self-description/reflection/instruction/questioning, rule-governed behavior, reading comprehension (verbal WM). (5) *Self-elicited emotions & motivation* → self-regulation of emotions & motivation, intrinsic motivation/activation to task demands. (6) *Self-directed play* → problem solving, goal-directed innovation, cognitive flexibility.

Diagnostic Evaluation[4,21,33]

AAP and AACAP Guidelines

currently require that DSM-IV criteria be met for ADHD diagnosis; AAP recently expanded guidelines from 6 to 12 yo to include children 4 to 18 yo. DSM-5 will likely lead to some changes (see above).

Complete Evaluation

Includes interview of patient and parent(s), DSM criteria, developmental hx, FH & psychosocial hx, physical/neurologic exam, ancillary reports (day care/teacher/ coaches reports, academic records), various symptom **rating scales** for ADHD & comorbid disorders (e.g., ADHD Rating Scale, Vanderbilt Parent & Teacher Scales, Conners Rating Scales—Revised, Brown ADD Rating Scales, etc.). Positive rating scales support diagnosis, but can arise from other causes of executive dysfunction (severe anxiety, depression, sleep apnea).

Screen for Comorbidities & ADHD Mimics

Screen for psychiatric (anxiety/OCD, depression, ODD, CD, bipolar), developmental (learning, language, other neurodevelopmental disorders), neurologic (tics, seizures, ALD in boys), medical/physical (sleep apnea, lead exposure).

Additional Studies

If PMH and exam unremarkable, do not need labs or other studies (EEG, MRI), clinical diagnosis only.

Psych/Neuropsych Testing

Psychiatric consult and neuropsych testing not mandatory for ADHD dx, but consider if signs of learning, neurodevelopmental, and/or psychiatric disorder. ADHD children may have "normal" neuropsych testing since structured setting of test (quiet room, one-on-one) may not capture "real-life" impairments in organization, attention, self-regulation.

Treatment

Stimulants

FDA-approved: methylphenidate-based (MPH) & amphetamine-based (AMP).

Mechanism of Action[34]

work to increase intrasynaptic catecholamines (DA & NE) in the PFC (see Pathophysiology above). **MPH:** inhibits DA reuptake by the DA transporter in presynaptic neuron; also inhibits NE reuptake. **AMP:** inhibits DA and NE reuptake; also stimulates DA release from vesicles into cytoplasm & stimulates release of DA (and NE) into synapse via reversal of transporter (DA released into synapse instead of reuptake). Also leads to increased 5-HT, so may have more mood side effects than MPH.

Administration Considerations

Tables 15.3 and 15.4.

TABLE 15.3 Duration of Action and Maximum Dosing of Stimulants

Duration Action	MPH-Based	AMP-Based
	(max 2 mg/kg/d except dex-MPH & MPH patch 1 mg/kg/d)	*(max 1.5 mg/kg/d except Vyvanse 1 mg/kg/d)*
Short-acting	[3–5 h] Ritalin, Methylin, Focalin (dex-MPH)	[4–6 h] Dexedrine (dextro-AMP), Dextrostat
Intermediate acting	[3–8 h] Ritalin SR, Metadate ER, Methylin ER	[6–8 h] Adderall (AMP mixed salts), Dexedrine spansules
Intermediate/ long-acting	[8–10 h] Metadate CD, Ritalin LA	
Long-acting	[10–12 h] Focalin XR, Concerta (OROS MPH), Daytrana patch, Quillivant XR (new liquid formulation)	[8–12 h] Adderall XR, Vyvanse (prodrug/ Lisdexamphetamine)

Wilens TE, Spencer TJ. Understanding attention-deficit/hyperactivity disorder from childhood to adulthood. *Postgrad Med.* 2010;122(5):97–109.
Note: Maximum dosing may exceed FDA recommendations.

TABLE 15.4 Pharmacokinetic Profile of Stimulants

Profile	Stimulants
Flat	Methylin ER, Ritalin SR (but in wax-based matrix; so only small amount absorbed & inconsistent delivery)
Ascending	Concerta (22:78), Metadate CD (30:70), Daytrana patch, Vyvanse, Dexedrine Spansule
Single "hump"	Ritalin, Focalin, Adderall, Dexedrine tablet
Double "hump"	Adderall XR, Focalin XR, Ritalin LA (all 50:50)

Clinical Response

About 65% to 75% patients show clinical response to a stimulant; increases to 85% if both MPH & AMP tried. Studies show 25% respond to MPH, 25% to AMP, 50% to both; currently unable to predict how/who will respond.[33]

Stimulant Linear Dose-Response Curve

Increase symptom reduction with increased dosing (think of "linear" to a point, but also consider inverted U-shaped curve mentioned above; can eventually reach level where too much DA and NE is impairing). Start at lowest dose and titrate up every 3 to 7 d; titrate dose up to max tolerable for symptom control and not according to mg/kg guidelines (use *best* dose, not lowest effective dose). Each patient has individual dose-response curve. Long-acting now preferred to short-acting for ease administration and increased adherence (youngest patients/preschool may prefer short-acting for smaller doses).[33]

Side Effects

If SE intolerable, often alleviated by change to different formulation of same stimulant or change to alternative stimulant (MPH to AMP or vice versa). See Table 15.5.

Side effect controversies

- Cardiovascular (CV) effects: May see very slight increase in SBP, not much DBP. ADHD meds not associated with increased risk of serious CV events.[35] Rate of sudden death in children on stimulants not shown to exceed base rate in population; obtain patient and FH of CV disease (e.g., WPW, sudden death, HOCM, long Qt); if no significant hx, EKG or ECHO screening not required.[33]
- Growth: Review showed stimulants in childhood had modest reduction in height and weight but dose-dependent and attenuated over time.[36]
- Tics: Stimulants not contraindicated. TACT (Treatment of ADHD & Tics) Study: double-blind placebo controlled trial showed no difference in tic exacerbation w/ MPH, clonidine, or placebo; combo MPH + clonidine best for both ADHD & tics. Tic severity decreased in all treatment groups vs. placebo (clonidine + MPH > clonidine > MPH alone > placebo).[4]

TABLE 15.5 Common Stimulant Side Effects and Strategies

Side Effects	Notes/Strategies
Sleep problems	Important to document any sleep issues prior to initiation of stimulants (often present at baseline) Review sleep hygiene If long-acting formulation → intermediate acting (i.e., Concerta → Metadate CD) Consider melatonin, α-agonist, amitriptyline
HA	Consider problem might be decreased fluid intake
Appetite suppression	Take with/after meals Encourage frequent snacks & eating when med not effective— breakfast, after school snack, dinner Drug holidays Consider adjunct Periactin or Nortriptyline
Abdominal discomfort	Take with food (but careful with AMP, see below)
Transient increase in tics	Start with lower doses (2.5 mg MPH) and increase slowly Tic increase often abates with time (few days) Stimulants NOT contraindicated in tics/do not cause tics Consider adjunct α2 agonist (see "Tic" section earlier in chapter)
Irritability/dysphoria/ "edgy"	Timing: during med effect or after wear-off (rebound/ withdrawal)? Alter formulation of same stimulant vs. change to another stimulant or non-stimulants For very young (5–6 yo), wait a few years & try again If just "edgy," consider change in formulation or stimulant class; consider adjunct β-blocker (propranolol) or α-agonist

Stimulant "Pearls" (Table 15.6)

Non-Stimulants

Often less effective than stimulants & delayed-onset action; good if stimulant nonresponsive/adverse effects or as adjunctive for partial response (indicated below).

Atomoxetine

(FDA-approved): Selective NE reuptake inhibitor (NRI). Start 0.5 mg/kg/d ×2 wk, then increase to 1.2 mg/kg/d, then 1.8 to 2 mg/kg/d if partial response in 6 wk. Start q.h.s. due to initial drowsiness then change to q.a.m. for better response. If GI SEs and/or afternoon symptoms, split dose b.i.d. Consider for ADHD w/ anxiety, tics, substance abuse. Great for comorbid anxiety; seems to work better on inattention than H/I.

α-Adrenergic Agonists

Guanfacine ER (Intuniv—take q.d.) and clonidine ER (Kapvay—take b.i.d.). Long-acting FDA-approved but often need short-acting in younger patients who can't swallow pills. Also consider clonidine patch (less sedating than p.o.). Guanfacine less sedating, less systemic SEs. Consider α-agonist for ADHD w/ tics, anxiety, sleep disturbance, emotional dysregulation, ODD.

TABLE 15.6 Stimulant "Pearls"

Issue	Considerations
MPH	Not affected by food Duration does not ↑ with ↑ dose Often needs dose ↑ in first 6–12 mo, even without growth Low bioavailability (20%–25%) & genetic polymorphisms may → ultraslow metabolizers Dex-MPH & Daytrana patch have higher bioavailability
AMP	Vit. C decreases absorption; alkalinizing agents (antacids) ↑ absorption Fatty food slows absorption Duration can ↑ with ↑ dose Higher (75%) & more consistent bioavailability than MPH Vyvanse (lisdexamfetamine/LDX) has longer half-life If minor reaction to Adderall (just don't feel good) but good clinical response, change to LDX might give same efficacy w/out SE
Attention to profiles	Does need 50% in a.m. or ascending profile?
Add IR onto long-acting	"Boost" in the morning For homework in afternoons On weekends if sleeping in too late
Daytrana patch	Approved for 9 h wear but can wear for up to 16 h Remove ~3 h prior to desired off-time Takes longer for onset; parents can place in a.m. while child sleeping (study shows improved a.m. symptoms & still eating breakfast) "Pink" under the patch is ok; if notable skin reaction try topical Benadryl or hydrocortisone prior to applying patch; rotate sites
Long-acting in young children who can't swallow pills	Sprinkles: Ritalin LA, Metadate CD, Adderall XR, Focalin XR New liquid Quillivant: use if need to titrate to an exact dose that can't be achieved with sprinkles
Only partial response on max MPH dose	MPH has low bioavailability and might not be absorbing as expected Check serum MPH level (want <50–60 ng/mL); if level low/normal, can increase PO dose or consider patch for better bioavailability; if high, change to another stimulant or adjunct non-stimulant

Seems to work better for H/I than inattention. Consider for younger children with dysphoric SEs from stimulants.

Non–FDA Approved but Demonstrated Benefit

Bupropion (NE & DA reuptake inhib), TCAs (imipramine, nortriptyline), modafinil (for arousal/motivation), melatonin (for sleep).

School and Home-Based Interventions

Medication can be ineffective for higher order EF deficits—need "surrogate frontal lobe." Accommodations (504 plan or IEP): extended time on tests, preferential seating, organizers, daily progress reports, tutors, home/classroom behavioral interventions, social skills remediation. CBT can be helpful for executive dysfunction and also in those with comorbidities

(anxiety/depression); consider CBT for child as well as parent training (e.g., for assistance with structure and discipline at home).

Outcome and Prognosis[37,38]

ADHD should be viewed as chronic condition across the life span. If older patient no longer meets full DSM diagnostic criteria, not equivalent to remission. Symptoms/impairment in adolescents/adults obscured by compensatory strategies, learned avoidance of ADHD-sensitive tasks, poor self-report. Typical DSM-IV symptoms differ/subthreshold in adolescents/adults: inner restlessness, impulsive decision making, poor focus in meetings, etc. DSM-5 criteria requires fewer symptoms for diagnosis (see "DSM-5 Changes" above).

ADHD have Increased Risk/Rates

Smoking & substance abuse (SA), with SA more severe and longer lasting; psychosocial deficits (poor self-esteem, fewer friends, social rejection); hospitalizations for accidental injuries; teen pregnancies; driving problems (speeding violations, accidents); academic difficulties (repeated grades, delinquency, need for special ed); employment & family/marital problems.

Adherence to Stimulant Treatment Shown to

Decrease risk for anxiety/depressive disorders, CD, and ODD; decrease risk SA; decrease rate of school failure/repeated grades; decreased rate of smoking to control levels; improve self-esteem and peer relations; improve driving.

SA

85% decreased risk of SA in adolescents if treated.[39] If followed into adulthood, no change in risk between ADHD treated w/ stimulants vs. non-treated ADHD (so stimulants did NOT increase/influence subsequent risk).[40]

Overall Costs (Treated & Untreated)

Estimated additional cost of ADHD (vs. controls) in US is $31.6 billion (including costs for pt and family member health care and work lost).

AUTISM SPECTRUM DISORDERS (ASD)

ASD are biologically based, highly heritable, neurodevelopmental disorders characterized by 3 domains: impairments in socialization, communication, and the presence of restricted and/or repetitive behaviors. Autism classified in DSM-IV under the general category of pervasive developmental disorders (PDD).[20] Definitions of autism are changing with publication of DSM-5; new diagnostic criteria combines socialization and communication into one domain (see "Diagnostic Criteria" below for details). The umbrella term of pervasive developmental disorder will change to autism spectrum disorder.

Definitions (per DSM-IV)

1. **Autistic disorder:** See diagnostic criteria below.
2. **Asperger disorder:** See diagnostic criteria below. Will be eliminated in DSM-5 and included under umbrella term "autism spectrum disorder."
3. **PDD–not otherwise specified (PDD-NOS):** Used for children who meet some, but not all, criteria for autistic disorder, including later

age of onset, atypical symptoms, subthreshold symptoms. Sometimes used for children <3 yo, even if autistic criteria met, due to concern for decreased accuracy of diagnosis in this age group. Will be eliminated in DSM-5 and included under umbrella term "autism spectrum disorder."

4. **Rett disorder:** See Chapter 10 for details. This will be removed from ASD section in DSM-5 and considered a separate disorder, although can still be diagnosed with ASD in addition to Rett, and ASD will include the specifier of "known genetic/medical condition."
5. **Childhood disintegrative disorder (CDD):** Marked regression in multiple areas of functioning after at least 2 y of normal development, occurring after age 2 y but before age 10 y; very rare; identical to autistic disorder other than history of normal development. Will be eliminated in DSM-5 (see below for details).

Diagnostic criteria

DSM-IV Criteria of Autistic Disorder and Asperger Disorder

See Tables 15.7 and 15.8.

TABLE 15.7 DSM-IV Criteria for Autistic Disorder

A. Three domains: ≥ 6 items from 3 categories

Category 1: **Impaired social interaction** (≥ 2 items)	Marked impairment in use of multiple nonverbal gestures (eye contact, facial expression, body posture, gestures regulating social interaction)
	Failure to develop appropriate peer relationships
	Does not spontaneously seek to share enjoyment, interests, or achievements with others (lack of showing, bringing, pointing)
	Lack of social or emotional reciprocity
Category 2: **Impaired communication** (≥ 1 item)	Delay/failure to develop spoken language
	If speech developed, impaired ability to initiate/sustain conversation
	Stereotyped and repetitive use of language or idiosyncratic language
	No developmentally appropriate, varied, spontaneous, make-believe play or social imitative play
Category 3: **Restricted, repetitive, stereotyped patterns** of behavior, interests, and activities (≥ 1 item)	≥ One stereotyped and restricted pattern of interest, abnormal in either intensity or focus
	Inflexible adherence to specific, nonfunctional routines or rituals
	Stereotyped and repetitive motor mannerisms (e.g., hand flapping)
	Persistent preoccupation with parts of objects
B. Onset Delay or abnormal function in ≥ one area with onset <3 y	Social interaction
	Language for social communication
	Symbolic or imaginative play
C. Exclusion criteria	Not better accounted for by Rett disorder or childhood disintegrative disorder

From American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, 4th ed, Text Revision (DSM-IV-TR).* Washington, DC: American Psychiatric Association; 2000.

TABLE 15.8 DSM-IV Criteria for Asperger Disorder

A. Two domains: ≥ 3 items from 2 categories

Category 1: **Impaired social interaction** (≥ 2 items)	Marked impairment in use of multiple nonverbal gestures (eye contact, facial expression, body posture, gestures regulating social interaction) Failure to develop appropriate peer relationships Does not spontaneously seek to share enjoyment, interests, or achievements with others (lack of showing, bringing, pointing) Lack of social or emotional reciprocity
Category 2: **Restricted, repetitive, stereotyped patterns** of behavior, interests, & activities (≥ 1 item)	≥ One stereotyped and restricted pattern of interest, abnormal in either intensity or focus Inflexible adherence to specific, nonfunctional routines or rituals Stereotyped and repetitive motor mannerisms (e.g., hand flapping) Persistent preoccupation with parts of objects
B. Impairment Criteria	Causes significant impairment in social, occupational, or other areas of functioning
C. Exclusion criteria (all of the following)	No clinically significant general delay in language No clinically significant delay in cognitive development of age-appropriate self-help skills, adaptive behavior (other than social interaction), and curiosity about the environment in childhood Criteria not met for other PDD or schizophrenia

From American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, 4th ed, Text Revision (DSM-IV-TR).* Washington, DC: American Psychiatric Association; 2000.

DSM-5 Criteria Changes for ASD[41–43]

1. **Category:** PDD category will be eliminated and everything now under diagnostic category of "autism spectrum disorder."
2. **Disorders included:** Rett syndrome will be separate disorder, no longer classified as an ASD. CDD will be eliminated entirely. Asperger, PDD–NOS, and autistic disorder will be collapsed under single diagnosis of ASD.
3. **Domains:** Change from three domains to two domains, with social impairment and communication impairment collapsed into one domain of "social communication" impairment. Second domain is restricted and repetitive behavior (RRB).
4. **New sensory symptom:** New symptom added to RRB domain to describe hyper-/hyporeactivity to sensory input.
5. **Age of onset:** Removal of criteria for onset <3 y.
6. **Severity:** ASD will have descriptor of one of three levels of severity.
7. **Diagnostic specifiers:** Describe pattern of onset/clinical course (e.g., loss of skills), etiologic factors (e.g., known genetic syndrome such as Rett), level of language or intellectual disability, associated medical conditions (e.g., seizures, anxiety, GI problems).
8. **Social communication disorder**: New diagnosis, separate from ASD, to account for impairment in social communication without restricted/repetitive behaviors (Table 15.9).

TABLE 15.9 Proposed DSM-5 Criteria for ASD

Two Domains	
A. Category 1: Impaired **social communication** (must have all 3 items)	Deficits in social–emotional reciprocity Deficits in nonverbal communicative behaviors used for social interaction Deficits in developing and maintaining relationships appropriate to developmental level
B. Category 2: **Restricted, repetitive, stereotyped patterns** of behavior, interests, and activities (≥ 2 items)	Stereotyped or repetitive speech, motor movements, or use of objects Excessive adherence to routines, ritualized patterns of verbal or nonverbal behavior, or excessive resistance to change. Highly restricted, fixated interests abnormal in intensity or focus Hyper- or hyporeactivity to sensory input or unusual interest in sensory aspects of environment (e.g., indifference to pain/heat/cold, excessive smelling/touching objects, adverse response to specific sounds/textures, fascination with lights/spinning objects)
C. Onset	Symptoms must be present in early childhood but may not become fully manifest until social demands exceed limited capacities
D. Impairment	Symptoms together limit and impair everyday functioning
Severity levels	Level 1: Requiring support Level 2: Requiring substantial support Level 3: Requiring very substantial support

From http://www.autismsupportnetwork.com/news/proposed-dsm-5-changes-regard-asd-3478294.

Recent study evaluated **sensitivity and specificity of DSM-5** criteria for identifying DSM-IV PDD diagnoses by matching DSM-5 criteria to parent report measure (ADI-R) and/or clinical observation (using ADOS). Just using parent report measure, DSM-5 identified 91% of DSM-IV PDDs, and specificity of DSM-5 was 0.53 overall, compared to DSM-IV specificity range of 0.24 for PDD-NOS and 0.53 for autistic disorder. DSM-5 specificity increased to 0.63 when requiring both parent report and clinical observation.[44]

Epidemiology

- Autism and Developmental Disabilities Monitoring (ADDM) Network evaluated records from 14 sites across the US for children 8 yo (age of peak prevalence) for presence of an ASD (including autistic disorder, PDD–NOS, and Asperger). Overall estimated prevalence in 2008 was 11.3 per 1,000 children: 1 in 54 boys and 1 in 252 girls (4.5 to 1, male to female). Increase from 9 per 1,000 in 2006 and 6.4 per 1,000 in 2002.[45]
- National Survey of Children's Health telephone survey of parent-reported ASD in ages 6 to 17 y found similar results in 2007 of 11 per 1,000 and found another increase to 20 per 1,000 in 2011 to 2012.[46]
- Unclear if increase in prevalence due to better awareness and access to services vs. true increase in prevalence.
- Male to female ratio ranges from 2:1 to 6.5:1.[47]

Clinical Presentation

(See Diagnostic Criteria above for specific details) no reliable/consistent markers in children <12 mo, significant clinical heterogeneity.

Red Flags

- Signs that should alert the pediatric neurologist to a possibility of ASD include poor eye contact, lack of pointing or looking where a caregiver points (impaired joint attention), delayed language development or atypical language that is not used for reciprocal communication (echolalia, difficulty with conversations, lack of first-person pronouns), stereotyped or even self-injurious motor mannerisms (hand flapping, spinning, head banging), preoccupation with parts of objects (the wheels of toy cars or other spinning objects, lights, water) or intense restricted interests (Thomas the Train, dinosaurs, the weather), lack of imitation, preference to play alone, lack of pretend play (should have this by age 2 y), notable difficulty with transitions or deviations from known routine, sensory sensitivities (oversensitive to certain sounds or textures such as tags on clothing or particular foods). Often have "uneven" skills—delayed in some areas and advanced in others.
- American Academy of Neurology (AAN) and Child Neurology Society (CNS) Practice Parameters provide absolute red flags that warrant immediate evaluation[48]: no babbling, pointing, or other gestures by 12 mo; no single words by 16 mo; no two-word spontaneous (not echolalic) phrases by 24 mo; ANY loss of ANY language or social skills at ANY age.

Associated Clinical Features[45,47]

Sensory

Sensory symptoms common. Include hypo- and hypersensitivities, even within same modality (e.g., hypersensitive to particular noises/sounds but appear hyposensitive to human voices, hyposensitive to pain but hypersensitive to soft touch). Being added to DSM-5 criteria (see above).

Motor

Often display motor "clumsiness." May include impaired coordination, dyspraxias, or hypotonia.

Activity Level and Attention

Some patients appear hypoactive and withdrawn. Some appear hyperactive and meet criteria for ADHD (although DSM-IV criteria exclude diagnosis of ADHD in ASD; this has changed in DSM-5; see ADHD section of this chapter for details).

Intellectual Disability

Per ADDM Network data from 2008, 38% have IQ ≤70, 24% have borderline range with IQ 71 to 85, and 38% have IQ >85.

Regression

Approximately 25% to 30% develop language and then show regression, usually between 15 and 24 mo. May also have loss of nonverbal communication (waving, pointing) and social skills, can be gradual or sudden. Be careful not

to attribute regression to environmental stressor, which can delay diagnostic workup for ASD.

Macrocephaly

Children with ASD typically have normal- to below-average–head circumference (HC) at birth but then show increased head growth during 1st year, leading to above-average HC or macrocephaly. About 20% to 30% of children with ASD have macrocephaly (>2 SD above mean). This declines into adulthood suggesting decelerated brain growth after childhood.

Seizures

Increased risk of seizures. Review study found epilepsy in 1.8% if no intellectual disability and <12 yo, 6.1% if <12 y with intellectual disability, 8.9% if >12 y and no intellectual disability, and 23.7% if >12 y with intellectual disability.[49] Children with ASD are also known to have higher rate of abnormalities on EEG without clinical seizures and may often have "seizure-like" events with no epileptic EEG correlate.[50,51]

GI

GI conditions are commonly seen in ASD; most common are constipation, abdominal pain with or without diarrhea and encopresis; also GERD and inflammation along GI tract. Symptoms can present as behavioral changes such as insomnia, self-injurious behaviors, PICA, and irritability.[52]

Sleep

Sleep problems seen in 40% to 86% of children with ASD; higher than in children with other developmental delays. Problems due in part to difficulties falling asleep, anxiety, wakefulness during the night.[53] Insomnia possibly due to core behavioral problems in ASD and/or associated comorbidities (psychiatric disorders, epilepsy, GI problems, sleep-disordered breathing). Multiple studies have shown problems with melatonin production/regulation. Melatonin supplementation may provide benefit.[54]

Psychiatric

Often have coexisting psychiatric conditions that interfere with functioning including anxiety, depression, ADHD (DSM-5 criteria changing to allow diagnosis in ASD), irritability, and agitation. OCD can be difficult to distinguish given the behavioral rigidity and adherence to routines and rituals found in ASD and OCD.

Associated Conditions[47]

Genetic syndrome or medical disorder is associated with ASDs in <10%, unclear if causative or associated. Includes: Fragile X (most common known genetic cause of autistic disorder), tuberous sclerosis, Angelman syndrome, Rett syndrome, Smith–Lemli–Opitz syndrome, Down syndrome (6%–7% meet ASD criteria despite typical Down's character of relatively intact social skills), CHARGE syndrome (almost 50% meet criteria for an ASD), fetal alcohol syndrome, PKU (now rare due to newborn screening).

Proposed Pathophysiologies and Etiologies[47]

Exact cause remains unknown and likely multifactorial. **Genetic** studies show recurrence risk 2% to 8% if older sibling with ASD; increases if 2 older siblings with ASD. No single **environmental factor** has been implicated but might interact with certain genetic risk factors to influence expression of ASD. **Functional neuroimaging** studies have shown disruptions

in connectivity of various neural networks using fMRI. The mirror neuron system has been implicated by some to explain deficits in empathy. **Brain volumetric studies** and **neuropathology** demonstrate increased overall brain size, regional gray and white matter volume differences, and abnormalities in sulcal and gyral anatomy. Abnormalities in serotonin synthesis have also been shown in ASD children.

Immunizations

While there may be an immunological role in autism, there is yet *no scientific evidence* supporting vaccines as a causal factor in autism.

- Concern regarding link between MMR vaccine and ASD arose after study in 1998 reportedly showed association between GI symptoms, MMR vaccine, and PDDs.[55] This report was later retracted and exposed as fraudulent.[56,57]
- Concern regarding thimerosal-containing vaccines arose after the FDA released a statement that the potential cumulative dose of ethyl mercury (the compound in the preservative thimerosal) from multiple visits might exceed the max methyl mercury recommended by the EPA. However, no evidence existed that neurotoxicity arose from the small amount of ethyl mercury in vaccines, and ethyl mercury does not cross the blood–brain barrier (unlike methyl mercury). Many large studies have subsequently found no evidence between autism and thimerosal vaccines.[58]
- The Institute of Medicine's Immunization Safety Review Committee reviewed published and unpublished epidemiologic and biologic studies and concluded that evidence favors rejection of a causal relationship between MMR vaccine and autism and between thimerosal-containing vaccines and autism.[59]
- However, a public misperception remains that vaccines cause autism; a parent survey in 2006 showed that 54% believed their child's ASD to be due to immunizations[60] despite the fact that a proposed relationship between autism and MMR/thimerosal-containing vaccines has been disproven.

Diagnostic Workup

American Academy of Pediatrics (AAP) Policy Statement[47]

ASD-specific screening should be performed on any child at risk (defined as $\geq$1 of following: sibling with ASD, parent concern, other caregiver concern, pediatrician concern) and on ALL children at 18 and 24 mo (to identify those who may regress after 18 mo) well child checks.

AAN/CNS Practice Parameters[48]

recommend two levels of investigation: (1) Routine developmental surveillance and screening specifically for autism to identify children at risk of atypical development and those at risk specifically for autism. (2) Diagnose and evaluate autism and differentiate from other developmental disorders.

Diagnosis of Autism

1. **Clinical examination** for DSM-IV or DSM-5 criteria for ASD.
2. **Screening tests/scales:**
   - Level-1 screens: used at 18 and 24 mo if no risk factors. Include Modified Checklist for Autism in Toddlers (M-CHAT/CHAT), PPD Screening Test-II, Primary Care Screener (PDDST-II PCS), and others.

- Level-2 screens: used to differentiate risk of ASD from other developmental disorders. Include Asperger Syndrome Diagnostic Scale (ASDS), Autism Behavior Checklist (ABC), Autism Quotient–Adolescent Version, Gilliam Asperger Disorder Scale (GADS), Gilliam Autism Rating Scale 2 (GARS-2).
- **Autism Diagnostic Observation Schedule (ADOS)** and **Autism Diagnostic Interview—Revised (ADI-R)** are considered "gold standard" but not typically used by pediatric neurologists in clinic due to length/time involved; these are more directed toward research. Neuropsychologists and developmental pediatricians may use the ADOS.

3. **History and Neurologic Exam**: History should include perinatal and developmental history including regression, encephalopathy, attention issues, seizure, depression/mania, behavior dysregulation, eating problems, sleep. Exam should include longitudinal HC, presence of dysmorphic features, neurocutaneous abnormalities (e.g., Wood's lamp for hypopigmented macules), verbal and nonverbal language, and play.

Differentiate from Other Disorders[48]

- **Audiology assessment:** Including behavioral audiometric measures, middle ear function assessment, and electrophysiologic procedures.
- **Lead screening:** If pica.
- **Genetic testing:** Fragile X and chromosomal microarray,[61] MECP2 testing for Rett Syndrome in girls with microcephaly, PTEN if microcephaly.
- **Selective metabolic testing:** If suspicious clinical features (e.g., lethargy, cyclic vomiting, early seizures, dysmorphic/coarse features, MR, questionable newborn screening).
- **Sleep-deprived EEG:** If clinical seizures or suspicion of subclinical seizures and history regression; should include slow wave sleep; EEG is not routinely recommended children with autism.
- **Neuroimaging:** Not recommended routinely for autism even with megalencephaly.
- **Not routinely recommended:** Thyroid studies, celiac Abs, allergy testing, immunologic testing, hair analysis, vitamin/micronutrient testing, intestinal permeability studies, mitochondrial testing (including lactate, pyruvate), stool analysis, urine peptides.

Management[62]

Behavioral and Educational Therapies (Table 15.10)

Program intervention is recommended as soon as diagnosis is made. Early intensive programs may result in substantially better outcomes.[63] Recommend:

- Year-round programs and services for 25 h/wk, including year-round developmentally appropriate educational programs.
- School programs should be individualized to address specific objectives for learning.
- School program classrooms with low student/teacher ratio, if not 1:1 ratio.
- Home-based program in addition to school program to help with generalization of school-based learning to home and community.

TABLE 15.10 Alphabet Soup of More Common Therapies for Children with Autism

Abbreviation	Name	Type of therapy
ABA	Applied Behavior Analysis	Systematic approach to change behavior by looking at how behavior & environment interact; uses learning theory; employs measurements of behavior, positive reinforcement and other behavioral principles; variety of techniques fall within realm of ABA
DTT	Discrete Trial Training (Lovaas therapy)	Type of ABA, highly structured, used in young children to teach attention, imitation, compliance, and emotional and socialization and language skills
ESDM	Early Start Denver Model	Comprehensive behavioral early intervention model using a developmental curriculum delivered by therapy teams and/or parents; uses ABA techniques
FBA	Functional Behavior Analysis	Assessment to determine antecedents of unwanted behaviors
DIR	Developmental, Individual-difference, Relationship-based model (Greenspan Technique)	"Floor-time"; play-based therapy to help children expand their "circle of communication" by meeting the child at his developmental level. Addresses development through focus on emotional development
TEACCH	Treatment and Education of Autistic and related Communication handicapped Children	Emphasizes a highly structured and predictable classroom environment and the use of visual learning

From http://www.autismspeaks.org. Myers SM, Johnson CP; American Academy of Pediatrics Council on Children with Disabilities. Management of children with autism spectrum disorders. *Pediatrics*. 2007;120(5):1162–1182.

- Social pragmatic program and inclusion based on child's ability to interact with and tolerate typical peers.
- Goals of educational programs: spontaneous communication, social skills (including play skills), adaptive functioning in home and community (including self-help skills), academic learning, generalize skills to different areas.

Speech therapy: Recommended year-round to help with communication and development of functional language. **Occupational therapy:** To help with fine motor skills and desensitization of hypo- or hypersensitivities to touch/smell/taste/vestibular sensation (sensory integration dysfunction).[64] **Physical therapy:** For hypotonia (common), poor coordination, and stretching of heel cords if tight (seen in toe walkers). **Augmentative and Alternative Communication (AAC) therapy:** To improve communication through picture exchange communication system (PECS) and now sophisticated computer devices.[65] **Social skills therapy:** Teach joint attention and reciprocal social interaction in a controlled setting, which is then generalized to other environments.[66] Social stories can help both with learning social skills and to reduce anxiety (Carol Gray's books on social stories are helpful).

Medications

No agent for core symptoms of ASD is approved by FDA. Drugs approved for associated symptoms such as aggression/irritability, attention, cognition, and RRBs. Focus therapy on specific symptoms:

- **Aggression/irritability/self-injury:** Atypical antipsychotics (esp. risperidone), α-agonists (clonidine, guanfacine), β-blockers (e.g., propranolol), mood stabilizers (valproic acid, topiramate)
- **Anxiety/RRBs/behavioral rigidity:** SSRIs, buspirone, mirtazapine
- **Hyperactivity/impulsivity/ADHD:** α-agonists and stimulants
- **Sleep disorders:** Melatonin, α-agonists, mirtazapine, trazodone

Anecdotal Therapies

Dietary

Gluten-free and casein-free diet, specific carbohydrate diet (gluten free and low sugar) offer anecdotal but not evidence-based improvements. Ensure adequate calcium and vit. D intake if on diet.

Complementary and Alternative Medicine (CAM)

Often tried by parents but not always reported to physician; treatments used but currently lacking scientific evidence include diets, dimethylglycine, hyperbaric oxygen therapy, vitamins, worm therapies, omega-3 fatty acids, IV chelation of heavy metals (particularly dangerous and unproven), antifungals/antivirals.

Transition to Adulthood

Issues include legal and financial guardianship, vocational, community programs and residential support. Various online resources can be found at Lurie Center and Autism Speaks. Families should also contact their individual state's Dept of Health and Human Services, Mental Health and Mental Retardation, and/or developmental disabilities organization.

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ONLINE RESOURCES

www.neurosymptoms.org – An excellent resource for patients and clinicians, gives specific information about somatoform symptoms and provides resources for treatment and patient support.

www.ADHDMedicationGuide.com

www.nichq.org (ADHD Toolkit)

www.schoolpsychiatry.org

Autism Consortium – www.autismconsortium.org

Autism Speaks – www.autismspeaks.org

First Signs – www.firstsigns.org

Lurie Center for Autism – www.luriecenter.org

Tourette Syndrome Association – www.tsa-usa.org

16 Pediatric Movement Disorders and Ataxia

Jeff Waugh and Nutan Sharma

PEDIATRIC MOVEMENT DISORDERS

Introduction

Movement disorders are clinically defined by the inability to execute skilled motor plans due to deficient targeting and/or timing. They are dynamic disorders, shifting in severity or distribution over time, distinguished from paresis, spasticity, other sequelae of corticospinal tract injury. Classically thought to arise from basal ganglia (BG) injury, now appreciated that lesion of any node within the motor control network (BG, cortex, internal capsule, thalamus, brainstem, cerebellum)[1] can produce a movement disorder. The concept of a lesion to a network, rather than to a discrete anatomical site, now informs much of the current understanding of the origins of movement disorders.

Taxonomy

Childhood movement disorders are diverse in appearance, timing, etiology, treatment, and prognosis; a systematic approach is required. Essential clues to diagnosis:

DISTRIBUTION: (1) Focal: Only one body part/region. **(2) Segmental:** ≥2 contiguous regions. **(3) Multifocal:** ≥2 noncontiguous regions. **(4) Generalized:** Legs, trunk, and ≥1 other region.

TIMING: Paroxysmal vs. static, progressive, characteristic ages of onset, rate of progression.

NATURE OF MOVEMENT: Hyperkinetic, hypokinetic, or ataxic.

ELLICITING/EXACERBATING FACTORS: Arise from rest, standing, with all movement, or only with skilled movement? Time of day? Worsened or improved with alcohol, caffeine, meds? (see Table 16.1.)

Chorea

Definition

Irregular, quick, continuous movement that may flow from one body part to another, often described as dance-like. Often incorporated into voluntary actions but cannot be resisted or suppressed. Most childhood chorea is secondary to injury, although rare genetic causes should be considered. **Athetosis:** Slower, writhing form of chorea. **Ballismus:** Forceful, flinging form of chorea; proximal > distal muscles, typically unilateral, often coexists with chorea.

Pathophysiology

Injury to basal ganglia, especially the striatal indirect pathway, is a common anatomic precipitant for many cases of chorea. The neurophysiology underlying chorea remains a mystery.

TABLE 16.1 Tips in Evaluating a Child with Abnormal Movements

1. If a picture is worth a **1,000** words a video is worth a million.
2. Many movement disorders are coexpressed with other movement disorders. Focus on each type of movement in turn describing it first in isolation. Look for interactions among the movements—e.g., tremor only in a dystonic limb or myoclonus of such severity that it masquerades as ataxia.
3. Watch for abnormal behaviors that are used to mask abnormal movements—incorporation into normal movements strange postures sensory tricks sitting on hands with chorea or akathisia.

Causes

Static injury: Kernicterus, hypoxic-ischemic insult, toxin (ethanol, methanol, toluene, bismuth, manganese, thallium, mercury), infections (mycoplasma, Lyme, legionella, toxo, HIV, HSV, measles, mumps, varicella, parvovirus B19), trauma, midline CNS malformation disorders. **Autoimmune/inflammatory:** Sydenham chorea (see below), SLE, anti-phospholipid antibody syndrome (APLS), Behçet syndrome, ADEM, CNS vasculitis, Rasmussen encephalitis, MS (rare symptom), acute necrotizing encephalopathy (late finding). **Endocrine/nutritional:** Hyper/hypoglycemia, hyper/hyponatremia, hyperthyroidism, hypoparathyroidism, hypoMg, B_{12} deficiency in infancy, chorea gravidarum. **Medications:** DA agonists, DA antagonists, AEDs (phenytoin, carbamazepine, PHB), calcium channel blockers (CCBs), anticholinergics, antihistamines, OCPs, lithium. **Neurodegenerative:** Huntington disease (HD), Wilson disease (WD) (see below), neuroacanthocytosis, Lesch–Nyhan, ataxia telangiectasia, mitochondrial disease (Leigh syndrome), PKAN, SCA, DRPLA, Fahr syndrome, leukodystrophy (Pelizaeus–Merzbacher disease). **Metabolic syndromes:** Glutaric acidemia, propionic acidemia, homocystinuria, PKU, Costeff syndrome (3-methylglutaconic aciduria), cerebral folate deficiency, sulfite oxidase deficiency, pyruvate carboxylase deficiency, biotinidase deficiency. **Structural lesions:** Tumor, CNS lymphoma, abscess, AVM, cavernous hemangioma. **Paroxysmal dyskinesias:** See later in this chapter.

Diagnosis

Signs of motor impersistence are most reliable: milkmaid's grip, touchdown sign (arms upright, palms in), harlequin tongue. Distinguish from **akathisia** (inner restlessness) and **tics** (repetitive, internal drive). **MRI:** Often indicated, especially in hemichorea or with focal neurologic signs. **Labs:** ASLO, anti-DNAse B, helpful in establishing a diagnosis of Sydenham chorea, but unreliable at predicting duration, progression, or recurrence. Chorea can herald a treatable disorder (*e.g.*, the antiphospholipid antibody syndrome), offering opportunity to prevent later disease progression.

Primary Chorea

Isolated chorea independent of a predisposing injury or toxic exposure; presumed to be genetic. Multigenerational family history is essential.

BENIGN HEREDITARY CHOREA (BHC): Occurs in normally developing children, 1st 5 y of life, nonprogressive after 1st decade. Generally improves (but not resolved) in adulthood. Does not impact intellect/behavior. Dominantly inherited, intra-familial heterogeneity; some carriers display athetosis, myoclonus or dystonia ± chorea.

HUNTINGTON DISEASE (HD): Most common genetic cause of chorea. **Genetics:** Dominantly inherited, anticipation secondary to CAG repeat expansion. **Pathology:** Degeneration of striatal medium spiny neurons. **Juvenile HD:** In <10% of cases (~1:10^5). Onset age <20 y, with school failure, depression, and attention deficits before chorea. Few teens, but most children <10 y develop the *Westphal variant:* dementia, parkinsonism, seizures, and dystonia as primary features. Children with HD progress much faster than adults. Most juvenile HD inherited through paternal lineage. May become symptomatic before fathers in cases of unusually large repeat expansion (see HD under "Parkinsonism" later in the chapter.)

Secondary Chorea

Resulting from outside injury. Five "I's" can lead to acute or semi-acute chorea or predispose to development of chorea months/years later: injury, infarction, infection, inflammation, and infiltrative processes.

SYDENHAM CHOREA (SC): Major criterion for rheumatic fever (RF) may be 1st/only manifestation, self-limited. **Pathophysiology:** Autoimmune, anti-basal ganglia antibodies follow group A β-hemolytic strep infection. **Epidemiology:** Most common acute chorea in children, almost never below 5 y, uncommon beyond puberty, F > M. 20% kids with RF get SC. Now rare in North America/Europe, given widespread antibiotic use. Diagnosed at pediatric centers 5 to 10 times/y. **Presentation:** SC can follow strep infection by up to 6 mo, often asymmetric, signs of motor impersistence (spooning of fingers, harlequin tongue, milkmaid's grip, touchdown sign) indistinct from other choreas. Important distinguishing features of SC are age and rapid-onset over hours/few days. Other neurologic signs less severe but common: hypotonia, akathisia, dysarthria, gait disturbance, personality change, emotional lability. ~20% develop attention deficits and/or OCD. **Diagnosis:** Clinical dx—does not require supportive testing. MRI indicated to rule out mass lesions, may have increased volume & T2 signal in basal ganglia. Throat cultures, ESR, CRP, ASLO, anti-DNAse B all have low sensitivity/specificity and may be negative at onset (since may be 6 mo s/p strep infection); sometimes useful if dx uncertain. Trending values does *not* improve diagnosis/predictive value. **Management:** Prevent recurrent SC with antibiotic prophylaxis, thorough screening for other RF sx. Treatment for mild SC debated since natural history is fluctuating improvement. Immunosuppression likely shortens course (prednisone if mild, IVIG if moderate-severe). Suppress chorea with benzodiazepines or valproate. **Prognosis:** Chorea resolves <6 mo in 50%; can take up to 2 y; permanent in rare cases. Recurs with subsequent strep infection in ⅓. 75% women with SC as child have recurrence with pregnancy or OCPs. Mild executive function deficits and bradykinesia are common into adulthood even if chorea resolved.

LUPUS-ASSOCIATED CHOREA: Uncommon complication of SLE, associated with anti-cardiolipin Ab or ischemia.[2] Chorea is 1st manifestation in majority of SLE with chorea. Consider in DDX of any new-onset chorea. Early diagnosis and treatment critical to limiting scope of disease.

POST-PUMP CHOREA: Very small fractions of patients develop persistent chorea after cardiac bypass or resuscitation. **Epidemiology:** Most common in patients <1 y but reported throughout the life span. **Predictors:** Longer hypothermia, esophageal temp <20°C, use of pH-labile intraoperative management, preop developmental delays. **Pathology:** Loss of neurons & myelinated axons essentially restricted to the globus pallidus. **Long-term sequelae:** Substantial—50% with persistent dyskinetic movements, all suffer cognitive impairment,[3] less common with improving cardiac anesthesia/bypass techniques.

Tremor

Definition

Any regular oscillation about a joint or plane. Frequency can vary with change of position or type of movement, but otherwise should remain constant. Must distinguish from movements that are semi-regular but better explained by another movement disorder (myoclonus can be semi-rhythmic; tremor in dystonic limb is secondary symptom of dystonia).

Pathophysiology

Can arise from cortex, basal ganglia, brainstem, cerebellum, or periphery—each location associated with distinct tremor distributions, frequencies, and eliciting factors (see Table 16.2). At least 3 distinct mechanisms: (1) Focal weakness with imbalance of agonist–antagonist muscles; (2) failure at fine-tuning a movement (with impaired cerebellar compare-and-correct functions); (3) dominance of nuclei that discharge in rhythmic patterns as part of normal mode of operation (thalamus, inferior olive, portions of basal ganglia, "central oscillators" that underlie orthostatic tremor), many of which are defined functionally but not yet anatomically.

TABLE 16.2 Types of Tremor

Tremor Type	Description	Anatomical Origin
Rest tremor	Attenuates or resolves with movement or antigravity strength. Worsens with agitation or inattention.	Basal ganglia, especially substantia nigra
Action tremor	Elicited by initiating movement or increasing force generated. Four subtypes.	
1. Kinetic tremor	Occurs relatively uniformly with all types of volitional movement.	
2. Intention tremor	May emerge or worsen as the movement approaches completion—the stage at which finest tuning is required. Finger–nose–finger task demonstrates this tremor.	Cerebellum, rarely parietal, or their connections
3. Isometric tremor	Produced by increasing force against a fixed target, without movement.	
4. Postural tremor	Occurs when holding a body part in a fixed position, resisting gravity.	Cerebello-olivary system
Rubral tremor	Coarse, jerky, irregular, large amplitude, low frequency. Combines rest and intention tremor (Holmes tremor or midbrain tremor).	Upper brainstem, thalamus, cerebellum
Physiologic tremor	Enhancement of normal motor oscillations with stressors. Nonpathologic. Seen only with particular situational challenges, *e.g.,* stress, caffeine, fatigue.	
Psychogenic tremor	Variability in tremor frequency, amplitude, distribution, and direction. Usually acute in onset but nonprogressive. Frequently distractable and demonstrates entrainment. The most common type of psychogenic movement disorder in both children and adults.	

Demographics

10% to 20% of children referred to movement disorders clinics. Frequent inpatient consult—often emerges in systemically ill or heavily medicated child, usually as one of many symptoms.

Diagnosis

Goal: Identification of body parts involved, presence at rest or with movement, eliciting/relieving factors. 1st step in evaluating child with tremor is casual observation, then proceed to movements that elicit the symptom. Ensure all limbs and trunk are visually accessible during all parts of evaluation, ask for videos (see Table 16.2).

Primary Tremor

Few conditions may produce tremor or tremor-like phenomena in children without other neurological symptoms. Many have self-limited, developmental conditions not requiring treatment; others are lifelong with predictable course.

DEVLOPMENTAL CONDITIONS: Developing motor control network occasionally produces paroxysmal and rhythmic benign movements. FH and exam are normal. Clinical diagnosis, but capturing events on EEG often provides reassurance for parent/physician. Resolution with normal neurodevelopment expected. **Jitteriness:** Symmetric, rhythmic oscillations involving arms, legs, or both. Occurs in 50% term infants in 1st wk of life. May reflect immaturity of spinal inhibitory pathways. Varies with arousal, often exacerbated by stimulation or crying, typically resolves in quietly awake state, suppressible with gentle pressure, passive manipulation of limb. Seen in normal and neurologically injured children. **Shuddering attacks:** Appear similar to shivering, last a few seconds, occur many times a day without provocation. Typically involve body above the diaphragm; onset 3 mo to 4 y, most common between 6 and 18 mo, duration typically few months to few years. **Spasmus nutans (SN):** 1 to 3 Hz oscillation of the head, either horizontal or vertical plane, onset between 6 and 12 mo, coexists with high-frequency pendular nystagmus. Postulated that head movements are compensatory for nystagmus. Head movements typically resolve within few months. Subclinical nystagmus persists several years, usually resolves. Rarely, SN-like pattern of head movement seen in patients with vision compromise, congenital nystagmus, or intracranial mass lesion—close observation and ophthalmologic evaluation are indicated.

ESSENTIAL TREMOR (ET): Epidemiology: Most common movement disorder in adults, ~4% of all adults at 40 y. Childhood onset (mean, 6–7 y). Two peaks of referral: school-age children: tremor produces anxiety in parents; late adolescence: tremor leads to social or sports-related anxiety. M = F in adults, M > F in childhood. **Genetics:** Dominantly inherited, variable severity and age of onset within family. Penetrance is 100% by 60 y. **Presentation/Clinical course:** In children, typically mixed postural and action tremor affecting hands >> legs, neck, or voice.[4] Always bilateral, may be moderately asymmetric, elicited, or exacerbated by stress, very slowly progressive (years to decades). **Support diagnosis:** Strong FH, adult family members report relief with moderate alcohol ingestion, normal development, and otherwise normal neurologic exam. **Question diagnosis:** Tremor sufficient to produce disability, presence of any other neurologic diagnosis or sign, progression within 1 to 2 y observation period.

Secondary Tremor

Very common neurologic symptom, consequence of many systemic diseases/CNS insults,[4] tremor unlikely to contribute substantially to diagnosis. Tremor

that is progressive in distribution/severity, or which causes substantial disability, is likely secondary to degenerative disease or injury and requires MRI.

POSTTRAUMATIC: Tremor occurs in >50% survivors of severe head trauma in children, may present immediately after injury or develop many months later, well into rehab. Resolves spontaneously in >50%.

BOBBLE-HEAD DOLL SYNDROME: 2 to 3 Hz bobbing of the head, usually in vertical plane ("yes–yes"), occasionally in horizontal plane ("no–no"); voluntarily suppressible, often accentuated by rhythmic motor activity (e.g., walking). Typical onset 2 to 5 y. Can be associated with mass lesions in 3rd ventricle or cerebral aqueduct with hydrocephalus. Occasionally seen in children with cerebellar malformations but no mass or hydrocephalus.

DRUG-INDUCED: Tremor not likely a late effect—consider new/changed medications first. Culprits: Stimulants, bronchodilators, thyroid hormone, corticosteroids. Dopamine depleting/blocking agents can produce rest tremor and parkinsonism. Valproate, lithium, SSRIs, tricyclic antidepressants, and cyclosporine can produce variable (commonly intention) tremor.

Treatment

Aimed at symptom relief since tremor mechanisms poorly understood. **First-line:** Propranolol 40 to 60 mg/d. **Second-line:** Primidone, topiramate, short-acting benzodiazepines (for acute stressors, not for daily symptoms). **Botulinum toxin** injection of affected muscles effective in head and voice tremors, less so in hand tremor, limiting utility in children.

Tics

Though tics have been regarded to be the most common movement disorder in children, this is a misconception, as the abnormality is the intense drive or impulse to act, not the movement itself. Historically they have been managed by general or behavioral neurology (see Chapter 15).

Myoclonus

DEFINITION: Brief, involuntary muscle jerk, nonsuppressible and generally no premonitory features, may be isolated finding or symptom of many diseases. Uncommon as isolated movement disorder in children—should always prompt evaluation for epileptic myoclonus.

Diagnosis

Considerations in evaluation.

EPILEPTIC VS. NONEPILEPTIC: **Suggestive of epileptic myoclonus** (see Chapter 5 for details): adolescent-onset, occurs just after waking; onset at 2 to 3 y with rapid evolution of multiple seizure types; onset in neonatal period; any alteration of consciousness with episodes. **EEG** is reasonable but nonobligatory. **EMG** of great value if uncertain etiology—distinguishes myoclonus vs. myoclonic seizures, negative myoclonus vs. astatic seizures, psychogenic vs. organically generated.

PRIMARY VS. SECONDARY: Myoclonus in isolation: Rare, suggests small/distinct DDX. **Secondary:** Follows traumatic or hypoxic CNS injury, or as part of larger cognitive/functional decline. *Metabolic encephalopathies:* Hepatic failure, uremia, metabolic alkalosis, hypercarbia, hyperglycemia. *Toxins:* Licorice, antacids, carbon monoxide, lithium, lead, mercury, bismuth, tetanus, acetone, toluene, organophosphate pesticides.

COINCIDENT WITH OTHER NEURO DISORDERS: Feature of neurodegenerative disorders and epilepsy syndromes. Prognosis/treatment based on unifying diagnosis, not on myoclonus.

ANATOMIC ORIGIN: Very useful for diagnosis and treatment, imaging sometimes helpful, careful exam more likely to localize. **(1) Cortical:** Most common, originates from sensorimotor cortex. Focal, distal, arrhythmic, affects arms > legs or trunk, spontaneous or induced by reflex or action. *Examples:* progressive myoclonic epilepsies, celiac disease, Angelman syndrome, Huntington disease, Rett syndrome, Gaucher disease, CJD, HIV encephalopathy, metabolic or toxic conditions. **(2) Subcortical:** Often consequence of anoxic or metabolic injury to thalamus/brainstem. Proximal and distal generalized, agonist and antagonist muscle groups, stimulus sensitive. *Examples:* hyperekplexia, palatal myoclonus, myoclonus-dystonia. **(3) Spinal:** Usually from thoracic generator, duration longer, more variable than cortical/subcortical myoclonus. Slow (<4 Hz), bilateral, and rhythmic not usually stimulus sensitive, often persists during sleep. *Examples:* Often a focal lesion—inflammatory plaque, syringomyelia, trauma, ischemic myelopathy, or infection. **(4) Peripheral:** Lesions of peripheral nerves alter sensory input, induce central reorganization. Typically arrhythmic jerks, not usually stimulus-sensitive. May persist during sleep. *Example:* Most common is hemifacial spasm.

Physiologic Myoclonus

Actually much more common than pathologic symptom of epilepsy or neurodegenerative disease. *Examples:* hiccups, eyebrow twitch, hypnic jerks.

BENIGN NEONATAL SLEEP MYOCLONUS: Onset late preterm to 1 mo postnatal, resolves by 6 mo, rarely persists past 1 y. Occurs only during sleep, resolves with arousal—key distinguishing feature. Worsens with soporific agents (e.g., benzodiazepines). Distal > proximal limbs, upper > lower extremities, usually bilateral, often with facial and axillary myoclonus. Typically irregular, occasionally rhythmic. Most have clusters lasting few seconds, rare cases with many minutes of continuous activity (without epileptiform correlate).

BENIGN MYOCLONUS OF INFANCY: Isolated abnormal movements or combinations of myoclonus, negative myoclonus (sudden loss of tone), shuddering, and brief tonic stiffening occur several times per day. Movements occur in clusters in 50%. Onset ~6 mo in previously normal child, requires epilepsy evaluation. If EEG and development normal, benign myoclonus of infancy is likely diagnosis.[5] No treatment indicated, resolves 6 to 18 mo after onset. Development remains normal, no increased frequency of epilepsy or cognitive impairment.

Inherited Myoclonus

Many syndromes include myoclonic epilepsy. Few have nonepileptic myoclonus: lysosomal storage disorders (Tay–Sachs, Sandhoff, Gaucher, sialidosis) and SCAs. Only few inherited conditions produce primary myoclonus in childhood.

ESSENTIAL MYOCLONUS (EM): Occurs in otherwise-normal individuals, nonprogressive. Idiopathic or dominantly inherited with low penetrance. About 20% to 30% with mutations of ε-sarcoglycan (*SGCE*) or D2 dopamine receptor (*DRD2*).[6] Families may have EM alone or combination of EM, essential tremor, and myoclonus-dystonia. Treat with benzodiazepines, valproate, or levetiracetam.

MYOCLONUS-DYSTONIA (M-D; DYT11 or DYT15): Onset in 1st or 2nd decade (mean 6 y), no progression after 2nd decade. Myoclonus precedes onset of dystonia, all develop myoclonus; only 50% develop dystonia. DYT11 (*SGCE*): dominantly inherited with reduced penetrance, most cases inherited via the father, consistent with maternal imprinting. M-D without *SGCE* mutation = DYT15. Myoclonus responds to ethanol and benzodiazepines.

HYPEREKPLEXIA: Persistent, nonsituational exaggerated startle response, electrophysiologically distinct from myoclonus. Present from birth, often with generalized hypertonia (trunk > limbs) during 1st year of life. In adulthood, brief hypertonia following startle leads to falls. Etiology is probably failure of central glycine-mediated neuronal inhibition. Most commonly inherited, but may occur after injury.

Acquired Myoclonus

More common, more ominous, harder to treat.

POSTHYPOXIC MYOCLONUS: Common and ominous finding in post-arrest patient. Myoclonic status epilepticus (MSE) is predictor of poor outcome and long-term disability. Very difficult to treat, often requires anesthetic doses of benzodiazepines/barbiturates. **Lance–Adams syndrome (LAS):** Distinct posthypoxic (respiratory > cardiac arrest) myoclonus with onset weeks to months after injury, following partial or complete recovery from hypoxic injury. Myoclonus resolves at rest, resumes with movement or intent to move. Independent of cognitive injury, may be present in individuals who have otherwise made complete recovery. Levetiracetam or benzodiazepines often effective.

OPSOCLONUS–MYOCLONUS–ATAXIA SYNDROME ("dancing eyes, dancing feet"): Rare, but dramatic, autoimmune disorder. **Epidemiology:** Most common between 1 and 5 y, but infantile/adult presentations occur. **Etiology:** In children, 50% with neuroblastoma. Presumed postinfectious, if no neuroblastoma, typically older (≥9 y), associated with *Mycoplasma*, *Salmonella*, rotavirus, cytomegalovirus, HHV6, HCV, enterovirus 71, HIV-1, and denge.[7] Majority of non-neoplastic cases remain idiopathic. **Presentation:** Commonly includes robust myoclonus, but any features can occur in isolation. Opsoclonus most distinguishing: multidirectional, darting, chaotic, conjugate eye movements. Ataxia, usually pancerebellar, rarely asymmetric. Excessive irritability, sleep disruption, mutism are common. **Diagnosis:** Clinical diagnosis, no pathognomonic lab or imaging changes. Neuroblastoma screen mandatory: abdominal US and/or MRI torso. Urine catecholamines & MIBG scan have low sensitivity, but indicated if imaging is normal. **Prognosis & Treatment:** Neurologic outcome generally poor, ~80% have recurrent motor attacks and/or cognitive sequelae. Early diagnosis and treatment (immune-suppressors/modulators) improve outcome. Trazodone for sleep/behavior disruption.

DRUG-INDUCED: Etomidate, propofol, radiographic contrast, tranexamic acid, DA agonists and antagonists, SSRIs, TCAs, opiates, valproate, carbamazepine, phenytoin, lamotrigine, vigabatrin, mefloquine, gatifloxacin, and gamma-hydroxybutyrate. Transient myoclonus from withdrawal of CNS depressants (benzodiazepines, baclofen).

Treatment

Targeted at symptom relief. Choice based on underlying cause, anatomic origin, and side effect profile. **First-line:** Clonazepam, valproate. **Others commonly used:** Levetiracetam, primidone, topiramate, and acetazolamide. Begin with a single drug, but may require several drugs in combination.

Dystonia

Definition

Painful or uncomfortable twisting movements and intermittent fixed postures, often elicited by specific actions. Agonist–antagonist cocontraction, overflow of movement from desired to neighboring muscle groups, and

bizarre, contorting postures are typical. 3rd most common movement disorder. Generalized in most children (onset in one body part and subsequent spread), in adults usually remains focal. Divided into **primary dystonias** (dystonia remains the sole/predominant movement disorder), **dystonia-plus syndromes** (dystonia co-occurs or is secondary to another movement disorder), and **secondary dystonias** (following known injury or as part of hereditary degenerative syndromes). Differential is extensive.

Pathophysiology

Dystonia is a circuit disorder, historically thought to arise from basal ganglia but now recognized to result from injury/malfunction in any of several nodes within the motor control network.[1]

Primary Dystonia

Dystonia ± tremor is the only finding on exam. Many have identifiable genetic mutation (see Table 16.3), but ~50% idiopathic. Childhood-onset typically spreads to involve more body parts within 1 to 4 y of onset. Symptoms can be managed early with medications but may progress, involving more body parts, and require surgical treatment.

Dystonia-Plus

Myoclonus-dystonia and **dystonia-parkinsonism** are most common combinations (see chapter sections on "Myoclonus" and "Parkinsonism").

Secondary Dystonia

Can arise from any type of injury or metabolic derangement. Occurs in 5% to 15% of children with CP. By far the most common type of childhood-onset dystonia, though receives much less attention than disorders with known genetic etiologies.

VASCULAR/HYPOXIC INJURY: Infarct, hemorrhage, or diffuse hypoxic-ischemic insult may produce dystonia. Most frequent sites of injury: caudate, putamen, thalamus, cerebellum. Less commonly produce dystonia: cortex, internal capsule. 1% of infants who suffer perinatal hypoxia develop dystonia,[8] may evolve decades following injury.

KERNICTERUS: Selective basal ganglia lesion from hyperbilirubinemia, now rare in developed world but still seen in home births and children born abroad. Dystonia, often with prominent athetosis, are cardinal features.

INFECTION: Predilection for basal ganglia by direct infection or cross-immunoreactivity are presumed mechanisms. Include bacteria (Group A strep, *M. pneumoniae* and tuberculosis, *Legionella pneumophila*, *S. viridans*, *H. influenzae*, *S. pneumoniae*, *N. meningitidis*), spirochetes (*B. burgdorferi*, *T. pallidum*), protozoa (*T. gondii*), viruses (varicella, HSV, echovirus, and HIV) and fungi (*Cryptococcus neoformans*).

AUTOIMMUNE/DEMYELINATING: NMDA-receptor encephalitis—84% develop movement disorder, 10% have dystonia or severe dyskinesias in acute phase.[9] Orolingual dyskinesias predominate. Dystonia reported in single cases of lupus, neuro-Behçet, and celiac disease. Uncommon presentation of demyelinating disorders, rare presentation (typically focal or segmental) in ADEM or MS.

TOXINS: Cause selective injury to basal ganglia. **To all regions basal ganglia:** Carbon monoxide, cyanide, heavy metals (Mn, Cu, Hg). **To putamen:** Methanol. **To putamen & globus pallidus:** Ethylene glycol. Each can produce dystonia, chorea, or parkinsonism; dystonia most common. Focal lesions on MRI (edema, hemorrhage, infarct, or metal deposit) are expected.

TABLE 16.3 Primary Dystonias and Dystonia-plus Syndromes

	Site of Onset	Age at Onset	Inheritance, Penetrance	Gene/Locus	Clinical Features
Primary Dystonias					
DYT1	Leg > arm, gait affected early	Mean 10 y	AD: 30%–40%	*TOR1A*	Rapid generalization, early loss of ambulation 80% of 1 dystonia in Ashkenazis, <50% in others
DYT2	Leg	Mean 6 y	AR: 100%	Likely multiple	Rapid generalization, plateau, exacerbation at puberty
DYT6	Orolingual > arm	Mean 16 y	AD: 60%	*THAP1*	All ethnicities, often involves speech Late, upper > lower limb involvement
Dystonia plus syndromes					
Segawa synd. (DOPA-rspnsv. Dystonia, DYT5a/b)	Both: legs predominate a: occasional arm onset	a: mean 7 y b: infancy to teen	a: AD: low F 2x > M b: AR: 100%	a: GCH1 b: *TH*	Sx worsen during day, improve with rest. a: Normal development. ↑'d mood d/o, OCD b: Mild deficiency = Normal development Severe = infantile onset, global delays
Myoclonus-dystonia, DYT11 or DYT15	11: arm, or trunk 15: arm, or trunk > leg, dystonia less severe than in 11	11: mean 6 y 15: childhood –adolescence	AD: only expressed in paternal inheritance	11: *SGCE* 15: 18p11	Myoclonus in all, responsive to alcohol. Dystonia present in ~50%. Psychiatric comorbidities are common.
DYT12, rapid-onset dystonia parkinsonism	Face or arm > leg	Mean 12 y, can occur at any age	AD: low	*ATP1A3*	Evolution over minutes, up to a few days, precipitated by injury, illness, stress. Low CSF homovanillic acid aids diagnosis
DYT16, early-onset dystonia parkinsonism	Leg > trunk	Mean 9 y	AR: ~100%	*PRKRA*	Progreses to oropharyngeal dystonia, most generalize. 50% have parkinsonism, ± developmental delay. Refractory to therapy

TABLE 16.4 Genetic Causes of Secondary Dystonia

Onset in Infancy	In Childhood	In Adolescence
AADC deficiency	Wilson disease	SCA3 (Machado–Joseph)
Glutaric academia I	Ataxia telangiectasia	SCA7
Familial Fahr disease	Fucosidosis	SCA17
NBIA2A and -B, PLAN and INAD	PANK-2 deficiency, NBIA I	Friedreich ataxia
	Juvenile Tay–Sachs disease	Huntington Disease
Methylmalonic aciduria	Huntington disease-like 3	NBIA3
Lesch–Nyhan disease	Niemann–Pick C, I and II	Kufor–Rakeb syndrome
Pelizaeus–Merzbacher	Woodhouse–Sakati syndrome	PARK2
Rett syndrome	Dystonia-deafness syndrome	Choreoacanthocytosis
Leigh syndrome	LHON, Marsden variant	

NEURODEGENERATIVE DISORDERS: See Table 16.4.

Treatment

Difficult to predict clinical response. Requires patience to identify optimal combo.

MEDICATIONS: (1) Levodopa: *Trial indicated in all children with idiopathic dystonia*, target of 20 mg/kg/d × 1 mo. Most will not respond, but in responders is curative. Most DOPA-responsive dystonias respond to very low doses (100 mg b.i.d.), often within days. Others require 3 mo and/or high doses for symptom improvement. **(2) Trihexyphenidyl:** Start at 0.05 mg/kg/d, increase weekly to 0.75 mg/kg/d, divided b.i.d. or t.i.d. Anticholinergic side effects are major limiting factors, but can be avoided by very slow increase. Children tolerate doses higher than adults, may require doses >1 mg/kg/d. Blunting of attention and memory are nearly universal; declining school performance is major contributor to discontinuation. **(3) Baclofen:** Used mostly as adjunct, may be useful in reducing severity and pain of spasms, most effective in children with both spasticity and dystonia. Start 5 mg 1 to 2×/d, increase in 5 mg increments every 3 to 4 d, observing for sedation or cognitive side effects. Intrathecal administration is favored by some centers, although its effectiveness in treating dystonia, rather than spasticity, has not been proven. **(4) Benzodiazepines:** Very effective in selected patients, though in general less efficacious than the above-mentioned agents.

SURGICAL TREATMENT: Deep brain stimulation (DBS) of globus pallidus internus (GPi-DBS) is effective in treatment of primary dystonias not responding to medical treatment. In DYT1, most common cause of childhood onset generalized dystonia, GPi-DBS produces improvement of disability in 60% to 70%, sizeable minority experience no benefit. In DYT6, improvement after DBS is less than in DYT1, but still promising. To date, tardive dystonia is the only secondary dystonia that has shown benefit from DBS. Trials of GPi-DBS in dystonic CP are underway.

Paroxysmal Dyskinesias

Definition

Intrusion of abnormal movements onto normal background, episodes lasting minutes to hours, athetoid, ballistic, choreic, and/or dystonic features. Normal cognition/arousal during episodes (vs. epilepsy). Normal exam, MRI, & EEG (except some cases PED). Primary forms much more common in childhood, secondary types are reported. Distinct forms distinguished by duration, frequency, eliciting factors. All types tend to decrease with age. For all types, avoidance of triggers is mainstay of management.

Paroxysmal Kinesigenic Dyskinesia (PKD, DYT10)

Distribution: Extremities > head/trunk, often asymmetric. **Preceded by:** Paresthesias, fatigue, tension in affected limb. **Elicited by:** Sudden movement, planning to move, startle, photic stimulation, yawning, or talking. Exacerbated by temperature extremes, stress, and menstruation. **Duration:** Seconds to 5 min. **Frequency:** At least 1×/d, may occur >100×/d. **Onset:** Infancy to 4th decade, mean 8 y. **Inheritance:** AD, ~50% of cases due to *PRRT2* mutations, 90% penetrance, variable severity. Associated with benign infantile convulsions or chorea, familial hemiplegic migraine.[10] **Treatment:** Highly responsive to anticonvulsants: carbamazepine, oxcarbazepine, phenytoin, clonazepam.

*Paroxysmal Nonkinesigenic Dyskinesias (*PNKD*, DYT8)*

Preceded by: Premonitory paresthesias, muscle cramping, diaphoresis, diplopia, flushing, or dizziness. **Elicited by:** Excitement, fatigue, stress/anxiety, illness, fasting, temp extremes, alcohol, caffeine, or chocolate; may occur spontaneously. **Duration:** Minutes to hours, rarely lasts days. **Frequency:** Few/week to few/year. **Onset:** Before 5 y, rare midlife onset. **Inheritance:** AD, *PNKD* gene, ~90% penetrance, variable expression within/between families. **Treatment:** Medications generally ineffective, although reports of improvement with benzodiazepines and levetiracetam. Avoidance of triggers is mainstay.

*Paroxysmal Exertional Dyskinesia (*PED*, DYT9)*

Distribution: Legs/feet > face/arms/trunk (usually occurs in patients with short-duration episodes), may involve exercised limbs exclusively. Typically asymmetric, hemidystonia common. **Associated with:** Epilepsy and mild cognitive impairment. **Preceded by:** No premonitory sensations (vs. PKD and PNKD). **Elicited by:** Emerges after 5 to 15 min of sustained exercise. **Duration:** 5 to 30 min, usually resolves <10 min after stopping exercise. **Onset**: Childhood. **Inheritance:** AD, mutations in *SLC2A1*, encodes brain-specific glucose transporter GLUT1. Dyskinesias thought to result from transient exhaustion of glucose stores within striatum. **Treatment:** Carbamazepine, levodopa, and gabapentin have limited success. Ketogenic diet can also reduce dyskinesias.

Parkinsonism

Definition

Parkinsonism is ≥2 features of Parkinson disease (PD)—rigidity, postural instability, bradykinesia, tremor at rest. Parkinsonism in isolation is the least common movement disorder in children, but relatively common as a late feature of degenerative syndromes.

Pathophysiology

PD results from primary degeneration of nigrostriatal DA neurons; parkinsonism results from direct basal ganglia injury, drug side effect, or secondary to a neurodegenerative disorder.[11] Can result from injury/deficit to striatum or substantia nigra, presynaptic and/or postsynaptic limbs of motor facilitation pathways.

Differential Diagnosis

Must distinguish between early PD and secondary parkinsonism (often characterized as much by accompanying features as by particulars of parkinsonism).

JUVENILE-ONSET PD: Childhood—typically presents with dystonia in lower extremities; adolescents—bradykinesia & rigidity predominate. Tremor is a late/inconsistent finding (vs. adult onset). 80% of AR parkinsonism with

onset <20 y due to *Parkin* mutations. Progresses more slowly than adult-onset PD, but patients eventually develop same complications/limitations.

STRUCTURAL: Embolic/hemorrhagic infarction, tumors, viral encephalitis, toxic-metabolic injury can cause secondary parkinsonism. Rare: Cranial irradiation, hydrocephalus.

NEURODEGENERATIVE: Many genetic causes of childhood parkinsonism; 2 disorders to always consider—HD and WD. **(1) Juvenile HD:** Onset <20 y, CAG expansion >60 repeats, earlier onset, rapid progression. Manifests as Westphal variant—prominent cognitive decline, regression of fine motor skills, parkinsonism, no or little chorea.[12] Extreme expansions may present as developmental delay, neurodegeneration, seizure disorder. HD testing should be done with help of skilled genetic counselor. **(2) WD:** *Genetics/Pathophysiology:* AR, copper-deposition disorder. *Presentation:* 40% to 60% present with isolated neurologic syndrome with subclinical hepatotoxicity. Neurologic features typically present in adolescence/early adulthood (mean 19 y), but reported as young as 6 y. Tremor is the most common presenting symptom, rapidly develop bradykinesia, orolingual rigidity, dysarthria, dysphagia, mask-like facial expressions (*risus sardonicus* = fixed grin*).* Psychiatric symptoms and academic decline common (20%–60%) at diagnosis. *Treatment/Prognosis:* Progression can be halted/slowed by Cu^{++} chelation, only liver transplant is curative. Neurologic symptoms may resolve following treatment. **(3) Other:** Variety of rare disorders to consider in children with movement abnormalities and developmental regression/delay: neurodegeneration with brain iron accumulation (NBIA); lysosomal disorders (Niemann–Pick type C, Gaucher disease III, GM1 gangliosidosis); POLG-related mitochondrial disorders; PKU; Lesch–Nyhan; neuronal ceroid lipofuscinoses (CLN1, CLN3, and Kufs disease); neuronal intranuclear inclusion disease and Rett syndrome. Consider tyrosine hydroxylase and sepiapterin deficiencies in infancy as many are responsive to DA replacement.

INFECTIOUS/INFLAMMATORY: Acute onset with infectious prodrome suggests encephalitis with predilection for basal ganglia. **Pathophysiology:** Unclear if direct infection or parainfectious autoimmune activation. **Neuroimaging:** Relatively selective edema/necrosis of bilateral basal ganglia. **Presentation:** Parkinsonism may be acute or late consequence, acute typically has faster, more complete recovery. **Etiology:** Viral causes: HIV, Japanese encephalitis virus, Western equine, St. Louis, varicella, mumps, coxsackievirus, measles (SSPE). Mycoplasma associated with both acute and late parkinsonism. In HIV/AIDS, 5% develop parkinsonism, consequence of *Toxoplasma* sp., *Treponema* sp., *Cryptococcus* sp., or PML. Rare complication of systemic inflammatory disorders: lupus, Behçet, sarcoidosis.

DRUG-INDUCED: Iatrogenic parkinsonism most common form in children. Almost always reversible in several months.[13] **Suggestive features:** Symmetric limb involvement, absent or mild rest tremor, perioral, high amplitude, low frequency "nibbling" movements (rabbit syndrome). **Most frequent offenders:** First-generation neuroleptics, DA-blocking antiemetics. **Less likely:** Valproate, phenytoin, SSRIs, lithium, captopril, CCBs (flunarizine, cinnarizine), amphotericin B, chloroquine, cyclosporine, vincristine, doxorubicin, vinca alkaloids, and cytarabine.

DYSTONIA-PARKINSONISM: Many rare causes, clinical heterogeneity among more common causes. **Inheritance:** AD, AR, or X-linked. **Rapid-onset dystonia parkinsonism (*ATP13A2*, DYT12):** AD. Progresses over hours to days, marked bradykinesia, postural instability, dystonia of face > arms > legs, prominent bulbar involvement (dysphagia, dysarthria); minimal/no response to levodopa. In acute setting, may use high-dose benzodiazepines,

unknown if improves outcome. Triggered by psychological stress, excessive alcohol consumption, high fevers, and excessive exercise[14] (see Table 16.3).

Treatment

DA replacement, same complications seen in adults: dyskinesias, wearing-off, waning efficacy. In secondary parkinsonism, first exhaustively evaluate underlying etiology. Trial of levodopa/carbidopa indicated in most children with parkinsonism. Start 1 mg/kg/d, escalate 1 to 2 ×/wk to max of 15 mg/kg/d. Most common side effects (limited by combination with carbidopa): nausea, sedation, orthostasis, and behavioral changes. T.i.d. dosing usually sufficient at initiation of DA replacement. Anticholinergics (benztropine, trihexyphenidyl) useful when levodopa is contraindicated or when complicated by dyskinesias.

ATAXIA

Definition

Failure of motor coordination leading to clumsiness, poor balance, irregularity of movements, inability to execute fine movements or smooth sequences of movement.

Pathophysiology

1° dysfunction of the cerebellum, or failure of proprioceptive/vestibular afferents, to reach cerebellum. Must exclude other causes of irregular movement: weakness, tremor, myoclonus, dystonia.

Diagnostic Approach

Numerous possible disorders. Begin by determining (1) onset (acute, subacute, or chronic), (2) stability (static vs. progressive), and (3) associated neurologic or systemic symptoms. Vertigo, intention tremor, nystagmus, dysarthria or scanning speech, hypotonia, pendular reflexes, or asymmetric/focal symptoms may provide valuable localizing information, but most ataxias in children are pancerebellar and lack localizing signs.

Acute-Onset ATAXIA

Rapid onset within 24 h. May present as refusal to walk in younger child, speech changes or loss of fine control in older child. Typically progress to marked gait abnormality with no motor modality spared. Majority with relatively benign, self-limited course.[15]

INTOXICATION: Most common cause : prescription or illicit drugs prescription/illicit drugs. Toxins (mercury, thallium, lead, toluene, organic solvents, organophosphate pesticides) may cause acute, but most present over weeks to months. **Urine toxic screen** essential, get **medical history** of caregivers.

INFARCTION/HEMORRHAGE: Vascular events in cerebellum frequently cause ataxia, usually combined with brainstem deficits. Reduced arousal and behavioral alterations common. If ataxia asymmetric, or with brainstem signs, **MRI** and **MRA** are mandatory.

INFECTIOUS/INFLAMMATORY: 3 relatively common causes of ataxia: acute disseminated encephalomyelitis (ADEM), acute cerebellar ataxia (ACA), and cerebellitis. MRI is mandatory. **(1) ADEM:** Reduced consciousness, altered mentation, multiple neurologic deficits. >50% have ataxia but never in isolation. MRI: Patchy, nonsymmetric lesions, often both supra- and infratentorial. Early/aggressive steroid treatment may speed recovery; even with steroid treatment, residual cognitive/motor symptoms common.

(2) ACA, and **(3) Cerebellitis:** Critical to distinguish between these, as prognosis and treatment very different. Both have symptoms isolated to cerebellum. **ACA:** Autoimmune targeting of cerebellar antigens, follows immune activation by 1 to 2 wk. Symptoms usually limited to ataxia, also nystagmus or CN palsies in 25%; fever, headache, systemic illness rare. MRI: Normal or without cerebellar involvement. Causes in vaccinated children: EBV, Lyme, coxsackievirus, rotavirus, nonspecific URIs. Prognosis is excellent, near-universal recovery by 3 mo. **Acute cerebellitis:** Life-threatening with variable prognosis. Only half present with ataxia; most have headache, vomiting, nonlocalizing signs of illness. MRI abnormalities are defining feature, commonly pancerebellar but may be unilateral or vermian. Cerebellar edema may develop rapidly, cause obstructive hydrocephalus and death.

Acute-Onset, Recurrent ATAXIAS

Serial acute presentations with complete remission between.

EPISODIC ATAXIA (EA): 7 distinct clinical syndromes; some linked to ion channel mutations, all with AD inheritance. **Duration** is key distinguishing feature—EA1: seconds–minutes, EA2: hours–days. **Onset:** EAs 1, 2, 6 in childhood/early adolescence; EAs 3, 4, 5 in late adolescence/adulthood. Only EA1 and EA2 likely encountered in clinical practice. **Treatment:** Many respond to acetazolamide, start 125 mg/d and progressively ↑ to 250 mg b.i.d. or higher as tolerated.

EPILEPTIC ATAXIA: May be seen during focal seizure or postictal. Presumably due to disruption of corticocerebellar connections. May be typical feature for individual.

OTHER: Complex migraine and systemic metabolic disorders often have episodic ataxia, but rarely in isolation.

Subacute, Progressive ATAXIA

Progresses over weeks to months. Many have mass lesions or degenerative syndromes. MRI required.

NUTRITIONAL: Sensory ataxia secondary to peripheral neuropathy from zinc excess or Cu^{++} deficiency; deficient vitamin B_1, B_3, B_{12}, or E. May also induce myelopathy (subacute combined degeneration). Toxic/prolonged B_6 elevation: sensory neuropathy and ataxia, but not reported in children and not at therapeutic doses used for epilepsy treatment. B_1 deficiency (Wernicke encephalopathy): nonalcoholic etiologies as common in children as adults.[16] Ataxia with isolated vitamin-E deficiency (AVED): neurodegeneration may be arrested or modestly improved with high-dose vitamin-E supplementation (100 IU/kg/d).

IMMUNE-MEDIATED: Opsoclonus–myoclonus–ataxia syndrome (OMS) is rare but unforgettable syndrome of darting, chaotic eye movements, myoclonus of trunk and limbs, cerebellar ataxia, behavioral disturbances, and sleep disruption. May present over days but usually progressive over weeks to months; associated with neuroblastoma or postinfectious (see "Myoclonus" section).

MASS LESIONS: Any posterior fossa mass can cause slowly progressive ataxia, either pancerebellar or hemispheric. Ataxia can worsen acutely due to hydrocephalus or hemorrhage.

Chronic Progressive ATAXIA

Diagnostic challenge, with many genetic syndromes affecting cerebellar cortex or nuclei, vestibular system, dorsal columns, or peripheral nerves.

Recent reviews of the dominant[17] and recessive[18] hereditary ataxias may be useful.

SPINOCEREBELLAR ATAXIAS (SCA): Dominantly inherited, cerebellar degeneration, now with 35 types, most extraordinarily rare. SCAs 1, 2, 3, 7, 13 have onset in childhood/adolescence. No treatment to prevent or slow progression.

FRIEDREICH ATAXIA: Most common inherited ataxia, >50% of cases in Caucasians. AR, triplet repeat, frataxin gene (encodes mitochondrial protein expressed in all tissues). Multisystem dysfunction: cardiomyopathy, dysrhythmias, diabetes, failure of vision/hearing, scoliosis, pes cavus. Loss of ambulation by ~15 y. Multidisciplinary approach to supportive treatment including cardiology, endocrinology, orthopedics. Studies have suggested possible efficacy of coenzyme Q10 (idebenone).

ATAXIA TELANGIECTASIA: AR, progressive, multisystem disorder of DNA repair. Increased incidence of immunodeficiency and neoplasias and in neurodegeneration, especially cerebellar Purkinje and granule cells, and striatal medium spiny neurons. Motor development initially normal, ataxia, dystonia, and/or chorea begin at 18 to 36 mo. Telangiectasias of bulbar conjunctiva and skin develop 1 to 3 y after abnormal movements. Alpha-fetoprotein levels 2× normal. Mean survival is 25 y, but early diagnosis is essential for family planning, avoidance of ionizing radiation, cancer screening, and vigilance regarding immunodeficiency and infection risk.

Static ATAXIA

Evident throughout motor development, often with delayed gross/fine motor milestones. If known injury occurred and ataxia nonprogressive, clinical observation alone is sufficient. If history raises possibility of vascular injury, or exam indicates presence of syndrome with characteristic CNS malformations, MRI is indicated. Most will benefit from physical/occupational therapy, even with long-standing symptoms. **Syndromes with static ataxia:** Joubert, Dandy–Walker malformation, pontocerebellar hypoplasia (6 types), vermian agenesis, cerebellar dysgenesis, rhombencephalosynapsis, and Chiari malformation (types 2 and 3).

PSYCHOGENIC MOVEMENT DISORDERS

Description

Abnormal movements not the result of a clear neurological injury or dysfunction. Most commonly conversion disorder but may be somatoform disorder. Many fold more common than most disorders discussed in this chapter. 25% of inpatient movement disorders consults are psychogenic.[19] Most common are: tremor (40%), dystonia (31%), myoclonus (13%), gait disorder (10%), parkinsonism (5%), tics (2%). Youngest reported PMD case was 3.5 yo, many reports <10 y. Prepubertal: boys = girls. Adolescence: girls 4× boys.[20] In children with unilateral symptoms, dominant limb most likely affected (vs. adults, nondominant more likely).

Outcome

Short duration of symptoms and acute onset are strongest predictors of recovery. Notable morbidity: Social withdrawal, missed school, injudicious medication use, or surgeries. Outcome best if rapidly diagnosed and resolved within 1 wk.

Treatment

Psychotherapy plus ongoing relationship with neurologist.

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ONLINE RESOURCES

Worldwide Education and Awareness for Movement Disorders – http://www.wemove.org/

Ataxia, clinical assessment and genetics – http://neuromuscular.wustl.edu/ataxia/aindex.html

ADDITIONAL RESOURCES

For more in-depth coverage of pediatric movement disorders, we recommend the excellent texts by Singer *et al.* (Saunders, 2010)[21] and Fernandez-Alvarez and Aicardi (Mac Keith Press, 2001)[22].

17 Pediatric Neuroimmunology

Leslie A. Benson, Riley Bove, and Mark Gorman

DEMYELINATING DISEASES (see Fig. 17.1 and Table 17.1)

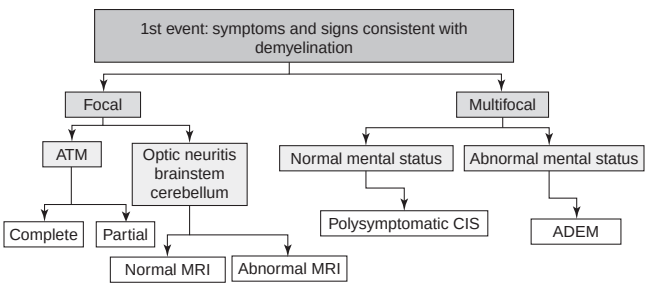


FIGURE 17.1 Flow Chart Demonstrates Approach to a First Demyelinating Syndrome Based on Focality of the Signs and Symptoms. CIS, clinically isolated syndrome. MRI is generally the first diagnostic testing choice to help categorize inflammatory etiologies. ATM, acute transverse myelitis; ADEM, acute disseminated encephalomyelitis.

TABLE 17.1 Major Causes of White Matter Changes and CNS Inflammation

	Autoimmune
Primary demyelinating	**ON, ADEM, TM, CIS, MS** (RRMS, SPMS, PPMS), NMO
Paraneoplastic	Paraneoplastic encephalomyelitis, OMS
Connective tissue dz	SLE, Behçet disease, RA, Sjögren syndrome, APLAS, HLH
Granulomatous	Wegener granulomatosis, sarcoidosis, lymphomatoid granulomatosis
Vasculitis	CNS and systemic vasculitides
	Other Demyelinating
Infectious	**CMV**, HIV → PML (JCV, usually in HIV), Lyme, neurosyphilis, HTLV1, SSPE, tropical spastic paraparesis/HTLV1–assoc. myelopathy, congenital toxoplasmosis
Metabolic	CPM, subacute combined degeneration (B_{12} & intrinsic factor deficiency)

(continued)

TABLE 17.1 Major Causes of White Matter Changes and CNS Inflammation (Continued)

	Other Demyelinating
Toxic	NO poisoning; drugs of abuse (toluene, ethanol, cocaine, MDMA/ecstasy, IV/inhaled heroin, psilocybin); radiation-induced necrosis; antineoplastic agents (methotrexate, carmustine, cisplatin, cytarabine, fluorouracil, levamisole, fludarabine, thiotepa, interleukin-2, interferon-α); immunosuppressants (Cyclosporine [posterior lobes], tacrolimus [parieto-occipital]); antimicrobials (amphotericin B, hexachlorophene, metronidazole); environmental exposure (carbon monoxide, arsenic, carbon tetrachloride).
Vascular & hypoxic-ischemic	**Migraine, PRES, HIE,** sickle cell disease, delayed hypoxic cerebral demyelination, CADASIL
Secondary demyelinating	X-linked adrenoleukodystrophy, metachromatic leukodystrophy, adrenomyeloneuropathy, Alexander, Canavan, Krabbe, Aicardi–Goutières syndrome
Hypomyelinating	Pelizaeus–Merzbacher, Cockayne syndrome
Mitochondrial disease	NARP, POLG1/Alpers, MELAS, Leigh syndrome
Neoplasm	**Glioma,** lymphoma, LCH

Note: Most common in **bold**.

ADEM, acute disseminated encephalomyelopathy; APLAS, antiphospholipid antibody syndrome; CADASIL, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; CIS, clinical isolated syndrome; CPM, central pontine myelinolysis; HIE, hypoxic ischemic encephalopathy; HLH, hemophagocytic lymphohistiocytosis/macrophage activation syndrome; JCV, JC virus; LCH, Langerhans cell histiocytosis; MELAS, multifocal encephalopathy lactic acidosis and strokes; MS, multiple sclerosis; NARP, neuropathy ataxia and retinitis pigmentosa; NMO, neuromyelitis optica; NO, nitric oxide; OMS, opsoclonus–myoclonus syndrome; ON, optic neuritis; PML, progressive multifocal leukoencephalopathy; POLG1, polymerase gamma 1; PPMS, persistently progressive MS; PRES, posterior reversible encephalopathy syndrome; RA, rheumatoid arthritis; RRMS, rapidly progressive MS; SLE, systemic lupus erythematosus; SPMS, secondary progressive MS; SSPE, subacute sclerosing panencephalitis; TM, transverse myelitis.

VACCINE CONSIDERATIONS: Empiric recommendation for no vaccines for 1 mo after Clinically isolated syndrome (CIS)/MS, 3 mo for acute disseminated encephalomyelitis (ADEM). Consult *Red Book* for patients on steroids, IVIG, and timmunosuppressants.

Acute Disseminated Encephalomyelitis (ADEM)

DEFINITION: A first clinical event with a polysymptomatic presentation including encephalopathy, with acute or subacute onset.

EPIDEMIOLOGY: 0.4 to 0.8 per 100,000 incidence in children & adolescents (average age 5–8 y); rare in adults.[1,2]

ETIOLOGY: ***Postinfectious***: ~75%; ***Postvaccination***: ~5%; Usually after MMR, but risk is greater and disease more severe w/ measles (1/1,000) and rubella (1/5,000) than MMR vaccine (1–2/million). *Others*: Rabies, HBV, influenza, DPT, Japanese B encephalitis, pneumococcal, polio, and rare cases in organ transplant patients. Typically within 4 to 14 d of infection or vaccination; must be <3 mo to be associated.

PATHOLOGY: Perivenular T-cell and macrophage infiltrates associated with demyelination.

PATHOPHYSIOLOGY: Proposed immune dysregulation in genetically susceptible individuals triggered by environmental stimulus. Anti-myelin oligodendrocytes (MOG) antibodies detected in some patients are of uncertain significance.

Diagnostic criteria[3]

- **Clinical Features: (1)** *First clinical attack* of inflammatory or demyelinating dz in CNS. **(2)** *Acute or subacute* onset (febrile illness <4 wk prior in 50%–75% children; max severity over 4–7 d). **(3)** *Polyfocal*: affects multiple areas of CNS. **(4)** *Polysymptomatic* (e.g., n/v, meningismus, cranial neuropathies including optic neuritis (ON); pyramidal signs, hemiparesis, ataxia, transverse myelitis (TM), seizure (in ~⅓) **(5)** Must include *encephalopathy*: Acute behavioral Δ (e.g., confusion or irritability) and/or alteration in consciousness (range: somnolence-coma). **(6)** *Subsequent improvement* by clinical/imaging measures (but may have residual deficits). **(7)** *No better explanation* (other etiologies ruled out). **(8)** *Relapse*s: new or fluctuating signs or MRI findings within 3 mo of inciting ADEM episode are considered part of the initial event.
- **Lesion Characteristics on MRI FLAIR and T2: (1)** Large (>1–2 cm) multifocal, hyperintense, bilateral, asymmetric lesions in supratentorial or infratentorial WM, <50% of patients have contrast enhancement (Fig. 17.2). Rarely: single large lesion. **(2)** May involve basal ganglia and thalamus. **(3)** Spinal cord may show confluent intramedullary lesions. **(4)** No radiologic evidence of prior destructive WM changes, e.g., no black holes (most ADEM lesions resolve at least partially vs. MS lesions).

Diagnostic testing

- **MRI w/ T2, FLAIR, and gadolinium.** Sequential imaging to evaluate. If new symptoms, consider multiphasic ADEM vs. MS.
- **LP:** r/o viral and bacterial meningitis/encephalitis. Send CSF for: protein, glucose, cell count, Gram stain, bacterial culture, and oligoclonal bands (OCB). Consider further infectious testing based on immune status, clinical scenario, CSF WBC count. CSF can be normal. May see pleocytosis and/or increased protein, OCB in <10% (nonspecific—also seen in MS, CNS infections).
- **Serum:** CBC; may have increased ESR and CRP.
- **Micro:** Studies negative.
- **EEG:** Background slow wave activity c/w encephalopathy.

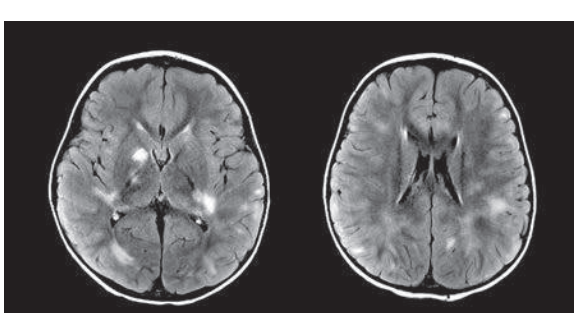


FIGURE 17.2 Typical MRI Features in ADEM. FLAIR sequences demonstrating multifocal fluffy, bilateral, asymmetric hyperintensities in the bilateral white matter and deep gray nuclei.

DIFFERENTIAL DIAGNOSIS: (1) Infectious: Viral/bacterial meningitis or encephalitis. **(2) Inflammatory demyelinating d/os:** CIS (encephalopathy required for ADEM dx, not typical for CIS/MS. CSF >50 WBC/mm, sometimes seen in ADEM, atypical for MS. MRI shows old lesions for MS), ON, TM, neuromyelitis optica (NMO), and others. **(3) CNS vasculitis** (PACNS; *see below*) **(4) Malignancy**—CNS lymphoma or glioma; workup with CSF cytology but dx requires brain biopsy. **(5) Mitochondrial disease**—w/ intercurrent infection. MRI w/ typical symmetric T2 signal in basal ganglia or parieto-occipital regions and lactate peak on MR SPECT; elevated serum and CSF lactate.

TREATMENT: No controlled trials to date. **(1)** *Antibiotics*: Consider empiric acyclovir & antibiotics until infectious etiology excluded. **(2)** *Steroids:* IV methylprednisolone 30 mg/kg/d (max 1 g/d) then 3- to 6-wk oral prednisone taper (+ PPI, Ca/vitamin D). Two studies suggest less early recurrences with taper >3 wk. **(3)** *Steroid alternatives*: If steroids fail or contraindicated, can use plasmapheresis (PLEX), IVIG.[3a,3b]

PROGNOSIS: *Overall good*: ~75% recover completely, <5% mortality. MRI can show complete recovery. Average recovery time of 1 to 6 mo. 3.3% with ADEM younger than 11.85 y develop MS.[4] *Motor deficits*: 8% to 30% residual; range from clumsiness to ataxia and hemiparesis. *Neurocognitive deficits:* attention, short-term memory, affect, behavior, verbal processing speed, but less severe than in MS, usually within 1 standard deviation from norm. *Poor prognostic factors*: adults, unresponsive to steroids.

ADEM VARIANTS: Multiphasic ADEM: New event meeting the criteria for ADEM 3 or more months after initial ADEM event. **Acute hemorrhagic leukoencephalitis**: Includes ***AHL***—acute hemorrhagic leukoencephalitis, ***AHEM***—acute hemorrhagic encephalomyelitis, and ***ANHLE***—acute necrotizing hemorrhagic leukoencephalitis (**Weston Hurst syndrome**). A hyperacute variant with necrotizing vasculitis (venules) w/ hemorrhage and edema, very rare (2% of ADEM), poorer prognosis (70% mortality usually within 1st wk; 70% survivors w/ residual deficits). Prognosis may be improved w/ aggressive treatment (corticosteroids, IVIG, cyclophosphamide, plasmapheresis). Most cases occur after URI. MRI: diffuse WM lesions within 72 h of onset, cerebral edema, ICH. CSF: increased WBC, RBCS, and protein.

Clinically Isolated Syndrome/Acute Demyelinating Syndrome (ADS)[3]: Isolated event of CNS demyelination

DEFINITIONS: Polyfocal—clinical features attributed to more than one CNS site without encephalopathy. **Monofocal**—clinical features attributed to only one CNS site (i.e., optic nerve, spinal cord, cerebrum, brainstem or cerebellum).

EPIDEMIOLOGY: ADS incidence 0.9/100,000 children in Canada (including ADEM).[5]

DIAGNOSTIC TESTING: Aimed at ruling out alternative diagnoses & evaluating risk of MS.

- **MRI brain w/ and without gad**: Include orbits if suspect ON. Consider spine in all cases.
- **LP:** Routine (protein, glucose, cell count/diff, Gram stain, and culture); IgG index, OCB (if present, increase risk of subsequent MS). Usual findings: mild pleocytosis, elevated protein, or OCBs.
- **Labs**: CBC (mild elevation in WBC in 50%), ESR, CRP, ANA, Lyme, EBV titers.
- **MANAGEMENT:** Follow-up imaging brain/spine MRI at 1 to 3 and 6 mo, then 6 to 12 mo depending on suspicion for dissemination, looking for new lesions and fulfillment of McDonald criteria (see MS diagnosis below).

PROGNOSIS: Risk of MS lower in children than adults. After monofocal CIS, 38% to 62% vs. 0% to 17% with ADEM developed MS.[6] Poor prognostic indicators include age >10 to 12 y, asymptomatic MRI brain lesions (strongest predictor), CSF OCB, HLA-DRB1*15, prior EBV infection, low 25-hydroxy vitamin D. MS risk after ADS is 1.9% w/ normal brain MRI, 28% with abnormal MRI in patients ≤11.85 y, and 60.6% with abnormal MRI in patients ≥11.85 y.[4]

Optic Neuritis (ON)

DEFINITION: Inflammatory demyelination of the optic nerve, causing acute visual loss. Can occur along any segment; termed retrobulbar if posterior to the optic nerve head. Common manifestation of MS.

EPIDEMIOLOGY: 1:1.4 female:male.[5] May be para-infectious.

CLINICAL FEATURES: ***Acute*: (1)** Binocular (more common in children than adults) or monocular visual loss over hours to days, peaking in 1 to 2 wk. **(2)** Loss of color vision—test for red desaturation. **(3)** Visual field defect—usually central scotoma. **(4)** Eye pain (56%)[7] in the orbital or retro-orbital region usually exacerbated w/ eye movement, which often precedes visual loss. ***Chronic:*** Uhthoff phenomenon: heat (showers, exercise) increases visual problems, which resolve when cooled off. ***Associations:*** MS, NMO, ADEM.

DIAGNOSTIC TESTING: A clinical diagnosis, but confirmatory testing is often necessary in children. In addition to CIS workup, consult ophthalmology, preferably neuro-ophthalmology.

- **Visual acuity (VA) testing:** Median VA <20/200 at peak in 70% of children.[7–9] Persistent visual loss (color vision, contrast sensitivity, light brightness, stereo acuity, motion detection) detectable in most at 2 y.
- **Color testing:** Ishihara plates or Farnsworth–Munsell 100 hue test can be used. Color vision loss in about 90% patients, out of proportion to decrease in VA. "Red" desaturation: appears "washed out" or darker in affected eye.
- **Flashlight test:** Relative afferent pupillary defect in unilateral or asymmetric ON. It can persist.
- **Visual fields:** Usually central scotoma. If extends to the periphery, consider compressive lesion.
- **Fundoscopic examination:** Papillitis w/ hyperemia and disk swelling, blurred disk margins, distended veins (60%–72% in pediatrics).[9,10] *Retrobulbar* neuritis w/ normal fundoscopic exam.
- Over time optic atrophy occurs, even if VA is normal, particularly temporal, extending beyond its margin into peripapillary.
- **MRI brain and orbits w/ and w/o gad:** Can have optic nerve inflammation with T2 bright signal w/ or w/o enhancement (T2 signal change best seen on coronal STIR) but normal does not r/o dx (Fig. 17.3). Brain MRI for prognosis (see below).
- **LP:** Role in isolated ON controversial. If brain parenchymal lesions, LP can help stratify MS risk.
- **Labs:** See CIS; consider NMO IgG in severe and/or bilateral cases.[11]
- **Visual evoked potential (VEP):** Consider if diagnosis not clear; will show decreased amplitude of N95 & delay in the P100.
- **Optical coherence tomography (OCT):** Detects thinning of retinal nerve fiber layer once early swelling is gone.

DIFFERENTIAL DIAGNOSIS: (1) Infectious *neuroretinitis (viruses, toxoplasmosis, Bartonella)* often bilateral, ± scotoma, ± pain. Exam: papillitis, macular edema, exudates. ± systemic signs/symptoms. **(2) NMO**.

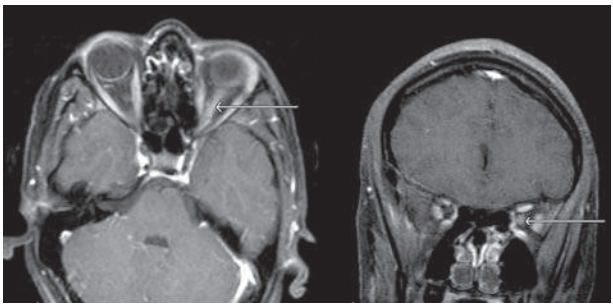


FIGURE 17.3 Typical Optic Neuritis. MRI orbits, T1–post-gad axial and coronal images demonstrate enhancement within the optic nerve (arrows) on the left (compared to the normal right nerve).

(3) Genetic: *LHON*: in boys with onset over weeks to months, can be unilateral or bilateral with central or cecocentral scotoma. Fundus with disc hyperemia; peripapillary telangiectasia. Not painful. MRI normal. Smoking assoc. w/ attack. **(4) Inflammatory:** Autoimmune (SLE, Sjögren), sarcoidosis. **(5) Neoplasms:** Optic nerve glioma—initial symptoms often identical. MRI with expansile enhancing mass of optic nerve. Can have proptosis and other orbital signs. Frequent in NF1. **(6) Compressive lesion. (7) Pseudotumor cerebri**—vision loss usually late and HA frequently present. **(8) Chronic relapsing idiopathic optic neuropathy** (CRION). **(9) White dot syndrome**. **(10) Toxic-metabolic:** Drugs, toxins, nutritional deficiency (vitamins B_1, B_{12}, folate), radiation. **(11) Traumatic optic neuropathy**. **(12) Conversion disorder**.

TREATMENT: Acute: No randomized clinical trials (RCTs). The ON treatment trial found more rapid improvement with IV steroids if VA <20/40 but no difference in long-term outcome. Most tend to treat. IV methylprednisolone (30 mg/kg up to 1 g IV daily ×3 to 5 d + PPI, Ca/vitamin D). *PO prednisone alone is NOT recommended.*[12,13] If poor recovery, consider 2nd-line agent such as IVIG or PLEX. If refractory, consider NMO.

Chronic/disease-modifying therapies (DMT): In children, no trials, but may consider treatment with 1st-line DMT in pediatric patients at high risk for MS (see MS Rx).

PROGNOSIS: (1) ***Visual recovery:*** 80% w/ 20/40 or better vision.[7,10] Recovery onset occurs within weeks, although often w/ residual deficits on low contrast sensitivity. **(2)** ***Recurrence:*** 5% to 10% recurrence (after >90 d, >30 d off-steroids by definition). If rapidly recurrent ON check NMO IgG. **(3) ON and MS**: 38% to 54% of patients have brain lesions and 17% to 36% are diagnosed w/ MS by 24 mo.[7,8] Good prognostic factors include normal brain MRI (strongest predictor), age <10 y, and papilledema.

Transverse Myelitis (TM)

DEFINITION: Transverse myelopathy due to inflammation, including demyelination, infection, or other inflammatory etiologies.

EPIDEMIOLOGY: M = F. 20% of TM occurs in pediatric patients. Bimodal <3 y & adolescent.[14]

ETIOLOGY: 47% parainfectious, 28% postvaccine, 10% to 45% idiopathic. Pathogens associated w/ TM include: (1) viruses: HSV, VZV, CMV, HHV6, EBV, HTLV, HIV, dengue, JEV, SLEV, WNV, WNV, tick-borne encephalitis,

influenza A, measles, mumps, rubella, coxsackievirus, echovirus, enterovirus, HAV, HCV, polio; (2) bacteria: *Mycoplasma*, Lyme, syphilis, TB; (3) fungus: *Actinomyces*, *Blastomyces*, *Coccidioides*, *Aspergillus*; and (4) parasites: neurocysticercosis, *Schistosoma*, *Gnathostoma*, Angiostrongylus.[14]

DIAGNOSTIC CRITERIA: (1) Inflammation (CSF WBC, elevated IgG index, MRI with gad enhancement), (2) absence of CNS infection, (3) exclusion of cause related to underlying disease or compression.

CLINICAL FEATURES: (1) Onset over days (mean nadir at 2 d but range 4 h–21 d). **(2) Sensory level**, numbness 75%, dysesthesias 54%. **(3) Motor function:** Depends on level, lesion extent. **(4) Bowel/bladder** dysfunction (urinary retention) 68%. **(5) Spinal shock:** Sometimes occurs in hyperacute stage (legs flaccid and areflexic). Then UMN signs develop. **(6) Pain:** Radicular back pain common. **(7)** 89% unable to walk and/or vent-dependent.[14]

DIAGNOSTIC TESTING[15,16]: In addition to CIS workup:

- **MRI spine:** Cervical and thoracic segments. Only need to include lumbar if suspect cauda equina lesion; sagittal T1 and T2, axial T2 spin-echo sequences, sagittal and axial T1 post-gadolinium.
- **CSF:** Consider cytology to evaluate intramedullary neoplasm.
- **Serum:** Consider B_{12}, MMA, folate, copper; CXR, blood cultures.

DIFFERENTIAL DIAGNOSIS: Monophasic/idiopathic, ADEM, MS, NMO, NMO spectrum disorder, compressive lesion, spinal cord infarct.

TREATMENT: Little evidence, but standard of care is high-dose steroids—IV methylprednisolone 30 mg/kg up to 1 g daily or IV dexamethasone 100 mg daily × 3 to 5 d (+ PPI, Ca/vitamin D). Consider IVIG, PLEX, and alternative diagnoses (i.e., vascular) if not responsive.

PROGNOSIS: Risk of death w/ high cervical lesions, although rare. **(1) Recurrence risk: Complete TM**: 89% are monophasic. Risk increased if + NMO IgG.[14] **Incomplete TM**: More likely to develop MS. Check brain MRI. **(2) Recovery**: May continue for 2 y. Better prognosis for recovery in older age, prompt diagnosis, lower level and shorter segment affected, no T1 hypointensity on MRI, no CSF WBC.[14]

Radiologically Isolated Syndrome (RIS)

MRI w/ lesions suggestive of MS but no clinical symptoms. Repeat brain and c-spine imaging at 3 mo and every 6 to 12 mo thereafter. Current practice is not to treat even if new lesions, unless there is an attack. Risk of progression to MS in children is unknown.

Pediatric Onset Multiple Sclerosis (POMS)

DEFINITION: Attacks of demyelination within the CNS, disseminated in time & space.

EPIDEMIOLOGY: 8,000 to 10,000 children in the US, 3% to 10% of MS patients have symptoms before age 18 y; 1:1 female:male before age 10 y, then F > M.[17] Disease is more severe in African Americans. 3% to 5% of MS patients have a 1st-degree relative w/ MS.[18]

PATHOPHYSIOLOGY: T lymphocytes attack oligodendrocytes, leading to decreased myelin production + damage to underlying axons. Process is potentiated by memory B cells. There is a multifactorial etiology with known genetic (HLA type, many additional SNPs) and environmental (prior EBV infection, smoking, latitude, vitamin D) risk factors.

DIAGNOSTIC CRITERIA: See Tables 17.2 and 17.3.

TABLE 17.2 MRI Analysis for Diagnosis of MS

Dissemination in SPACE (DIS) Criteria	Dissemination in TIME (DIT) Criteria
• ≥1 T2 lesion in at least 2/4 areas of the CNS: periventricular juxtacortical infratentorial spinal cord • GEL not required • If brainstem or spinal cord syndrome is present, symptomatic lesions are excluded from the lesion count	• 1 new T2 lesion and/or GEL on follow-up MRI, with reference to baseline scan, irrespective of timing of baseline MRI • Simultaneous presence of asymptomatic GEL and non-enhancing lesions at any time

GEL, gadolinium-enhancing lesion.

CLINICAL FEATURES

Optic Neuritis (see "ON" above).

Brainstem Symptoms: (1) Oculomotor dysfunction; diplopia. Most classically internuclear ophthalmoplegia (INO). **(2)** Generalized brainstem processes (ddx: central pontine myelinolysis, Behçet). **(3)** Vertigo, nystagmus, (ddx: broad). **(4)** Cerebellar ataxia (ddx: ADEM, cerebellitis, acute cerebellar ataxia). **(5)** Facial nerve palsy (ddx: Lyme; sarcoidosis).

Cerebral Symptoms: Focal weakness, sensory changes, etc.

Spinal Cord Symptoms: Transverse myelitis (***see "TM" above***).

Pain Syndromes: (1) Lhermitte sign: Neck flexion causes electrical sensation down back; not specific to MS but indicates cervical pathology; **(2)** Tonic spasms (ddx: NMO, spinal strokes). **Cognitive/mood changes**: Decreased processing speed and working memory; language and memory deficits; change in school performance, fatigue, depression, and anxiety.

MS ATTACK/RELAPSE: A patient-reported or objectively observed event typical of an acute inflammatory demyelinating event in the CNS, with duration of at least 24 h, in the absence of fever or infection. **DDx for Attack:** Rule

TABLE 17.3 Revised McDonald Criteria 2010

No. of Clinical Attacks	No. of Lesions Clinically Evident	Additional Criteria for Dx
≥2	≥2 or 1+ reasonable historical evidence of prior attack	None
≥2	1	DIS or await 2nd attack implicating new site
1	≥2	DIT or await 2nd clinical attack
1	1	DIS by MRI *and* DIT by MRI *or* 2nd clinical attack

Note: Specifically inclusive of POMS. DIS criteria more sensitive than international pediatric MS study group (IPMSSG) criteria. Approx. 50% pediatric MS patients meet 2010 criteria at 1st MRI.[41,42]

out pseudorelapse (recrudescence of old deficits) from infection. **Routine w/u** (minimal): Look for trigger as indicated by presentation and consider MRI w/ and w/o gad.

DIAGNOSTIC APPROACH: MUST r/o MS mimics.

- **H and P:** Systemic symptoms (rash, arthralgias); recent infections, fevers, or vaccinations; prior episodes of motor/visual/sensory loss; recent trauma; family history.
- **Serum**: Lyme in endemic regions, B_{12}, HIV if risk factors, ESR, ANA, ACE if suggestive features or risk factors for sarcoidosis.
- **MRI:** (T1 axial w/ gadolinium, T2/FLAIR axial and sagittal). *Brain:* Multifocal WM lesions, usually >3 mm. Corpus callosum involvement most specific. ***Dawson Fingers:*** Periventricular ovoid lesions w/ long axis perpendicular to ventricles. T2-hyperintense lesions (**T2H**): stable, shrink, or grow. T1 hypointensities = ***"black holes"*** = old plaques representing axonal loss; may persist for years. Acute plaques = gad-enhancing lesions (**GEL**), fade after 4 to 6 wk. *Spinal Cord*: usually cervical, peripheral, partial TM, <1 cord segment, although in POMS may be longer, may be asymptomatic.
- **CSF:** WBC <50, rarely higher, although younger patients can have higher; **IgG index** = (CSF IgG/ CSF albumin) / (serum IgG/serum albumin); normal range 0.34 to 0.66; **oligoclonal bands** (OCB): + in CSF and not serum (present in 92% pediatric patients, although may not be present at time of 1st attack[19]).
- **VEP**: Delayed but preserved wave form if history of ON; studies show abnormalities in unaffected eyes as well. VEPS are not done routinely for diagnosis with current diagnostic criteria.

Clinical Patterns: (1) RRMS: Relapsing remitting MS; **98%** RRMS in POMS. **(2) PPMS:** Primary progressive MS (VERY rare in POMS; requires extensive w/u to rule out differential considerations); **(3) SPMS:** Secondary progressive MS (RRMS initially, later progressive). ~20 to 30 y to develop in untreated POMS patients.

Red Flags Suggestive of Possible Alternative Diagnosis[20]: (1) Hearing loss, especially bilateral; **(2)** Progressive or stroke-like onset; **(3)** Elevated ESR, CSF: protein >100 mg/dL, WBC > 50 mm^3, presence of PMNs, or normal CSF; **(4)** MRI: Normal, unilateral lesions; **(5)** Systemic: Coexisting systemic/autoimmune d/os, peripheral nervous system symptoms; **(6)** Atypical MRI: Gray matter involvement, anterior temporal lobes, punctate, tumorlike mass, spinal cord lesion extent >3 vertebral segments.

DIFFERENTIAL DIAGNOSIS: Infectious (viral, Lyme, West Nile virus), genetic/metabolic disorders (CADASIL), ADEM, endocrinopathies, vasculopathies, inflammatory disorders, leukodystrophies, mitochondrial disorders, nutritional deficiencies, neoplasms.[20]

TREATMENT

ACUTE: **IV methylprednisolone (Solu-Medrol)** 30 mg/kg, max 1 g/d ×3 to 5 d ± 10 to 14 d PO prednisone taper (usually not indicated). Give H2 blocker or PPI and check urine for glucose. If glucosuria, check finger stick and consider insulin if persistently elevated. Steroids speed recovery but do not improve long-term outcomes. **Plasmapheresis:** Fulminant cases refractory to steroids.

CHRONIC: Disease modifying therapies (DMT). See Table 17.4.

Indication: Approved only for RRMS in adults. **None approved for POMS.** Some case series of 1st-line DMTs in POMS.

TABLE 17.4 Disease-Modifying Therapies (DMTs)

Drug	Notes/Dose	Mechanism	Monitoring	Side Effects
1st Line				
Beta-IFNs	*Neutralizing Antibody (Nab) formation*[1] Premedicate with NSAID to improve tolerability	Enhance suppressor T cells, ↓ release of metalloproteinases & pro-inflammatory cytokines, prevent helper T-cell adhesion to BBB, down-regulate antigen presentation	CBC & LFTs @ baseline, 1 mo, 3 mo, 6 mo; then q3–6 mo. TFTs q6 mo	Injection site inflamm, HA; flu-like Sx, rhinitis, fatigue. *Rare*: depression, szs, thyroid abnls, suicide, ↓ plts, lymphopenia, ↑ LFTs, symptomatic hepatitis
1a = Avonex	30 µg IM q wk			
1a = Rebif	22 or 44 µg SC 3×/wk (titrate over 4 wk)			
1b = Betaseron	8 MIU SC q.o.d. (0.25 mg; titrate over 6 wk)			
1b = Extavia	Similar to Betaseron			
Glatiramer Acetate = Copaxone	20 µg SC daily	Acetate salt of synthetic polypeptides → MBP mimic. Possibly bind MHCs & cause shift from TH1 to TH2 cells	None	Local injection site rxn. Localized lipoatrophy. Postinjection reaction—"rush", flushing, &/or transient panic
2nd Line[2]				
IVIG	2 g/kg divided over 2 d 1st dose, then 1 g/kg monthly		Consider baseline IgA, if low, cannot receive IVIG	Allergic reaction, aseptic meningitis, HTN, HA, venous thrombosis, pulmonary edema, allergic rxns, dermatitis

Solu-Medrol = methylprednisolone	30 mg/kg up to 1g IV monthly		None w/ intermittent dosing	Rare with intermittent dosing; HTN, ↑ glucose, osteopenia, avascular necrosis of the hip
Natalizumab = Tysabri[3]	300 mg IV q.mo. Most often reserved for refractory cases. Very effective (↓ relapse rate 68%)	Ab to alpha-4 integrin → ↓ T-cell crossing BBB	JCV Ab—q6 mo, to date no JCV neg pts have developed PML; MRI q6–12 mo looking for PML. Dermatology exams. (↑WBC common)	Hypersensitivity rxn (d/c if occurs); fatigue, anxiety, pharyngitis, sinus congestion, peripheral edema; ↓ risk melanoma, hepatic injury; **PML** (risk ~1/1,000 @ 18 mo.[43] Abs (6% patients, ↓ clinical effectiveness & ↑ infusion rxns. Test @ 6M if ongoing MS activity or persistent infusion rxns; if +, retest 3M later & if still +, d/c)
Fingolimod = Gilenya[4]	0.5 mg PO daily. Use in POMS under 18 y limited—concerns re-effect on developing immune system. Contraindicated in long QT, concurrent heart rate slowing medications	sphingosine-1-phosphate receptor modulator → sequesters lymphocytes in lymph tissue	VS observed for 6 h after 1st dose, EKG before & after 1st dose, baseline Mg, baseline and 6 mo ophthalmology exam, verify VZV immunity before; varivax ×2 separated by 1 mo if not immune	Cardiovascular: transient ↓ HR after 1st dose & sustained ↑ BP, opportunistic infections (2 deaths in trial—HSV encephalitis, disseminated zoster), macular edema (↑ DM patients)
Cyclophosphamide = Cytoxan	500–750 mg/m^2 IV q4wk or 10 mg/kg q2wk	Alkylating agent → ↓ lymphs	CBC w/ dif,	Infection, hair loss, nausea, menstrual irregularities, infertility, malignancy long term

(continued)

TABLE 17.4 Disease-Modifying Therapies (DMTs) (Continued)

		2nd Line		
Drug	**Notes/Dose**	**Mechanism**	**Monitoring**	**Side Effects**
Rituximab = Rituxan	1 g IV on days 0 and 14 or 375 mg/m^2 weekly × 4. Safe treatment duration unknown	Monoclonal Ab against CD20 on B lymphocytes, causing B-cell depletion	B-cell subsets/CD 19 count 2 wk after last dose to confirm depletion, repeat q3–6 mo; consider repeat course when B cells return	Allergic reaction, infection, PML reported in non-MS patients, long-term risks unknown
Dimethyl Fumerate (DMF, BG-12)[5]	120 mg PO BID × 7 days, then 240 mg BID	Mechanism unclear	CBC w/dif, baseline and intermittently	Lymphopenia, flushing, GI upset

[1]a/w more frequent, higher doses; ↑ rate of relapses, & new T2H. *Conflicting guidelines.* Consider: Test @ 12 to 24 mo. If Nab pos, recheck in 3 to 6 mo; if still pos, consider switch to alternate DMT. If Nab neg, no further testing needed.
[2]**Second-line DMT:** Use only recommended by physicians with experience prescribing these medications.
[3]**RISK MGT:** (1) Reserve for: (a) failed/developed intolerance to initial DMTs. (b) aggressive initial dz. (2) Rx via TOUCH (Tysabri Outreach: Unified Commitment to Health) risk mgt program. (3) d/c steroids & immune modulators 1 mo prior to Natalizumab initiation.
[4]See current label for restrictions & monitoring parameters.
[5]Newly approved at the time of publication without experience in pediatrics. At this time it is unclear if this will become first or second line therapy.

Utility: Decrease severity and number of relapses, fewer steroid courses and hospital stays, fewer MRI lesions, and decrease disability accumulation and brain atrophy.

Principles of use: **(1)** Recommend once diagnosis is established. **(2)** Selection based on compliance likelihood, tolerance of side effects, presence of mood disorder. **(3)** If persistent breakthrough, increase dose (for IFN) or switch DMT class. **(4)** Check MRI every 6 to 12 mo after starting DMT to evaluate efficacy.

Vitamin D: No RCTs showing efficacy of supplementation, but low levels have been associated w/ conversion to MS and higher relapse rate. Goal 25-hydroxy vitamin D level at least 30 ng/mL. If <30, 50,000 IU once a week ×6 wk with Ca supplementation, then 1,000 to 2,000 IU/d. All patients should be on at least 1,000 IU vitamin D, the current RDA.

SYMPTOMATIC

General Guidelines[21]**:** Careful history and exam; r/o non-MS causes (e.g., fatigue vs. insomnia due to poor sleep schedule). Tackle one problem and one intervention at a time, to avoid polypharmacy. Encourage social support groups; refer to the MS Society Web site (www.nationalmssociety.org). Attend to cognitive, developmental, psychosocial consequences and familial coping.

Frequent in POMS

Cognitive Symptoms: Common and underappreciated in POMS. *Workup:* Neuropsychologic evaluation. *Rx:* Avoid cannabis, which decreases cognition,[21a] school accommodations (extra test time, excused absences for flares and appointments, preferential seating), compensatory strategies (e.g., notebook, calendar, pill cases, PDA, mnemonics), treat fatigue (see below). DMTs may limit disease progression and help, although may also contribute, especially IFN causing/exacerbating depression.

Affective Symptoms: Depression, anxiety—combined psychotherapy and antidepressants.

Visual: ON: Rx: visual rehab referral, preferential seating, magnifying glass, high-contrast reading materials or electronic material to increase font.

Fatigue: Most common disabling symptom of MS. Identify causes (e.g., depression, pain, sleep disorders, medications, comorbid conditions). Rx: Amantadine 100 mg daily; Modafinil 100 to 200 mg q.a.m. and midday, stimulants.

GU: (1) Failure to store—workup urgency and frequency by ruling out UTI and evaluating with urodynamic studies. Treat with scheduled voiding and/or anticholinergic medication. Try long-acting or selective muscarinic antagonists if dry mouth or cognitive occur. **(2) Failure to void:** Workup urinary retention with post-void residual (abnormal if >100 cc or >10% of voided volume remain). Treat with scheduled voiding. **(3) UTIs:** Urologic w/u if frequent despite optimal treatment.

GI: Constipation: Eliminate pharmacologic causes, increase fluid and fiber intake, give stool softeners (lactulose, polyethylene glycol, docusate sodium).

Less Frequent in POMS

Motor: Weakness, spasticity—Rx OT/PT/rarely muscle relaxants/antispasticity medications. **Gait fatigue:** Rx: dalfampridine may improve mobility,

although not approved <18 y. **Dose:** 10 mg PO b.i.d. for adults. **Sensory disturbances:** Consider neuropathic pain meds (e.g., gabapentin, pregabalin, duloxetine).

DISEASE MONITORING

Relapses: Rate is usually annualized per year and is higher in POMS than adults.

Disability Scales: Expanded Disability Status Scale (**EDSS**) (0–9): 0 = normal neurologic exam, 2 = minute disability, 4 = ↓ walking, 6 = needs assistance, cane, 7 = wheelchair, 9 = helpless, bed-bound, 10 = death. 50% MS patients go from 0 to 6 in 10 y. This adult scale is weighted for ambulation (vs. cognition, fatigue, and pain). Felt to be insensitive in POMS given usual lack of motor signs and not sensitive to cognitive disability.

MRI: area/activity: Obtain MRI brain w/ and w/o gad q6 mo if active, yearly if stable both clinically and radiographically. MRI: C and T spine w/ and w/o gad approximately every other scan depending on spine lesion activity. In POMS it is common to see MRI changes in the absence of clinical activity, thus the best approach is uncertain.

PROGNOSIS: Compared to adult onset, POMS has a higher relapse rate, longer time to similar disability and SPMS but disease burden accumulates by a younger age. Significant cognitive and school issues are common.

VARIANTS: Tumefactive demyelination: May occur in isolation or in MS. MRI demonstrates a large, usually solitary mass w/ mass effect, edema, ring enhancement, and T2-hypointense border (ddx: tumor, abscess).

Neuromyelitis Optica (NMO; Devic disease, opticospinal MS)

DEFINITION: A demyelinating disease predominantly affecting the ON and spinal cord. The relapsing form tends to be more aggressive than MS w/ increased severity of attacks and poor recovery from attacks.

EPIDEMIOLOGY: Unknown prevalence in adults and children. In adults >3:1 female:male and may be more common in non-Caucasian populations, esp. Asian and African, 73% non-Caucasian.[22–25]

PATHOPHYSIOLOGY: Antibodies to aquaporin-4 bind at astrocytic foot processes leading to astrocytic damage, which leads to inflammatory lesions predominantly in aquaporin-rich regions and demyelination resulting in necrotic, cystic lesions.

DIAGNOSTIC CRITERIA[26]:

Major criteria, require both: TM and ON

Supportive criteria, require ⅔: (1) MRI spine with contiguous T2 abnormality over ≥3 vertebral segments; (2) NMO IgG +; (3) Brain MRI not consistent w/ MS criteria (see Tables 17.2 and 17.3).

CLINICAL FEATURES[22]: (1) Course: Relapsing (93%). NMO spectrum disorders include monophasic ON + TM, relapsing ON, and relapsing TM. **(2) TM:** Longitudinal extensive TM (LETM; spans >3 vertebral segments). **(3) ON:** Onset more often acute and bilateral than idiopathic ON. More widespread injury than in MS is seen on imaging. **(4) Brain lesions** are more common than initially described (68%) in aquaporin-rich regions (periventricular in the medulla > supratentorial and infratentorial WM > midbrain > cerebellum > thalamus > hypothalamus). Encephalopathy; ophthalmoparesis, ataxia, seizures, intractable vomiting or hiccups are common (45% have one or more of these). Endocrinopathies and PRES can occur.

(5) Associated d/os: In children 42% have a concurrent autoimmune d/os (SLE, Sjögren, juvenile RA, Grave disease, autoimmune hepatitis).

Diagnostic testing:

- **Serum:** + serum NMO IgG (anti-aquaporin4-Ab) (73% sensitive, 91% specific for NMO)[27]; + in 47% of NMO, 78% of relapsing NMO.[23] If serum negative but there is a strong suspicion, check CSF NMO IgG, although serum more often.
- **CSF**: Usually pleocytosis (can have eosinophils, PMNs). No OCBs bands in >80%. IgG index normal or transiently increased.
- **MRI ± gad**: Spine: TM (LETM spans >3 vertebral segments), although less common in pediatric NMO than adult; Brain: lesions are frequent in NMO+ patients (see clinical presentation for location of lesions).

TREATMENT[28]:

ACUTE: IV methylprednisolone 30 mg/kg up to 1 g daily ×5 d, followed by "slow" steroid taper (*recommended steroid duration and taper duration unclear, but 4–6 mo advisable*). If symptoms progress despite steroids or improvement is insufficient, give 2nd steroids course or plasmapheresis (up to 7 exchanges every other day) may minimize EDSS.[29]

CHRONIC: No RCTs or FDA-approved treatments. Aim for humoral suppression to prevent attacks leading to disability. Treat all NMO IgG+ patients even after 1st attack, and all relapsing patients, even if NMO IgG negative.

First-Line: Mycophenolate mofetil (CellCept) 30 to 50 mg/kg divided b.i.d. up to 3 g/d PO b.i.d. OR Rituximab 375 mg/m^2 weekly ×4 or 1,000 mg ×2 d and 14 w/ reinfusion after 6 to 12 mo (optimal frequency unknown) OR azathioprine (Imuran). **Alternatives:** Cyclophosphamide (Cytoxan) (choose if concurrent SLE/Sjögren), IVIG, methotrexate, intermittent PLEX.

PROGNOSIS: Generally expect some improvement within weeks of onset. 90% of patients have residual disability (54% visual, 44% motor deficits). ***Relapsing* NMO:** There was better motor recovery after initial TM event[22]; 98% of seropositive children (4–18 yo) have ON, TM, or both within 12 mo; 93% of attacks were recurrent, 90% had residual disability; ***Monophasic NMO:*** 20% have permanent visual loss and 30% have permanent paralysis in at least one leg. Good predictors of monophasic course at 1st attack include male sex, concurrent TM and ON, NMO Ab negative. ***Secondary progressive*** course is controversial and rare.

NMO VARIANTS

NMO SPECTRUM DISORDER: (1) Recurrent or monophasic LETM; **(2)** bilateral monophasic or recurrent isolated ON; **(3)** Monophasic NMO: both TM and ON w/o recurrence. This tends to have fulminant onset (12.5% NMO Ab +)[23]; **(4)** Asian optic-spinal multiple sclerosis can have CNS involvement similar to MS; **(5)** LETM or ON associated w/ systemic autoimmune dz.

NEUROINFLAMMATORY NON-DEMYELINATING DISEASES

Acute Necrotizing Encephalopathy (ANE)

DEFINITION: Recurrent episodes w/ acute onset encephalopathy w/ characteristic MRI pattern (Fig. 17.4) triggered by infection in genetically susceptible patients.

EPIDEMIOLOGY: Most present in early childhood (range, infancy–adult). Most commonly seen in Asia.

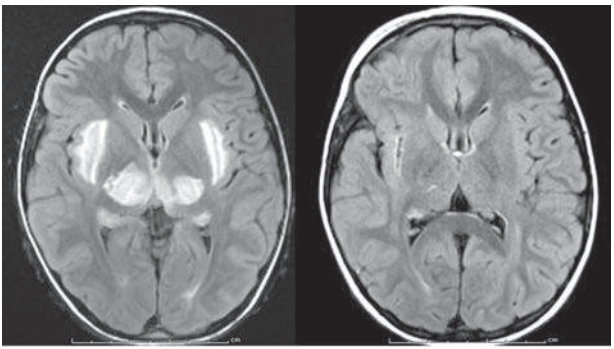


FIGURE 17.4 Typical acute necrotizing encephalopathy (ANE) with bilateral thalamic and external capsule T2/FLAIR hyperintense lesions during acute attacks with almost complete resolution at follow-up.

PATHOPHYSIOLOGY: Majority associated w/ an autosomal dominant mutation in RANBP2 w/ incomplete penetrance. Attacks are classically triggered by influenza A.

TREATMENT: Methylprednisolone 30 mg/kg IV (Max 1g) daily × 5 d may be effective. IVIG is not effective.

PROGNOSIS: Ranges from full recovery to death. Better if treated early with high-dose steroids. Worse outcome if brainstem involvement.

Vasculitis

(aka angiitis; note different than adult vasculitis, especially small vessel form in pathology and prognosis)

PRIMARY VASCULITIS: Includes small and large vessel subtypes. *Calabrese criteria:* (1) newly acquired neurological deficit, (2) angiographic or histological evidence of CNS vasculitis, and (3) absence of an associated systemic condition.[30]

LARGE VESSEL VASCULITIS: Involvement of the large- or medium-sized vessels which are visible by MRA or angiography. Progressive (30%) or nonprogressive (70%).[31]

CLINICAL FEATURES: 81% acute hemiparesis, 79% hemisensory deficits, 56% headaches, 37% cognitive dysfunction, 26% mood/personality changes.[31]

DIAGNOSTIC TESTING: Same as for stroke. MRI commonly shows ischemic lesions in a vascular territory (anterior circulation most frequent), unilateral (93%), supratentorial (98%).[32] MRA, conventional angiography w/stenosis, beading, or occlusion. Biopsy not indicated.

TREATMENT: Antiplatelet agents are typically used. *Progressive:* see small vessel protocol below. *Nonprogressive:* Controversial; Toronto group recommends 3 mo of steroids to decrease recurrent stroke.[33]

SMALL VESSEL VASCULITIS: Involvement of small vessels not visible on MRA or angiography.

CLINICAL FEATURES: Fever, headache (90%), behavioral/cognitive changes (95%–100%), focal neurologic deficit (63%), seizures (80%), refractory status epilepticus (16%), ON (20%), myelopathy (17% of those who had cord imaging).[34]

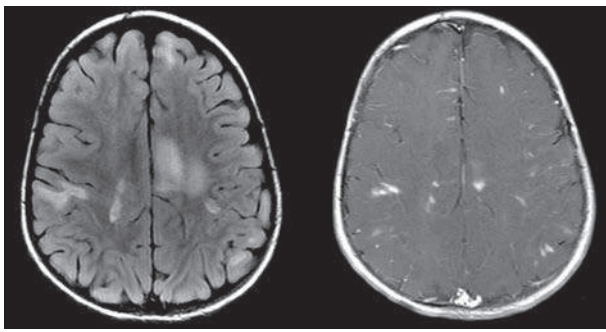


FIGURE 17.5 Pediatric Small Vessel CNS Vasculitis. MRI findings can range from normal to meningeal enhancement to gray and white matter lesions anywhere in the CNS. Bilateral, diffuse T2/FLAIR hyperintensities involving gray and white matter with lesional and meningeal enhancement is shown.

DIAGNOSTIC TESTING

- **MRI**—T2-hyperintense lesions involving gray and white matter, may be bilateral or unilateral, usual multifocal that do not conform to a vascular territory, enhancement 40%, meningeal enhancement in 30% (Fig. 17.5).[34] MRA normal.
- **Conventional angiography**—depending on center, is generally still done to rule out large vessel involvement but controversial.[35]
- **Serum:** *ESR, CRP, von Willebrand factor antigen* (marker of vessel wall injury). Consider Lyme, *Mycoplasma*, EBV titers, ANA, ANCA, ACE, ENA (extractable nuclear antigens) if ANA + antiphospholipid antibodies (lupus anticoagulant, anticardiolipin antibodies, β-2-microglobulin antibodies), vitamin B_{12} to rule out alternative diagnoses.
- **LP:** *Opening pressure, CSF pleocytosis, and elevated CSF protein* are all nonspecific markers. Consider Mycoplasma PCR, EV, HSV, EBV, VZV PCR, VZV IgM and IgG, cytology.
- **Brain biopsy** is required for diagnosis. Lesional (preferred, ideally enhancing) or nonlesional, right frontal, 1 cm^3 including meninges, gray and white matter en bloc. Demonstrates intramural lymphocytic inflammation within small vessels w/ vascular wall injury. Results are affected by steroids, thus ideally biopsy within 2 wk of starting steroids. (Note does not require necrosis or granuloma as in adults). If there is suggestion of systemic vasculitis, consider biopsy of involved organ rather than brain.

DIFFERENTIAL DIAGNOSIS: ADEM, autoimmune or infectious encephalitis, mitochondrial disorder (MELAS).

TREATMENT: Toronto protocol: 30 mg/kg (up to 1 g) IV methylprednisolone followed by 2 mg/kg (up to 60 mg) daily w/ taper qwk 50, 40, 30, 25, 20 by 2.5 mg until off. Calcium and vitamin D supplements while on steroids.[34] Cyclophosphamide (500–750 mg/m^2 IV q4wk ×7 doses, or 10 mg/kg q2wk ×6 mo), followed by 18 mo of mycophenolate mofetil. PCP prophylaxis while on Cytoxan and 6 mo after. TNF blockers have been used as second-line. Treat symptomatically—seizures, spasticity, psychiatric symptoms, school support.

PROGNOSIS: Largely unknown. Majority of treated seem to do well with stabilization and improvement, but this may take years to reach new baseline.[34] Early and aggressive therapy appears to improve prognosis. Minority continue to progress or have relapses.

SECONDARY/SYSTEMIC (i.e., lupus, inflammatory bowel disease, infectious, postinfectious)

TREATMENT: Treat underlying disease.

RARE VARIANTS

Susac Syndrome

INTRODUCTION: A rare microangiopathy of unknown etiology affecting the arterioles of the brain, retina, and cochlea, predominantly affecting young, healthy women.

CLINICAL FEATURES: Classic triad: (1) subacute encephalopathy, (2) visual loss due to branch retinal artery occlusion, and (3) sensorineural hearing loss.

DIAGNOSTIC TESTING: Fluorescein retinal angiogram, MRI brain w/ and w/o gad can show enhancing gray and white matter T2 hyperintensities, particularly of the corpus callosum (often white, fluffy, round "snowball"), audiometry.

TREATMENT: There is no standard due to rarity. Early treatment appears to improve prognosis. Steroids, IVIG, cyclophosphamide, antiplatelets, antithrombotic agents, plasmapheresis, and hyperbaric oxygen have been used.

Cogan Syndrome

INTRODUCTION: A chronic autoimmune disease of unknown etiology causing bilateral sensorineural hearing loss, vestibular symptoms, ocular inflammation (⅔ have classic, interstitial keratitis) ± systemic autoimmune disease.

EPIDEMIOLOGY: Rare, although described more than Susac syndrome. Typically affects young Caucasian adults.

CLINICAL FEATURES: Often starts w/ isolated ocular, auditory, or vestibular involvement.

DIAGNOSTIC TESTING: CBC, ESR, CRP, syphilis, ophthalmology exam, audiometry, and ENT evaluation. Neuroimaging is often normal.

DIFFERENTIAL DIAGNOSIS: Often misdiagnosed as Meniere syndrome initially.

TREATMENT: Methotrexate, cyclophosphamide, cyclosporine, ASA, steroids, cochlear implantation.

Autoimmune Encephalopathies

DEFINITION: Encephalitis is encephalopathy with any of the following: fever, seizure, focal neuro finding, CSF pleocytosis, EEG finding, or neuroimaging finding. If lab indicators suggestive of autoimmune etiology and other causes including infection are ruled out, consider autoimmune encephalitis. Full attempt to find specific markers of autoimmune entity should be pursued before trial of immunosuppression.

EPIDEMIOLOGY: Etiology for 63% of cases in the California Encephalitis Project remained classified as unknown after extensive infectious investigation.[36] Later some of these were reclassified as NMDA-receptor encephalitis.

Some of the unknown are likely autoimmune entities that have not been described.

DIAGNOSTIC TESTING: 1st must rule out infection. Beyond routine studies and PCR for EBV and HSV, workup should be tailored based on presentation, location, season, immune status, and exposures. Priority should be given for testing treatable diseases. Obtain MRI brain, MRA if vasculitis is considered, MRS if metabolic etiology is considered.

DIFFERENTIAL DIAGNOSIS: Infectious encephalitis, ADEM, ANE, vasculitis, MELAS, or other mitochondrial disorder.

VARIANTS

Hashimoto Encephalopathy (SREAT—Steroid-Responsive Encephalopathy Associated with Autoimmune Thyroiditis)

DEFINITION: Steroid-responsive encephalopathy with elevated TPO (thyroperoxidase) and/or TG (thyroglobulin) antibodies. This is likely not a distinct autoimmune encephalopathy or disease, but a subset of patients with autoimmune encephalitis may have thyroid antibodies.

EPIDEMIOLOGY: Rare and controversial.

PATHOPHYSIOLOGY: Unknown.

DIAGNOSTIC TESTING: Test for other autoantibodies and paraneoplastic antibodies. If more specific antibody present, would use more specific diagnosis.

Paraneoplastic Syndromes

DEFINITION: Antibody-associated disorders that are classically associated with a tumor, although not always. These can also be qualified as autoimmune encephalopathies. The well-defined intraneuronal antibody disorders (anti-Ma, Hu, Yo) are typically associated with adult cancers, minimally responsive to immunotherapy and exceedingly rare in children. A growing list of neuronal surface and synaptic antibody-mediated disorders are variably associated with neoplasms, more immunotherapy responsive in general and relevant to children, particularly anti-NMDA receptor (NMDAR) encephalitis. Others include anti-AMPA, anti-$GABA_B$, anti-LGI1, and anti-Caspr2 receptor encephalitides.[37] What was initially thought to be VGKC Abs, has been identified as several antibodies to the protein complex, including LGI1.

Anti-NMDA Receptor Encephalitis[38,39]

DEFINITION: Autoimmune encephalitis caused by antibodies to NMDA receptor that may or may not be associated with a tumor.

EPIDEMIOLOGY: 40% of patients are ≤18 y, 18% male. Ovarian teratoma is present in females (56% ≥18 y, 31% ≤18 y, 9% ≤14 y). No tumors identified to date in boys under 10 y.

PATHOPHYSIOLOGY: Antibodies bind the NR1 subunit of NMDAR, causing receptor endocytosis and subsequent neurologic dysfunction.

CLINICAL FEATURES: 87% present with behavioral/psychiatric change, 9.5% dyskinesias or dystonias, 3% speech reduction. Symptoms progress over days to weeks. Features: 77% seizures, 84% stereotyped movements (45% orolingual dyskinesias, 32% choreoathetosis), 86% autonomic instability, 23% hypoventilation (less frequent than adults), enuresis, sleep disturbance, muscle rigidity, elevated CK.

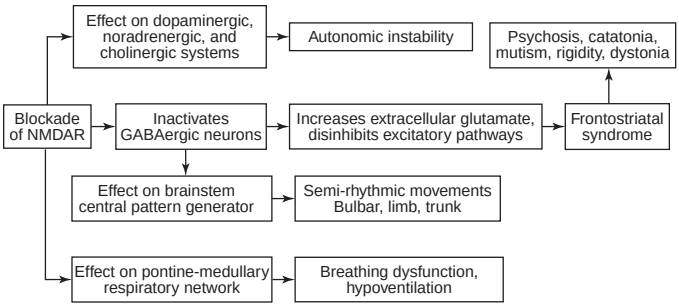


FIGURE 17.6 Treatment approach for anti-NMDA receptor encephalitis.[40]

Diagnostic testing

- **NMDAR Ab testing:** Must be positive in CSF or serum for diagnosis. CSF is more sensitive. Treatment may normalize antibodies, so test or save samples before. CSF was abnormal in 94% (87% lymphocytic pleocytosis, 13% elevated protein, 83% OCB unique to the CSF), 31% had abnormal MRI, 100% had abnormal EEG (28% epileptiform). Other autoantibodies may be present indicating a tendency to autoimmunity.
- **Look for tumor**—ultrasound of abdomen and pelvis in females, testicles in males, *and* MRI abdomen and pelvis. Periodic MRI or ultrasound is recommended.

DIFFERENTIAL DIAGNOSIS: Viral encephalitis, neuroleptic malignant syndrome, psychosis, catatonia (85% initially presented to psychiatrists), other autoimmune encephalitis, vasculitis, ADEM, epileptic encephalopathy, Sydenham chorea, encephalitis lethargica.

TREATMENT: See Figure 17.6.[40]

***ACUTE*:** (1) All patients should be admitted and provided supportive care as indicated. (2) Tumor resection, if present. (3) Methylprednisolone 30 mg/kg (max 1 g) IV daily ×5 d, IVIG 2 g/kg over 2 to 5 d, and plasma exchange are used first-line.

***CHRONIC*:** Rituximab, cyclophosphamide, or both (see MS section above for dosing regimens).

PROGNOSIS: Median time to improvement 6 wk. Better prognosis if teratoma that is removed. 25% have one or more relapses, 74% substantial or full recovery, although short follow-up. Adult studies show continued improvement over 2 y.

Opsoclonus–Myoclonus Syndrome

See Chapter 16, Pediatric Movement Disorders and Ataxia.

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ONLINE RESOURCES

National MS Society—www.nationalmssociety.org

Guthy Jackson Foundation (NMO charity)—http://www.guthyjacksonfoundation.org/

CNS Vasculitis—www.aboutkidshealth.ca/En/HealthAZ/ConditionsandDiseases/InflammatoryConditions/Pages/CNS-Vasculitis.aspx

18 Stroke and Vascular Neurology

Kevin A. Shapiro and Ferdinando S. Buonanno

OVERVIEW OF STROKE IN INFANTS AND CHILDREN

DEFINITION: A clinical syndrome of rapidly developing focal or global disturbance of brain function lasting >24 h or leading to death with no obvious nonvascular cause (WHO). Problematic in children because (1) children may have infarcts despite rapid resolution of symptoms; (2) presentation may be nonspecific (seizures, headaches); (3) children often present with stroke mimics: migraine, postictal paresis, ischemia due to metabolic disease (e.g., mitochondrial disorders).[1]

EPIDEMIOLOGY: Varies by age. **Neonates:** Estimates vary but rate of stroke is ~1:4,000 to 1:5,000 live births,[2] equivalent to annual incidence of large-vessel ischemic stroke in adults; if late-presenting presumed perinatal strokes are included, incidence may be as high as ~1:2,500; 80% ischemic, remainder cerebral venous thrombosis (CVT) or hemorrhage. **Children:** Variable estimates; in children <16 y, most studies estimate incidence of 2.3 to 2.7/100,000 per year; however, some studies suggest incidence as high as 13/100,000 per year. Approximately 55% are ischemic and 45% are hemorrhagic, although the proportion varies across studies; about 10% of hemorrhages result from CSVT. All varieties of childhood stroke have a male predominance; African American children have a higher risk even after accounting for sickle cell disease (SCD).[1,3,4]

RISK FACTORS: Risk factors for all stroke types include infections, leukocytosis, anemia, prothrombotic state. **Arterial ischemic stroke (AIS):** Underlying conditions include SCD, heart disease; acquired conditions include head and neck trauma. **Venous stroke:** Underlying conditions include inflammatory bowel disease, autoimmune disorders; acquired conditions include dehydration, infections of the head and neck (e.g., otitis media).

STROKE AND CEREBROVASCULAR DISEASE IN NEONATES

Perinatal Ischemic Stroke

Defined as stroke occurring between 28 wk gestation and 7 d of life.

PATHOPHYSIOLOGY: Thought to occur most often before ~72 h of postnatal life, as early as the second trimester; usually involves middle cerebral artery (MCA) territory (L > R); may result from thrombosis of intracranial vessels, cardioembolism, or embolism from extracranial vessels or placenta (through patent foramen ovale [PFO]).

Maternal risk factors: Maternal infertility, oligohydramnios, preeclampsia, prolonged rupture of membranes, umbilical cord abnormality, chorioamnionitis, primiparity, monochorionic twin gestation, maternal drug use (cocaine or amphetamines), diabetes, antiphospholipid antibodies.

Fetal risk factors: Prothrombotic disorder (68%) including: lipoprotein(a) (20%), factor V Leiden, prothrombin gene mutation, MTHFR mutation, antiphospholipid antibodies, and protein C deficiency; polycythemia; congenital heart defects.

Peri- and postnatal risk factors: Traumatic delivery, perinatal asphyxia, dehydration, hypotension, infection, portal vein thrombosis, intravascular catheters.

CLINICAL PRESENTATION: May present in the immediate postnatal period or after several months or years (presumed perinatal ischemic stroke). **Early (<72 h):** Typically seizures, usually focal motor; hypotonia; apnea; encephalopathy; may also have no clinical signs or symptoms (50%). **Late (>4–6 mo):** Early handedness, seizures, or developmental delay.[5]

EVALUATION: Should focus on establishing presence of injury and potential etiologic mechanisms.

- **Radiology:** *Cranial ultrasound* has low sensitivity for detecting AIS; unilateral decreases in MCA flow velocity may be seen. *Computed tomography (CT)* is insensitive for venous thrombosis and early AIS, but relatively quick and sensitive for hemorrhagic lesions. *Magnetic resonance imaging (MRI)* is modality of choice for arterial stroke in the newborn; diffusion-weighted imaging (DWI) can reliably detect ischemic injury within 24 h of onset (Fig. 18.1), but may pseudonormalize within 7 d (although at this stage T1- and T2-weighted imaging should be abnormal). Encephalomalacia and calvarial hypertrophy (Dyke–Davidoff–Masson phenomenon) can be seen as late sequelae of perinatal stroke (Fig. 18.2). *Magnetic resonance angiography (MRA)* of the neck should be obtained if there is a history of traumatic delivery or other reason to suspect neck trauma resulting in injury/dissection of cervicocephalic vessels. *Echocardiography* should be performed to exclude congenital heart defects and intramural thrombi. *Doppler ultrasound of the umbilical vessels and portal vein* should be performed if umbilical catheters are present.
- **Laboratory:** Initial laboratory evaluation should include hematocrit and prothrombotic risk factors: activated protein C resistance for factor V Leiden, protein C, protein S, lipoprotein(a), antithrombin III, prothrombin gene mutation, homocysteine/MTHFR gene mutation, antiphospholipid antibodies. Repeat testing in 6 to 8 wk is recommended for protein C, protein S, antithrombin III, lipoprotein(a), and antiphospholipid antibodies.[6]
- **Placental pathology**: Often informative due to presence of placental infarcts, vasculopathy, or evidence of perinatal infection.

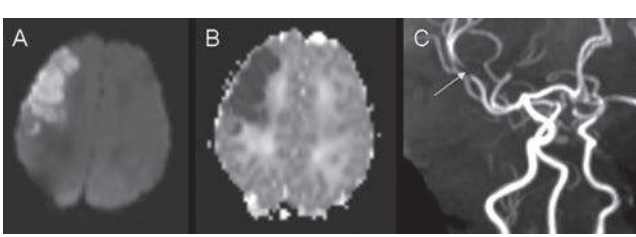


FIGURE 18.1 Corresponding axial slices from diffusion-weighted imaging (DWI) (**A**) and apparent diffusion coefficient (ADC) (**B**) MR sequences demonstrating a right frontal arterial ischemic infarction in a 2-day-old boy who developed focal seizures at 29 h of life. The MR angiogram (**C**) shows focal occlusion of the anterior division of the right middle cerebral artery (*arrow).*

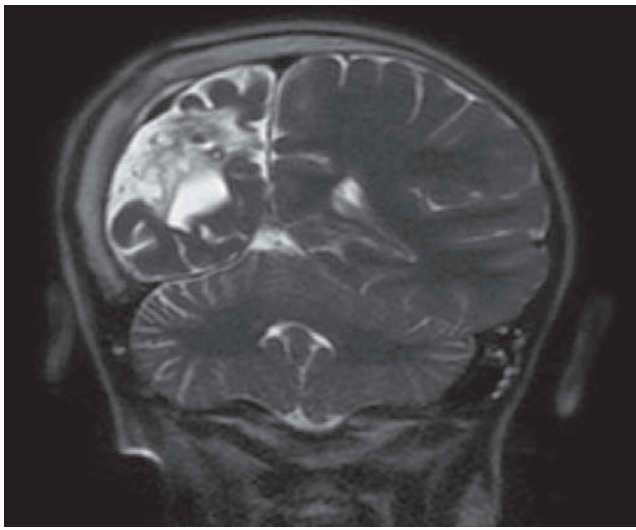


FIGURE 18.2 Coronal T2-Weighted MR Image from an 8-Year-Old Boy with Presumed Perinatal Arterial Ischemic Infarct Affecting the Right Middle Cerebral Artery. The image demonstrates encephalomalacia and atrophy of the right hemisphere, with overlying calvarial hypertrophy (Dyke–Davidoff–Masson phenomenon).

MANAGEMENT: Mainstay of management includes basic neuroprotective strategies: normothermia, normotension, normoglycemia, and control of seizures. Treatment of dehydration and anemia are recommended. Consider folate and B-complex vitamins in infants with MTHFR mutations. Consider anticoagulation in infants with severe thrombophilia or multiple emboli; may also be considered if the etiology is clearly cardioembolic; suggested regimen is enoxaparin 1.5 mg/kg SC b.i.d. *Thrombolytic agents are not currently recommended.*

OUTCOME: Vast majority (>95%) survive into adulthood,[7] but about 64% of children have one or more neurologic disabilities.[8,9]

Risk factors for disability: *Concomitant involvement of cerebral hemisphere, internal capsule, and basal ganglia* is almost always associated with abnormal outcome. Involvement of only one or two of these regions may be associated with normal outcome; involvement of internal capsule is most highly predictive of abnormal motor outcome. Presence of *neonatal seizures* and/or abnormal EEG increases risk of abnormal neurodevelopmental outcome.[10,11] *Neonatal encephalopathy* is predictive of poorer outcomes.[12]

Types of disability: Hemiplegic *cerebral palsy* is a common outcome (37% of children with perinatal AIS recognized in newborn period).[8] A *seizure disorder* may develop, though incidence of epilepsy after the perinatal period is <50% in most studies.[13] Other neurologic comorbidities include delayed language development, visual abnormalities, cognitive and behavioral disorders.

Recurrence of stroke is rare (<2%), although long-term follow-up has been limited; risk factors for recurrence include prothrombotic states and complex congenital heart disease.[14]

Neonatal Hemorrhage

For germinal matrix hemorrhage in preterm infants, see Chapter 19.

EPIDEMIOLOGY: Overall prevalence of intracranial hemorrhage may be as high as 26% if preterm intraventricular hemorrhage and mild bleeding in vaginally delivered term neonates are included. Symptomatic perinatal hemorrhage occurs in ~6/100,000 live births. Types of perinatal hemorrhagic stroke include subdural, subarachnoid, intracerebral, and intraventricular hemorrhage.

RISK FACTORS: Thrombocytopenia; cavernous malformations; genetic diseases (e.g., *COL4A1* mutations); maternal consumption of salicylates, anticoagulants, or anticonvulsants. Infants born to mothers taking warfarin, barbiturates, or phenytoin should receive a higher dose of vitamin K after birth to prevent bleeding. Hemorrhage may also be secondary to CVT.

PRESENTATION: Most present acutely with encephalopathy and/or seizures.

DIAGNOSIS: Often discovered by head ultrasound, but this modality lacks sensitivity and specificity; can be confirmed radiographically by CT or MRI (with gradient-echo and susceptibility-weighted imaging). MRA and MRV are indicated to exclude vascular malformations and venous thrombosis. Laboratory evaluation should include platelet count, coagulation studies, screening for bleeding diatheses (e.g., von Willebrand disease); if thrombocytopenia is present, maternal and infant platelet antibodies should be checked.

MANAGEMENT: Correct underlying coagulopathy with platelet transfusion, coagulation factors, and vitamin K is important. Basic neuroprotective strategies include maintaining normothermia, normotension, normoglycemia, and control of seizures. Surgical evacuation of intracranial hematoma is indicated if there is evidence of increased intracranial pressure. Head circumference should be monitored closely in infants at risk for posthemorrhagic hydrocephalus (e.g., IVH); in these cases, ventricular shunting or third ventriculostomy may be required.

Neonatal CVT

EPIDEMIOLOGY: Neonates account for 43% of CVT in childhood.[15] Superficial venous system is most often involved. Deep venous thrombosis is a common cause of intraventricular hemorrhage in term neonates.

Risk factors in neonates include infection, dehydration, and anemia.

PRESENTATION: Typically presents with seizures or encephalopathy in the 1st few weeks of life.

DIAGNOSIS: In neonates, hemorrhage associated with venous thrombosis may be demonstrated on *head ultrasound*; Doppler ultrasound may be used to interrogate flow within the dural sinuses. On *MRI*, subacute thrombus may be T1 hyperintense; acute thrombus is isointense on T1-weighted images and hypointense on T2-weighted images; T2* (susceptibility)-weighted imaging is most sensitive of MR sequences (Fig. 18.3). *MR venography* can confirm presence of thrombus.

MANAGEMENT: Predisposing factors such as dehydration and systemic infection should be treated. Low molecular weight heparin may be used in neonates with symptomatic CVT, although there is a risk of ICH.

PROGNOSIS: Developmental delays noted in 28% to 58% of children after neonatal CVT; 6% to 28% have cerebral palsy. Seizures after the neonatal

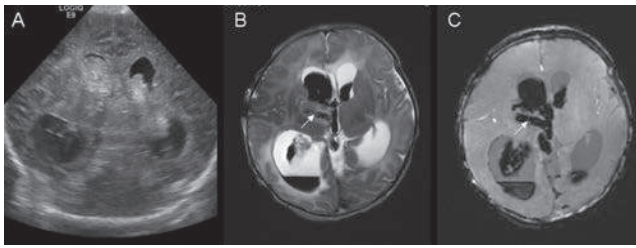


FIGURE 18.3 Coronal transfontanel head ultrasound image (**A**) from a 1-day-old boy with seizures, showing bilateral intraventricular hemorrhage and associated ventriculomegaly. Axial T2-weighted (**B**) and susceptibility-weighted (**C**) MR images illustrate thrombosis of the right internal cerebral vein (*arrows*).

period occur in 6% to 20%. CVT with infarction is associated with worse neurodevelopmental outcomes than CVT without infarction. Recurrence risk is thought to be low, although data are limited.[15,16]

AIS in Children

Most AIS in children are due to arteriopathy, and vascular imaging is normal in only 21% of children with AIS.[17,18] Many arteriopathies are acquired, including cervicocephalic artery dissection, post-varicella arteriopathy, and transient cerebral arteriopathy of childhood; others include arteriopathy due to moyamoya syndrome and SCD. Nonarteriopathic ischemic strokes may be due to cardiac disease or thrombophilia without obvious arteriopathy. Specific causes are discussed in detail below.

RISK FACTORS: In ⅔ of cases, a vascular risk factor can be identified. *Risk of recurrence is 6% to 14%;* predictors include elevated lipoprotein(a), protein C deficiency, other thrombophilic states, and moyamoya syndrome.[19,20] Substances associated with increased risk of ischemic stroke (generally in adults) include cocaine, amphetamines, ecstasy, phentermine, ephedrine/pseudoephedrine.

Hypercoagulable states: One or more prothrombotic states can be identified in 20% to 50% of children presenting with AIS.[21]

PRESENTATION: Acute onset of a new neurologic deficit including hemiparesis, aphasia, visual disturbance or at times, seizure. Most children with nonarteriopathic causes of AIS have abrupt onset (72%); children with arteriopathic causes of stroke more often have a progressive, stuttering, or recurring onset (68%).[22]

EVALUATION: See Table 18.1.

Radiology: *MRI* is modality of choice for evaluation of suspected stroke; should include T1, T2/FLAIR, T2* (susceptibility), DWI with ADC. *CT* is sensitive for detection of hemorrhage and may identify early findings consistent with ischemic stroke; rapid acquisition useful in unstable patients. Vascular imaging should be obtained in all children with stroke; *MRA* is typically of high quality in children; *CTA* has high spatial resolution but results in a large radiation dose. *Catheter angiography* is preferred for evaluation of tertiary branches and small cerebral arteries (e.g., in suspected vasculitis and moyamoya); potential complications include damage to vessels at sites of access, catheter-induced dissection or perforation, thrombosis, and complications of contrast administration or anesthesia.

TABLE 18.1 Recommended Evaluation for Children with Arterial Ischemic Stroke

Radiology	MRI with contrast-enhanced MRA of head and neck • Consider T1 fat-saturated images of neck if high suspicion for arterial dissection • CT and CTA may be helpful if MRI/MRA contraindicated
Echocardiogram	Transthoracic echocardiogram (TTE) with agitated saline to evaluate for: • structural heart disease • cardiomyopathy • mural thrombus • intracardiac or extracardiac shunts
Laboratory	• CBC with differential, electrolytes, BUN/Cr • PT, PTT, fibrinogen, d-dimer • Urine β-HCG (in postpubertal girls) • Serum and urine toxicology screen • Blood cultures • Protein C, protein S, antithrombin III, activated protein C resistance (factor V Leiden), prothrombin gene mutation • Homocysteine • ESR, CRP, ANA, anticardiolipin antibodies, anti-β 2 glycoprotein antibodies, lupus anticoagulant • Lipoprotein panel • Hemoglobin electrophoresis

MANAGEMENT: Depends on underlying etiology.

- **Supportive measures** include avoidance of hypoxemia and hyperthermia, maintaining normal blood glucose. *Thrombolytic therapy (tPA) for acute stroke is currently not recommended in children* due to lack of evidence, but is sometimes used in older adolescents who meet adult tPA eligibility criteria.
- **Short-term anticoagulation** may be initiated in children until the cause of stroke is determined and continued for up to 1 wk. Low molecular weight heparin: 1 mg/kg every 12 h; monitor anti-factor Xa activity drawn 4 to 6 h after dose (goal 0.5–1 U/mL). Unfractionated heparin may also be used, especially in situations where need for reversal of anticoagulation is anticipated.
- **Long-term anticoagulation** is indicated in children with risk of recurrent cardiac embolism, arterial dissection, and certain hypercoagulable states. Low molecular weight heparin usually initial choice; may be continued or transitioned to warfarin or newer oral anticoagulants (e.g., rivaroxaban).
- **Antiplatelet agents** may be used for secondary prevention of strokes in children without SCD who are not known to have high recurrent risk of embolism or severe hypercoagulability. Aspirin is usually dosed at 3 to 5 mg/kg/d; if dose-related side effects occur, may reduce to 1 to 3 mg/kg/d. Clopidogrel 1 mg/kg/d has been used in children unable to tolerate aspirin.
- If homocysteine is elevated, it is reasonable to supplement with folate, B_{12}, or pyridoxine. Oral contraceptives should be discontinued in children with ischemic stroke.

PROGNOSIS: Mortality in childhood ischemic stroke may reach 20%, about half of which is related to underlying illness rather than stroke itself.

Between 50% and 80% of surviving children have neurologic sequelae, most commonly hemiparesis; other problems include poor attention, behavioral problems, and cognitive deficits. Poorer outcome is associated with systemic disease, multiple risk factors, infarct size, cortical involvement, thromboembolism, and moyamoya.[1]

NONATHEROSCLEROTIC VASCULOPATHIES

Cervicocephalic Artery Dissection

EPIDEMIOLOGY: Carotid and vertebral artery dissection accounts for ~7.5% of childhood ischemic stroke[23,24]; may occur spontaneously or after blunt or penetrating trauma. More common in younger patients, patients with family history of dissection; associated with connective tissue disorders (Ehlers–Danlos type IV, Marfan syndrome), aortic coarctation, autosomal dominant polycystic kidney disease, osteogenesis imperfecta, atherosclerosis, extreme arterial tortuosity, moyamoya syndrome, and pharyngeal infections.

DIAGNOSIS: *Angiography* (conventional, MRA, CTA) may demonstrate "string sign"; double lumen sign; short, smooth, tapered stenosis; occlusion of parent artery. *MRI with fat-saturated T1 imaging of the neck* and *contrast-enhanced MRA* are generally used as first-line evaluation; CTA not recommended in children.

MANAGEMENT: Studies in adults show no evidence for superiority of antiplatelet therapy or anticoagulation; either may be used in children. Anticoagulation with LMWH, warfarin (goal INR 2.0–3.0), or newer oral anticoagulants (e.g., rivaroxaban) is typically continued for 3 to 6 mo, but may be extended if symptoms recur; anticoagulation is avoided in patients with intracranial dissections (due to risk of subarachnoid hemorrhage) and at least initially in patients with large infarcts (due to risk of hemorrhagic conversion). Antiplatelet therapy is a reasonable alternative and may be continued longer than 6 mo, especially when radiologic abnormalities persist.

Moyamoya Disease and Moyamoya Syndrome

Chronic progressive stenosis of intracranial internal carotid arteries; less often stenosis of middle, anterior, and posterior cerebral arteries and basilar artery; may be unilateral or bilateral; moyamoya (Japanese: "puff of smoke") refers to hazy angiographic appearance of fine collateral vessels. Accounts for up to 6% of all childhood strokes.[25,26]

EPIDEMIOLOGY

Moyamoya disease: Idiopathic; most common in Japan (3 per 100,000); rarer in the United States (0.086 per 100,000); more frequent in Asian (OR 4.6) and black children (OR 2.2) compared to white children.[27,28] Bimodal age distribution: children in the 1st decade of life (more likely to present with ischemic events) and adults in the 4th decade (more likely to present with hemorrhage). Genetic factors likely important (familial incidence of affected first-degree relatives is 6%–12%), but poorly understood; has been associated with specific HLA haplotypes (HLA B40, B52).

Moyamoya syndrome: Diagnosed in individuals with well-recognized associated conditions, including history of cranial radiation, Down syndrome, neurofibromatosis 1, SCD.

PRESENTATION: Strokes and transient ischemic symptoms classically occur in the setting of hyperventilation and crying (due to cerebral vasoconstriction), coughing or straining (due to decreased cerebral perfusion pressure), or fever (due to increased metabolic demand).

DIAGNOSIS: Based on distinct angiographic appearance on MRA, CTA, or conventional angiography, but other modalities may yield important diagnostic information.

- CT/MRI may show small areas of infarction in cortical watershed zones, basal ganglia, deep white matter, or periventricular regions. MRI may show absence of flow voids in ICA, MCA, and ACA with abnormal flow voids from basal ganglia and thalamic collaterals (Fig. 18.4).
- EEG shows slowing of the background rhythm after hyperventilation ("re-buildup").
- TCD may assist with diagnosis and postoperative follow-up.
- Various techniques used to determine resting perfusion/blood flow reserve and to predict improvement in functional perfusion after therapy (xenon CT, PET, MR perfusion, acetazolamide SPECT).
- Screening (with MRA) may be considered in individuals with common high risk–associated conditions or prior history of unilateral disease (27% eventually develop bilateral involvement).

MANAGEMENT: Despite extensive literature, there are no controlled clinical trials to guide medical vs. surgical therapy or type of surgical therapy.

- **Surgical revascularization** (by direct or indirect anastomoses) is used in patients with cognitive decline or recurrent or progressive symptoms.[25] Meta-analyses suggest that 87% derive symptomatic benefit from revascularization, but no differences between types of procedures.[29] Potential complications: postoperative stroke, spontaneous or traumatic subdural hematoma, ICH. Perioperative management includes sedation and analgesia (to prevent crying and hyperventilation), avoidance of hypotension, hypovolemia, hyperthermia, and hypocarbia.
- **Antiplatelet therapy** (aspirin 3–5 mg/kg) may be used when patient has a poor operative risk or has mild disease, or routinely after surgery.
- **Calcium channel blockers** may improve intractable headaches and reduce frequency and severity of refractory TIAs.

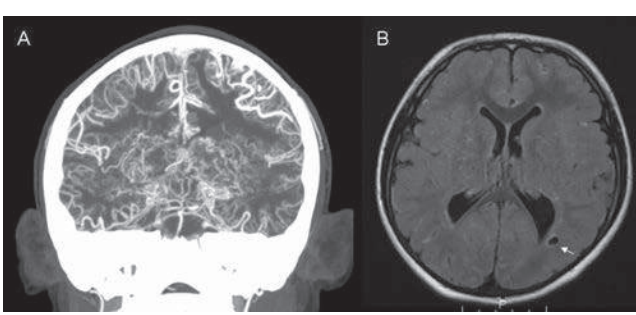


FIGURE 18.4 CTA (**A**) and FLAIR MRI (**B**) in an 8-year-old boy with trisomy 21 and moyamoya syndrome. CTA shows terminal stenosis of the bilateral internal carotid arteries distal to the origin of the posterior cerebral arteries, with exuberant deep collaterals (moyamoya vessels) as well as pial collaterals. MRI shows chronic white matter infarcts (*arrow*) in the posterior–middle cerebral artery border zones.

Fibromuscular Dysplasia

Nonatherosclerotic segmental noninflammatory arteriopathy, typically affecting renal arteries and extracranial ICA (3–4 cm from bifurcation); 20% to 30% have cerebrovascular involvement. Stroke due to stenosis or dissection of affected artery, or embolism from stenotic artery; aneurysms in ~7% of patients.[1] Antiplatelet therapy or anticoagulants often used; angioplasty and/or stenting or endarterectomy can be considered if symptoms recur. Other surgical therapies include coiling of cerebral aneurysms.

Fabry Disease

X-linked sphingolipidosis caused by deficiency of α-galactosidase, leading to accumulation of glycosphingolipids with α-D-galactosyl moieties. Primary cause of vasculopathy is progressive accumulation of globotriaosylceramide (Gb3) in endothelial and vascular smooth muscle cells, causing small-vessel stenosis/occlusion, more prominent in the vertebrobasilar system. Additional factors leading to increased stroke risk may include higher prevalence of cardiac disease and BP dysregulation (hyper- or hypotension), dilation and dolichoectasia of large vessels leading to flow stagnation and thrombosis, prothrombotic state, premature atherosclerosis, and autoimmunity.[30]

EPIDEMIOLOGY: Incidence ~1/117,000 live births and ~1/40,000 men[31]; >400 mutations in α-*GAL* gene have been identified, including de novo mutations. Estimated that 1.2% of cryptogenic strokes in patients younger than 55 y are attributable to mutations in α-*GAL*.[32] Stroke more common in women with FD (27%) than men (21%), but women tend to be older at onset of stroke (43.4 y) compared to men (28.8 y).[33,34]

CLINICAL PRESENTATION: Stroke may be the first manifestation of Fabry disease[34] and commonly affects the posterior circulation; brain MRI typically shows progressive white matter T2 hyperintensities characteristic of small-vessel disease. Manifestations outside the CNS in children include pain crises due to peripheral neuropathy (acroparesthesias), fever, hypohidrosis, and exercise intolerance; numerous organ-specific manifestations (Table 18.2).

TABLE 18.2 Nonneurologic Manifestations of Fabry Disease

Dermatologic	Angiokeratoma
	Hypohidrosis/anhidrosis
Renal	Proteinuria
	Renal tubular dysfunction
	End-stage renal disease
Ocular	Whorled corneal opacities (verticillata)
	Lens and posterior opacities (Fabry cataract)
	Anterior capsular or subcapsular wedge-shaped lipid deposit
	Retinal vascular changes (vessel tortuosity)
Gastrointestinal	Episodic diarrhea, vomiting, or constipation
	Postprandial bloating and pain
	Early satiety
	Weight loss
Cardiac	Hypertrophic cardiomyopathy
	Systolic or diastolic dysfunction
	Valvular disease (mitral regurgitation)
	Coronary artery disease
	Arrhythmia

TREATMENT: Enzyme replacement therapy (ERT) with α-galactosidase 1 mg/kg IV every 2 wk significantly reduces vascular endothelial Gb3 accumulation and is recommended in all patients with FD as soon as clinical signs and symptoms are observed. ERT effectiveness for prevention of neurologic deterioration and stroke remains unclear.

Sneddon Syndrome

Noninflammatory arteriopathy characterized by livedo reticularis and cerebrovascular disease; genetic basis unknown, but some reports suggest autosomal dominant inheritance. Include multifocal cerebral infarctions, occlusion of small- and medium-sized cerebral vessels, and moyamoya-like arteriopathy; livedo reticularis precedes cerebrovascular involvement by ~10 y. Annual incidence of ~4/1,000,000; more common in women and usually presents in young adulthood; associated with development of antiphospholipid antibodies in 40% to 60%.[35,36]

Familial Arteriopathies

CADASIL (Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy)

Results from mutation of *NOTCH3* gene; progressive small, deep white matter infarcts leading to subcortical dementia.[37]

CARASIL (Cerebral Autosomal Recessive Arteriopathy with Subcortical Infarcts and Leukoencephalopathy; Maeda Syndrome)

Small-vessel arteriopathy reported mostly in Chinese and Japanese populations, caused by mutations in *HTRA* gene; presents with subcortical infarcts and lacunar strokes beginning in early adulthood; associated with alopecia and spondylosis.[38]

AD-RVCL (Autosomal Dominant Retinal Vasculopathy with Cerebral Leukodystrophy)

Microvascular endotheliopathy resulting in retinopathy, migraine, Raynaud phenomenon, and strokes; associated with mutations in *TREX1* gene. **HERNS** (hereditary endotheliopathy, retinopathy, nephropathy and strokes) is a subtype of RVCL characterized by progressive visual loss, macular edema, perifoveal microangiopathic telangiectasias, migraine-like headaches, recurrent strokes, dementia, and renal insufficiency. No effective therapy is available.[39]

Connective Tissue Disorders

Ehlers–Danlos Syndrome Type IV

Caused by mutations in *COL3A1* gene, leading to abnormalities in collagen type III; inheritance may be AD or AR; associated with prominent cerebrovascular abnormalities and high risk of intracranial aneurysm, carotid-cavernous fistula, arterial rupture, and dissection.

Marfan Syndrome

Caused by mutations in fibrillin-1 gene (*RBN1).* Stroke may result from aortic or cervicocephalic artery dissection or cardioembolism in the setting of cardiomyopathy.

Pseudoxanthoma Elasticum

Autosomal recessive disorder caused by mutations in *ABCC6* gene; characterized by calcification and degeneration of elastic tissue leading to cutaneous, ocular, and vascular abnormalities. Cerebrovascular complications

may be due to premature carotid atherosclerosis or vascular abnormalities (cavernous-carotid fistulas, aneurysms, subarachnoid hemorrhage) or complications of associated cardiac abnormalities (coronary artery disease, congestive heart failure); about 25% also have hypertension.

COL4A1-*Related Disorders*

A spectrum of clinical phenotypes characterized by small-vessel cerebral disease, eye defects, and systemic findings including muscle cramps, nephropathy, cardiac arrhythmia, and Raynaud phenomenon. May present in infancy with hemiparesis and seizure due to hemorrhage or infarction or later in life with stroke, hemorrhage, dystonia, intellectual disability, or migraine with aura. Neuroimaging may demonstrate porencephalic cysts due to antenatal or perinatal hemorrhage, leukoencephalopathy, lacunar infarctions, and cerebral microhemorrhages.[40]

Inflammatory Vasculopathies

May occur with intracranial infections or noninfectious inflammatory disorders; can affect large, medium-sized, or small arteries.

Infectious Vasculitis

Stroke is common in children with chronic infections (e.g., tuberculous meningitis) and acute purulent meningitis (up to 25%); infectious agents associated with stroke and vasculitis include malaria, aspergillus, syphilis, mycoplasma, *Borrelia*, *Bartonella*, *Brucella*, *Rickettsia*, coxsackie 9 virus, California encephalitis virus, paramyxovirus.

Postinfectious Vasculitis

Historically, up to ⅓ of children with AIS between 2 and 10 y of age have post-varicella angiopathy with unilateral stenosis of the distal ICA, proximal MCA, or ACA.[41]

Transient Cerebral Arteriopathy (Nonprogressive Primary Angiitis of the Central Nervous System)

Disorder of unknown etiology that mimics the appearance of post-varicella angiopathy without preceding history of varicella infection; relatively common and usually self-limiting.[42]

Noninfectious Inflammatory Vasculitis

Systemic rheumatologic disorders associated with vasculitis include systemic lupus erythematosus and Takayasu arteritis (Fig. 18.5). Primary angiitis of the central nervous system is a rare, granulomatous, necrotizing angiopathy typically presenting with headaches and altered consciousness.

Susac Syndrome (Retinocochlear Vasculopathy)

Rare microangiopathic disorder of the brain, retina, and inner ear, believed to be more common in children than in adults; characterized by branch retinal artery occlusion, sensorineural hearing loss, and encephalopathy due to cerebral microinfarcts; etiology is poorly understood but therapeutic benefit from corticosteroids and cyclophosphamide suggests an inflammatory component.

DIAGNOSIS: Systemic inflammatory markers may be normal; CSF usually abnormal due to elevated protein or lymphocytic pleocytosis. MRI with gadolinium usually abnormal (>90%); angiographic studies may show segmental narrowing, occlusions, or peripheral aneurysms, or may be normal. Leptomeningeal biopsy is the most specific diagnostic test, but may be negative.

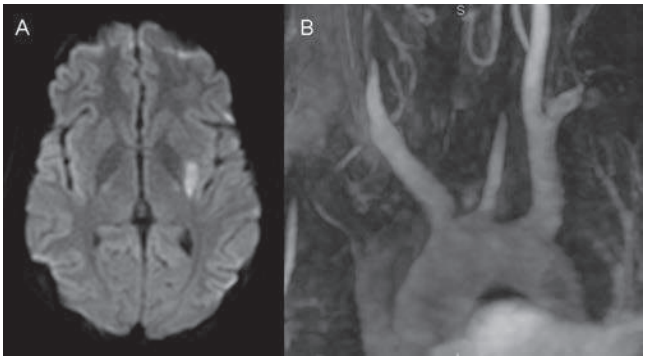


FIGURE 18.5 Axial diffusion-weighted MR image (**A**) showing a left middle cerebral artery territory infarction in a 15-year-old girl with Takayasu arteritis. MR angiography (**B**) demonstrates occlusion of the right and left common carotid arteries.

TREATMENT: Progressive noninfectious inflammatory vasculitides are usually treated with corticosteroids and cytotoxic agents (e.g., cyclophosphamide).

DISORDERS OF ACCELERATED ATHEROSCLEROSIS

Homocystinuria

Autosomal recessive disorder classically caused by deficiency of cystathionine β-synthase, leading to elevated levels of plasma homocysteine and methionine; may also be due to defects in homocysteine methyltransferase and methylenetetrahydrofolate reductase (MTHFR). Hyperhomocysteinemia thought to cause endothelial dysfunction because of decreased bioavailability of endogenous nitric oxide, leading to oxidative stress and accelerated atherosclerosis; mechanisms of stroke include intra-arterial thrombosis due to arteriopathy and arterial dissection.[43]

EPIDEMIOLOGY: Estimated frequency is highly variable worldwide (~1/58,000 to ~1/1,000,000); >90 mutations described.

CLINICAL PRESENTATION

Neurologic manifestations include stroke (small-vessel and artery-to-artery thromboembolism), seizures, mental retardation, and neuropsychiatric problems.

Systemic manifestations include myopia, osteoporosis, thinning and lengthening of long bones (dolichostenomelia), ectopia lentis, and thromboembolism including peripheral arterial and venous thrombosis and myocardial infarction. Risk of vascular thromboembolic event is 25% before age 16 y and 50% by age 30 y; 32% of reported vascular events are strokes.[44]

TREATMENT: Treatment is vitamin B_6 supplementation (300–600 mg/d) to enhance metabolism of homocysteine to cysteine (although high doses are associated with development of peripheral neuropathy). Folate, betaine, and vitamin B_{12} are also used to promote metabolism of homocysteine to methionine; methionine-free diet with cysteine supplementation is recommended. Antiplatelet therapy is used for prevention of recurrent thromboembolic events.

Dyslipoproteinemias

Vessel changes in hereditary dyslipoproteinemias may represent lipoprotein-mediated endothelial damage; usually involve intracranial vessels

TABLE 18.3 Hereditary Dyslipoproteinemias Associated with Stroke

Syndrome	Inheritance	Gene(s)	Laboratory	Clinical Features
Familial hypercholesterolemia	AD	*LDLR*	Increased cholesterol, bound to LDL receptor	Tendon xanthomas, corneal arcus, coronary artery disease
Familial hypertriglyceridemia	AD	*APOA5, LIPI*	Increased triglycerides	
Familial hypoalphalipoproteinemia	AD	*APOA1, ABCA1*	Decreased HDL	Premature atherosclerosis, early coronary artery disease
Tangier disease	AR	*ABCA1*	Decreased HDL	Hyperplastic orange tonsils, hepatosplenomegaly, lymphadenopathy, neuropathy, hypocholesterolemia, premature atherosclerosis

rather than carotid bifurcations (as in typical atherosclerosis). A number of familial dyslipoproteinemias associated with stroke have been described (Table 18.3). *Elevated lipoprotein(a)* also a known risk factor for stroke in childhood. Some patients with progeria syndromes (de Lange, Deckel, Bloom, Cockayne) may have decreased HDL, increased LDL and VLDL, leading to death from vascular disease in adolescence.

STROKE IN CARDIAC DISEASE

Accounts for ~15% to 25% of ischemic strokes in children from 1 mo to 18 y of age.[45]

Congenital heart defects. Most common cardiac risk factors for stroke in children under 15 y are associated with congenital heart defects. **Structural risk factors:** Intracardiac shunts (e.g., atrial or ventricular septal defects). **Hematologic risk factors:** Polycythemia, anemia, coagulation abnormalities. **Perioperative risk factors:** Perioperative hypoxemia and low cardiac output states, gaseous and particulate embolization with cardiopulmonary bypass, hypoperfusion.

Shunts: Right-to-left shunts predispose to paradoxical emboli (venous clots bypassing the pulmonary circulation). Foramen ovale usually closes at birth, but remains patent in up to 35% of people between 1 and 29 y.[46] Prevalence of PFO may be greater in individuals with otherwise unexplained stroke, but unclear at this time whether closure is beneficial in the absence of other risk factors. Paradoxical embolism may also occur in pulmonary arteriovenous fistulas. If shunt is discovered in a patient with stroke, reasonable to evaluate for deep venous thrombosis with *Doppler ultrasound of the upper and lower extremities*; *MR venography* may show May–Thurner anatomy (compression of left common iliac vein by right common iliac artery), which can predispose to iliofemoral thrombosis (Fig. 18.6).

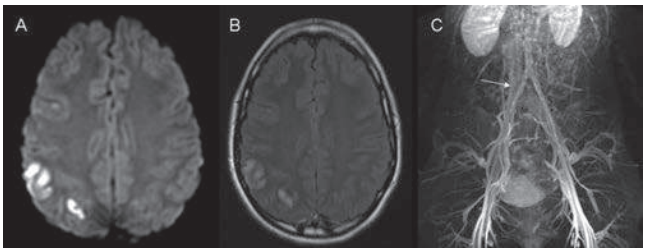


FIGURE 18.6 Axial DWI (**A**) and FLAIR (**B**) sequences demonstrating embolic infarcts in the right parietal lobe in a 17-year-old girl subsequently found to have patent foramen ovale. MR angiography of the pelvis (**C**) demonstrates May–Thurner anatomy, with compression of the left common iliac vein by the right common iliac artery (*arrow*).

Valvular heart disease: Neurologic complications occur in 20% to 40% of patients with infective endocarditis involving the left side of the heart; most often strokes or transient ischemic attacks due to MCA territory embolism; hemorrhage (due to septic emboli or ruptured mycotic aneurysms) may also occur. Noninfectious valvular lesions predisposing to stroke include: rheumatic mitral stenosis, Libman–Sacks endocarditis, valvular tumors (myxomas, fibroelastomas), calcifications (rare in children, but may be seen as early as the 2nd decade of life with bicommissural aortic valve or earlier with unicommissural valve).

Cardiac arrhythmias: Arrhythmias are a rare cause of stroke in children, but atrial fibrillation may occur in children with hyperthyroidism, rheumatic heart disease, or after surgery for congenital heart disease.

Congestive heart failure: May predispose to cardioembolic stroke; associated with mitochondrial disorders, muscular dystrophy, congenital myopathies, Friedreich ataxia, infectious agents (Chagas disease, coxsackievirus).

MANAGEMENT: Surgical repair should be undertaken for congenital heart defects and major septal defects (other than PFO) as well as atrial myxoma. For children at high risk of recurrent cardioembolic stroke (unrelated to PFO), guidelines suggest starting unfractionated and low molecular weight heparin and continuing anticoagulation with either LMWH or warfarin for at least 1 y or until the culprit lesion has been corrected. For children with low or unknown risk of recurrent stroke, guidelines suggest therapy with aspirin for at least 1 y. Optimal management of stroke in the setting of PFO is not known, but reasonable to consider anticoagulation and/or closure if risk factors for recurrent thromboembolism are identified. Anticoagulation is not recommended for children with native valve endocarditis.

HEMATOLOGIC DISORDERS

Sickle Cell Disease

SCD increases risk for both thrombotic and hemorrhagic infarcts.

EPIDEMIOLOGY: Incidence of ischemic stroke in children with SCD is 238/100,000 per year; incidence of hemorrhagic stroke is 47.5/100,000 per year.[47] Risk varies by age: overall stroke risk with HbSS is 11% by age 20 (24% by age 45 y); much lower risk by age 20 in HbSC (2%). Highest rate of first stroke at 2 to 5 y of age (incidence ~1% per year), then 6 to 9 y of age (~0.7% per year). Incidence of ischemic stroke is lowest, and incidence of hemorrhage is highest, between ages 20 and 29 y.[48]

Many patients without a clinical history of stroke are found to have "silent" infarctions on MRI (~20%), often in frontal and parietal cortical, subcortical, and border zone areas. Risk of ischemic stroke is higher in patients with history of TIA, systolic hypertension, recent acute chest syndrome, low hemoglobin value, high white cell count, high blood flow velocity on TCD, and asymptomatic lesions on MRI.

CLINICAL PRESENTATION: Presentation of stroke in SCD is variable. Large-vessel vasculopathy most often affects supraclinoid internal carotid arteries, proximal middle cerebral arteries, and anterior cerebral arteries. Frequently presents with acute MCA ischemia or infarction; less frequently anterior and posterior cerebral artery territories are involved. Watershed infarctions may occur, and there may be secondary development of moyamoya syndrome (see above). Small-vessel infarctions may be symptomatic or asymptomatic; most often affect basal ganglia and deep white matter within the anterior circulation. Cerebral hemorrhage may occur due to ruptured aneurysm, venous sinus thrombosis, or rupture of fragile moyamoya vessels.

MANAGEMENT: Acute stroke management: Hydration, correction of hypoxemia, and systemic hypotension. Most experts also recommend exchange transfusion to hemoglobin S <30%. **Primary and secondary prevention of stroke in SCD:** *Regular blood transfusions to maintain Hb S <30%* are the mainstay of prevention; practice is based on Stroke Prevention Trials in Sickle Cell Anemia (STOP I and II). High risk children between ages 2 and 16 y are identified by TCD (2 velocities > 200 cm/s). In STOP trials, untreated children had stroke risk of 10% per year. Children treated with periodic transfusion to maintain Hb S <30% had stroke risk of <1% per year (STOP I). *Discontinuing transfusions is not recommended* because of risk of reversion to high risk TCDs (34% in 4–9 mo) and risk of stroke despite normal TCDs (5%) (STOP II).[49] *Hydroxyurea* may be an alternative to transfusion for primary prevention, but has not been studied adequately. *Bone marrow transplantation* may stabilize cerebrovascular disease. *Surgical bypass procedures* may be considered in SCD patients with moyamoya syndrome.

Screening for stroke risk by TCDs recommended at age 2 y and above:

TCD Evaluation of Children with SCD
Normal TCDs (<170 cm/s): repeat annually
TCDs 170–184 cm/s: repeat every 6 mo
TCDs 185–199 cm/s: repeat every 3 mo
TCDs > 200 cm/s: repeat in 1 mo; begin periodic transfusions if TCDs remain elevated

Acquired Anemias

Iron deficiency anemia is highly prevalent in children and has been implicated as a risk factor for transient ischemic attack, AIS, and CVT. Among previously healthy children with no identifiable stroke risk factors, more than half have iron deficiency anemia (10 times greater likelihood than children without stroke).[50]

Microangiopathic hemolytic anemias can cause ischemic or hemorrhagic infarction leading to seizures and focal neurologic impairment. In hemolytic-uremic syndrome, neurologic dysfunction predicts poorer outcomes and increased need for dialysis.[51]

Polycythemias

Polycythemia rubra vera and other polycythemias associated with mutant hemoglobins, abnormal metabolism of 2,3-diphosphoglycerate, or autonomous production of erythropoietin, have rarely been associated with stroke

in childhood. Thrombocythemia may cause transient ischemic attacks due to microvascular occlusion or stroke due to venous or arterial thrombosis.

Platelet Defects

Hereditary platelet defects (e.g., Wiskott–Aldrich syndrome, thrombocytopenia-absent radius syndrome) may predispose to hemorrhagic stroke and can cause fatal intracranial hemorrhage in infancy.

Dysfibrinogenemias

Autosomal dominant disorders due to mutations in fibrinogen alpha subunit gene (*FGA*) cause various alterations in the structure and stability of fibrinogen; some dysfibrinogenemias are associated with venous and arterial thrombosis.

Prothrombotic States

Inherited and acquired prothrombotic states are significantly associated with stroke in childhood (Table 18.4). At least one prothrombotic state can be identified in 20% to 50% of children with AIS and 33% to 99% of children with CVT.[21] **Hereditary coagulation abnormalities** identified in children with AIS and CVT include antithrombin III deficiency, factor V Leiden mutation, protein C and protein S deficiency, and prothrombin gene mutation (*G20210A*).[6,52] **Protein C and protein S deficiency** can be inherited (AD) or acquired. Hereditary deficiencies most often heterozygous with reduced plasma protein concentration (type I), normal protein concentration with decreased functional activity (type II); in protein S deficiency can also see normal total protein concentration with reduced levels of free protein and decreased functional activity (type III). Clinical manifestations are variable.

TABLE 18.4 Prothrombotic States Predisposing to Arterial Ischemic Stroke (AIS)

Hereditary prothrombotic disorders
• Protein C deficiency
• Protein S deficiency
• Antithrombin III deficiency
• Factor V Leiden
• Dysfibrinogenemias
Hyperhomocysteinemia
• Cystathionine β-synthase deficiency (classic homocystinuria)
• MTHFR deficiency
• Cobalamin defects
• Defects of methionine metabolism
Antiphospholipid antibody syndrome
Microangiopathic hemolytic anemia
• Hemolytic-uremic syndrome
• Thrombotic thrombocytopenic purpura
• Disseminated intravascular coagulation
Paroxysmal nocturnal hemoglobinuria
Polycythemia and thrombocythemia
Pregnancy
Oral contraceptive use

Homozygous deficiencies may present with widespread thrombosis in the neonatal period (neonatal purpura fulminans); homozygous protein S deficiency generally considered incompatible with life. Acquired causes of protein C deficiency include hepatic disease, septic shock, disseminated intravascular coagulation, postoperative states, chemotherapy (methotrexate, cyclophosphamide, L-asparaginase). Acquired protein S deficiency seen with pregnancy, oral contraceptive use, disseminated intravascular coagulation, HIV infection, nephrotic syndrome, hepatic disease, and with L-asparaginase chemotherapy. Use of age-based norms for specific laboratories is critical to interpretation of protein C and S measurement in children; concentrations are significantly lower in newborns and young infants compared to normal adults. **Antiphospholipid antibody syndrome** can be primary or secondary to another disorder (systemic lupus erythematosus and other rheumatologic diseases, Sneddon syndrome); associated with thrombocytopenia, prolonged activated partial thromboplastin time (aPTT), painful leg ulcerations, cardiac valve abnormalities, livedo reticularis. **Pregnancy** is an important acquired prothrombotic state in adolescent girls, due to alterations in multiple plasma phase risk factors (increased platelet adhesion; increased fibrinogen and factors VII, VIII, IX, X, XII; decreased protein C and S and circulating plasminogen activator). Arterial ischemic strokes more common during pregnancy; CVT more common in the puerperium. Anticoagulation with warfarin is contraindicated during pregnancy due to risk of teratogenesis. **Oral contraceptive use** is associated with a dose-related increase in risk of cerebral thrombosis.

METABOLIC CAUSES OF STROKE

Mitochondrial Disease

Stroke-like episodes occur most frequently in **MELAS syndrome** (mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes), but have also been reported in MERRF syndrome (myoclonic epilepsy with ragged red fibers), Kearns–Sayre syndrome, and Leigh syndrome. Cause of stroke-like episodes is not well understood; may be due to mitochondrial angiopathy (caused by small-vessel mitochondrial and vascular dysfunction leading to ischemia) or mitochondrial cytopathy (oxidative phosphorylation failure leading to ATP depletion and cytotoxicity secondary to energy imbalance).[30,53]

EPIDEMIOLOGY: MELAS is most commonly attributable to mtDNA mutation m.3243A>G (80%)[54]; no known ethnic predilection, but prevalence varies widely (~8/100,000 in Northeast England, ~236/100,000 in Australia).[55] Symptom onset is typically in young adulthood by age 40 y; can become symptomatic in childhood; younger age at onset is a poor prognostic sign.

CLINICAL PRESENTATION: Stroke-like episodes are usually associated with migraine headache and seizures; spreading nature of stroke-like lesions on MRI similar to cortical spreading depression in migraine. Manifestations outside CNS similar to other mitochondrial disorders (see Chapter 8).

TREATMENT: Some studies suggest improvement with infusion of L-arginine (0.5 g/kg) shortly after the onset of a stroke-like episode; subsequent supplementation with L-arginine (0.15–0.3 g/kg/d) may decrease frequency and severity of recurrent events; reports also suggest utility of idebenone (synthetic coenzyme Q_{10} analog) for prevention of stroke-like episodes.[30,53]

Organic Acidurias and Other Metabolic Disorders

Patients with propionic and methylmalonic aciduria may have symmetric basal ganglia ischemic strokes; etiology is largely unknown but may be

attributable to impaired aerobic metabolism and energy failure. Cerebellar hemorrhage has been described in isovaleric, propionic, and methylmalonic aciduria.[43]

Glutaric aciduria type I classically presents with acute neurologic crisis characterized by hypotonia or diffuse rigidity, encephalopathy, and dystonia, usually precipitated by common childhood infection; neuroimaging demonstrates bilateral striatal necrosis thought to be due to a stroke-like mechanism.[56]

Stroke-like episodes have been described in **urea cycle disorders** (ornithine transcarbamylase deficiency, carbamoyl phosphate synthetase I deficiency, citrullinemia) and congenital disorder of glycosylation 1a.[43]

Migraine and Stroke

Relationship between migraine and stroke is complex and not entirely understood. Some strokes in migraineurs are attributable to migrainous infarction, but this is probably rare; diagnostic criteria are strict (ICHD-II, 2004). Other causes may include local and systemic vascular disease, paradoxical embolism, underlying genetic or metabolic disease, and medications (e.g., triptans).

Diagnostic Criteria for Migrainous Infarction
Previously established diagnosis of migraine with aura
Infarction must occur during the course of a typical migraine attack
One or more aura symptoms persist for >60 min
Neuroimaging confirmation of ischemic infarction
Other causes of infarction excluded

EPIDEMIOLOGY: Estimated that 1% to 17% of strokes in patients <50 y of age can be attributed to migraine. Incidence of migraine-related stroke is unknown in children (estimated at 6.9/100,000 per year in persons 15–44 y of age). Risk of stroke is highest with migraine with aura (attributable risk 1.8–4 cases of ischemic stroke per 10,000 women per year, higher in women under 45 y); risk of stroke is unlikely to be increased with common migraine. Additive risk factors include oral contraceptives, cigarette smoking, presence of antiphospholipid antibodies.

PATHOPHYSIOLOGY: Several mechanisms have been proposed.

Migrainous infarction: Initial event in migraine aura postulated to be spreading depolarization (slow potential change due to breakdown of Na^+ pump-mediated homeostasis). With sufficient energy supply and intact metabolism, this leads to spreading depression (electrical silence of brain activity due to depolarization block) with rise in rCBF (spreading hyperemia) due to increase in NO production resulting in vasodilatation. Under pathologic conditions (e.g., in the setting of decreased NO availability), severe arteriolar constriction may lead to prolonged hypoperfusion (spreading ischemia).[57]

Vasculopathy: Migraine is associated with endothelial dysfunction and changes in systemic and vascular reactivity, with increased circulating prothrombotic and proinflammatory factors (vWF, matrix metalloproteinases) and vasoactive peptides; some of these may mediate increased risk of cervicocephalic artery dissection.[58]

Patent foramen ovale: Intermittent right-to-left shunting may be implicated in the pathogenesis of migraine with aura as well as paradoxical embolism; however, this association is controversial.

Medications: In vivo studies show that triptans cause vasoconstriction and increased vasopressor response[59,60]; often avoided in basilar migraine,

hemiplegic migraine, and migraine with prolonged aura for this reason, although some series have reported no adverse effects.[61] Risk of stroke is greatly increased with exposure to estrogen-containing OCPs in women with migraine without aura.

Genetic disorders associated with migraine and stroke: Migraine may also occur as part of genetic syndromes associated with stroke: MELAS, CADASIL, hereditary hemorrhagic telangiectasia (HHT), Sneddon syndrome. Familial hemiplegic migraine (FHM) may result in permanent neurologic deficits. Most episodes are associated with complete recovery, but permanent weakness may occur after multiple attacks. Recurrent ischemic strokes after minor head trauma have been reported in *CACNA1A* (FHM1), *ATP1A2* (FHM2), *SCN1A* (FHM3) gene mutations.

MANAGEMENT: Avoid oral contraceptives, triptans, ergots, β-blockers. Recommended treatments: topiramate, lamotrigine, valproic acid, amitriptyline. Acetazolamide is often helpful in FHM due to *ATP1A2* and *SCN1A* mutations and in CADASIL; verapamil may be most helpful in FHM with *CACNA1A* mutations. Antiplatelet agents are used for secondary stroke prevention.

CVT in Children

ETIOLOGY: Many children have multiple risk factors for CVT. General risk factors include dehydration and hypoxia. Septic thrombosis may complicate meningitis, sinusitis, and otitis media. Systemic illnesses predisposing to CVT include diabetes (in the setting of ketoacidosis), inflammatory bowel disease, systemic lupus erythematosus, Behçet disease, homocystinuria (see below), and chronic anemias (hemolytic anemias, β-thalassemia, SCD, iron deficiency). Prothrombotic disorders are found in as many as ⅔ of children with CVT.[15,21] Drugs that increase risk of thrombosis include steroids, contraceptives, epoietin, and L-asparaginase.

PRESENTATION: Can present with seizures, headache, symptoms of increased intracranial pressure or hydrocephalus, or focal neurologic dysfunction due to intracranial hemorrhage or infarction.

DIAGNOSIS: Unenhanced CT may demonstrate linear densities in deep and cortical veins, or hemorrhage associated with venous thrombosis; contrast-enhanced CT may show filling defects in the dural sinuses (empty delta sign), although this may be falsely positive in children; MRI can demonstrate acute or subacute thrombus and associated hemorrhage (Fig. 18.7). CT venography and MR venography are preferred for confirmation of the diagnosis.

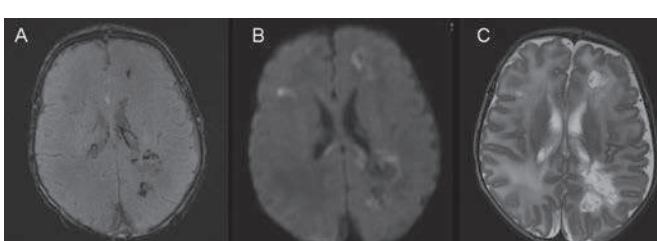


FIGURE 18.7 Axial MRI Images in a 2.5-Month-Old Boy with Extensive Deep Venous Thrombosis. Susceptibility-weighted image (**A**) shows hypointense signal corresponding to thrombosis within the deep medullary veins and left dorsal thalamic vein. Diffusion-weighted image (**B**) demonstrated associated venous infarction. A follow-up T2-weighted image obtained several months later (**C**) shows progression of the infarcted areas to cystic encephalomalacia.

MANAGEMENT

- **Supportive measures** include hydration, prevention of seizures, and control of intracranial hypertension; appropriate antibiotics should be used in cases of proven or suspected septic thrombosis.
- **Anticoagulation:** Studies in adults suggest a clear benefit of anticoagulation with unfractionated or low molecular weight heparin; small studies in children have shown that anticoagulation is safe and may reduce mortality and recurrence. Current consensus guidelines recommend anticoagulation for 3 to 6 mo for children without hemorrhage. There is little data regarding surgical and endovascular therapy.
- **Follow-up imaging** within the 1st 3 to 6 mo may demonstrate recanalization or persistent thrombosis.
- **Ophthalmological examination** should be performed to assess for visual loss due to papilledema.

PROGNOSIS: In one series, 6% of children with CVT had recurrent thrombotic episodes within 3 y; of these, 60% involved intracranial vessels; higher risk of recurrence in children older than 2 y of age with persistent occlusions, prothrombin gene mutation, or those not treated with anticoagulation.[62] Some children may have cognitive and other neurologic sequelae requiring rehabilitation and long-term therapy.

Nontraumatic Hemorrhagic Stroke in Children

ETIOLOGY: Probable cause can be identified in a vast majority of children with hemorrhage (85%–90%).[63] A plurality has vascular malformations; other risk factors include arterial hypertension, inherited and acquired bleeding diatheses, arteriopathies, intracranial tumors, illicit drug use, and certain genetic disorders.

In children with *disorders of hemostasis,* severity of thrombocytopenia or coagulation defects correlates with risk of hemorrhage; in hemophilia, spontaneous hemorrhage may occur with severe factor deficiency, but with milder deficiencies bleeds are usually precipitated by trauma. *Arterial hypertension* is defined as blood pressure >95th percentile for age, gender, and height; unlikely to be the sole cause of ICH in children and co-occurs with disorders that have increased risk of vascular malformations and aneurysms. About 80% of children with ICH have arterial hypertension preceding the vascular event, but few have long-standing arterial hypertension or markedly elevated blood pressure.

DIAGNOSIS: ICH may be detected initially by CT or MRI.

- CTA or MRA is indicated to evaluate for an underlying vascular malformation.
- Given the high percentage of hemorrhages in children attributable to vascular malformations (see below), conventional cerebral angiography should be performed if other studies are unrevealing (Fig. 18.8).
- Initial laboratory evaluation should include CBC, PT, PTT; elevated PT or PTT should prompt evaluation for specific factor deficiencies. If no underlying structural lesion is identified, it is reasonable to evaluate for other bleeding diatheses (thrombin time, platelet aggregation studies, von Willebrand factor antigen, factor XIII).

MANAGEMENT: Supportive measures include optimization of respiratory support, control of systemic and intracranial hypertension, and prevention of seizures. Surgical evacuation of supratentorial hematomas is not generally recommended, but may be considered with very large hematomas or in infratentorial hemorrhage, as a means of averting brain herniation. Treatment of underlying risk factors such as vascular malformations and coagulation defects is recommended.

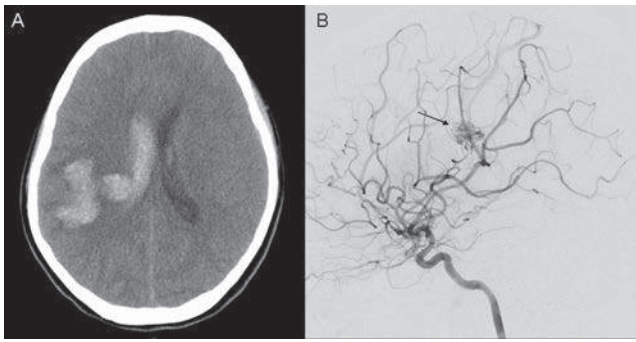


FIGURE 18.8 Head CT (**A**) in an 11-year-old girl showing a large intraparenchymal hemorrhage in the left parietal lobe with extension into the left lateral ventricle. Conventional angiography (**B**) revealed a nidus of tortuous vessels (*arrow*) consistent with an arteriovenous malformation.

Vascular Malformations and Aneurysms

Vascular Malformations

Most common reason for spontaneous intracranial hemorrhage in children (>40%).[63]

Arteriovenous malformations (AVMs) account for 30% to 50% of nontraumatic ICH; typically occur in the supratentorial region (80%) and may present with hemorrhage (75%), seizures, focal neurologic deficits, or intracranial hypertension. Estimated annual hemorrhage risk is 2% to 4%; about 25% of hemorrhages are fatal.[64,65] Multiple AVMs may be seen in HHT and may also be a feature of other genetic conditions. Ruptured or severely symptomatic AVMs may be treated by embolization, microsurgical obliteration, or stereotactic radiosurgery. Treatment of unruptured AVMs is controversial; observation with symptomatic medical management may be preferred.

Cavernous malformations can occur throughout the brain and spinal cord; multiple in 13% of sporadic cases and 50% of familial cases. Risk of recurrent hemorrhage from untreated lesions is 4.5% per year, but risk of bleeding from deeper lesions may be higher.[66] Up to 75% of familial cases have lesions in *CCM1, CCM2,* or *CCM3* genes.[67] MRI with T2*-weighted gradient-echo sequences is most sensitive for cavernous malformations, which may not be visualized by angiographic techniques.

TREATMENT: AVMs may be treated by embolization, microsurgical obliteration, or stereotactic radiosurgery. Cavernous malformations may be treated with microsurgery or stereotactic radiosurgery.

Intracranial Aneurysms

Most children with aneurysms present with subarachnoid hemorrhage (SAH); however, children are less likely than adults with aneurysms to develop SAH; other presentations include intraventricular and intraparenchymal hemorrhage (especially with mycotic aneurysms).

Saccular aneurysms are relatively uncommon in children; most occur at branch points of major intracranial arteries. Compared to adults, children are more likely to have giant aneurysms (>10 cm) and posterior circulation involvement[68,69]; about 5% have multiple aneurysms. Symptom onset is most often before age 2 y or after age 10 y,[70] but ruptured aneurysms have been

described even in newborns. First-degree relatives of patients with aneurysms have fourfold increase in prevalence of aneurysms; siblings of affected individuals have highest risk. Risk of intracranial aneurysms is increased in coarctation of the aorta, autosomal dominant polycystic kidney disease, connective tissue disorders, fibromuscular dysplasia, and SCD. **Mycotic aneurysms** may occur in children with infectious endocarditis, chronic pulmonary infections, meningitis, or sinusitis; tend to occur in distal cerebral vasculature.

TREATMENT: Saccular aneurysms may be treated with coil embolization or surgical clipping. Surgical treatment of mycotic aneurysms is usually not warranted with appropriate antibiotics.

Vein of Galen Malformation (VGAM)

Aneurysmal dilatation of the median prosencephalic vein of Markowski due to anomalous arteriovenous shunts from choroidal arteries; persistent shunting prevents normal development of vein of Galen; thus VGAM is a misnomer. Primary VGAM accounts for 30% of all congenital vascular anomalies. Aneurysms of the vein of Galen itself (caused by adjacent parenchymal arteriovenous malformations) comprise a separate entity, sometimes called secondary VGAM.[71]

PRESENTATION: Most present in the neonatal period with high-output cardiac failure; increased venous return and presence of right-to-left shunts can exacerbate pulmonary hypertension and end-organ ischemia. Infants may present with macrocrania and seizures due to hydrocephalus, which can be obstructive (compression of cerebral aqueduct by VGAM) or communicating (intracranial venous hypertension leads to decreased CSF absorption). Rarely, older children or adults present with headaches or intracranial hemorrhage.

DIAGNOSIS: Bedside examination may reveal macrocrania and presence of a cranial bruit on auscultation. *Head ultrasound* can demonstrate presence of VGAM and hydrocephalus; initial mapping of angioarchitecture should be performed by *MR angiography* (preferred over *CT angiography* in children). *Conventional angiography* is gold standard; should be performed with endovascular intervention. Ancillary evaluation includes *echocardiogram* (to evaluate for cardiac insufficiency), *EEG* (to evaluate for seizures in ICU patients), *renal and liver function tests* (to evaluate for end-organ ischemia). **Prenatal diagnosis** is possible by routine ultrasound screening and fetal MRI.

MANAGEMENT

- **Supportive measures** are used to stabilize cardiac and systemic function prior to endovascular or surgical intervention; diuretics, inotropes, and vasodilators may be used to decrease flow to VGAM.
- **Endovascular intervention** is the mainstay of therapy and is aimed at restoring physiologic hemodynamic balance; embolization typically performed in a stepwise fashion to avoid rapid hemodynamic changes, which can lead to hemorrhage or thrombosis. Initial intervention optimally at 4 to 5 mo, with subsequent treatments at 4 to 8 wk intervals; emergent embolization may be required in neonates with severe symptoms.
- **Surgical therapy** used as a last resort if endovascular interventions fail; if hydrocephalus does not resolve with embolization, CSF diversion may be required.

PROGNOSIS: Untreated VGAM leads to cerebral atrophy and irreversible brain damage as a result of persistent venous congestion; severely affected

neonates may show rapid parenchymal atrophy ("melting brain"); infants and children may experience progressive neurocognitive decline due to development of cerebral atrophy, calcifications, and seizures.

Overall mortality 10.6% with endovascular therapy; intervention in neonatal period associated with significantly higher mortality (52%) than intervention in infants (7.2%) and children (0%). On follow-up, 74% have good neurocognitive outcome; remainder have developmental delays (15.6% moderate, 10.4% severe).[72]

Vascular Disorders of the Spinal Cord

Spinal cord vascular malformations are rare but potentially devastating causes of cord injury. Neurologic symptoms may result from direct compression, hemorrhage, and ischemia.[73] Most are diagnosed by MRI and spinal angiography.

Arteriovenous Malformations

Thought to be congenital lesions; about half of patients present with symptoms of chronic ischemia, while half present with acute events. Approximately 20% have associated vascular anomalies, including Klippel–Trénaunay–Weber syndrome, Osler–Weber–Rendu syndrome, or other spinal or intracranial vascular lesions.

Glomus Arteriovenous Malformation

Compact, complex nidus of arteriovenous channels without intervening parenchyma. Usually located in cervical cord, but reported at all levels. Typically present with neurologic deficits in the 3rd decade. Treated by surgical resection or embolization.

Juvenile Arteriovenous Malformation

Large nidus with dilated channels and multiple feeding vessels spanning a long segment of cord, with intervening parenchyma. Rare; most common in cervical and upper thoracic cord. Due to extent of cord involvement, treatment often requires a staged approach including embolization and resection.[74]

Perimedullary Arteriovenous Fistula

Direct connection between intradural extramedullary vessels (usually anterior spinal artery branch and paraspinal draining vein); most common in the thoracic and lumbar cord and conus medullaris. Patients typically present in the 3rd decade with gradual onset of symptoms due to spinal cord ischemia (Foix–Alajouanine syndrome); larger, more aggressive lesions may present in childhood and adolescence.[75] These are treated by surgical or endovascular obliteration (endovascular approach preferred for larger, high-flow lesions).

Cavernous Malformations

Similar to cerebral cavernous malformations, but less common (Fig. 18.9). May present with acute hemorrhage, subacutely progressive deficits, or episodic neurologic deficits. Rarely seen on spinal angiography. Treatment of symptomatic lesions is surgical resection.

Complex Vascular Malformations

Very rare malformations involving tissues surrounding the spinal cord, including vertebrae and skin (Cobb syndrome) and sometimes abdominal or thoracic organs; seen in Osler–Weber–Rendu syndrome.



FIGURE 18.9 Sagittal T2-weighted MRI of the thoracic spine in a 19-year-old girl, demonstrating a hypointense intramedullary lesion at the T7 level (*arrow*) consistent with a cavernous malformation. There is associated hyperintensity and cord expansion extending from T3 through T10.

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19 Neonatal Neurology

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INTRACRANIAL HEMORRHAGE

Intra-axial Hemorrhage

Germinal Matrix/Periventricular–Intraventricular Hemorrhage (IVH)

- Most common type of neonatal intracranial hemorrhage.

Incidence

- Reported incidence in the preterm newborn ranges from 13% to 65%, but overall ~20% to 25%.[1]
  - Risk of IVH correlates inversely with gestational age.
- Varies among different hospitals and regions.
- Newborns born to hypertensive mothers have a lower risk of IVH.[2]
- Improvements in perinatal and neonatal care have led to a reduction in the overall incidence of IVH in the premature newborn; however, increased survival of the extremely premature newborn means that IVH remains a major source of mortality and morbidity in this population.
- Incidence is much lower in term newborns than in preterm ones; the incidence of all types of intracranial hemorrhage in term newborns was 2.7/10,000 live births in one report.[3,4]

Pathogenesis[5]

Intravascular Factors

- Ischemia and reperfusion (e.g., following treatment of hypotension or hypovolemia)
- Impaired cerebral autoregulation
- Fluctuating cerebral blood flow
- ↑ Cerebral blood flow (e.g., due to hypercarbia, volume expansion)
- ↑ Cerebral venous pressure (e.g., with pneumothorax)
- Coagulation abnormalities

Vascular Factors

- Germinal matrix capillaries vulnerable to rupture: thin walls with large lumen
- Arterial development immature: acute transition from large vessels to a capillary network without gradual arborization

Extravascular Factors

- Increased fibrinolytic activity
- Poor vascular support in cerebral tissue

Grading of IVH (per Volpe)[5]

- Grade I: Hemorrhage confined to the germinal matrix.
- Grade II: Hemorrhage within the lateral ventricle (10%–50% of ventricular area on sagittal view).

- Grade III: Hemorrhage within the lateral ventricle (>50% of ventricular area or distends ventricle).
- Periventricular hemorrhagic infarction (PHI)—parenchymal echodense lesion associated with large ipsilateral IVH; often referred to as Grade IV IVH.
  - This venous infarction is caused by (usually) large IVH obstructing venous drainage of the periventricular white matter.

Management of IVH

- Supportive care (including correction of coagulopathies, circulatory and respiratory support)
- Daily monitoring of fontanelle and head circumference and serial head ultrasound (US) examinations in newborns with IVH ≥ Grade II to monitor for development of progressive ventricular dilation

Complications of IVH (Table 19.1)

Periventricular Hemorrhagic Infarction

- As above, this is a complication of large IVH but is often referred to as Grade IV IVH.

Progressive Ventricular Dilation (PVD)/Posthemorrhagic Hydrocephalus

- Occurs in 25% of preterm newborns.[6]
- PVD usually caused by impaired reabsorption of the cerebrospinal fluid (CSF) by arachnoid villi.
- Obstructive hydrocephalus rarely caused by obstruction of the aqueduct or foramen by clot.
- PVD needs to be differentiated from stable ventricular dilation due to cerebral atrophy.

Death

- Death may occur with catastrophic presentation of large bilateral IVH.
- Mortality rate is higher in patients who develop PVD than in those without PVD.

Neurologic Sequelae in Survivors

- There is a strong association between periventricular leukomalacia (PVL) and IVH. It is unknown to what degree the relationship is

TABLE 19.1 Complications of Intraventricular Hemorrhage (IVH) in the Preterm Newborn

Severity of IVH	Mortality (%)	Progressive Ventricular Dilatation (%)	Neurologic Sequelae (%)
Grade I	5	5	5
Grade II	10	20	15
Grade III	20	55	35
Periventricular hemorrhagic infarction	50	80	90

causal or whether the two entities develop in parallel because of common pathologic processes. There are data to suggest that IVH may exacerbate PVL, due to the presence of non–protein-bound iron in the CSF.[7]

- The likelihood of later cerebral palsy, major neurosensory disability, and cognitive dysfunction increases with size of IVH, particularly with complications of PHI &/or PVD.
- PHI often results in mild, moderate, or severe hemiplegia.
- Long-term cognitive impairments with school difficulties are frequent.
  - Deficits in verbal learning and verbal memory particularly common.
  - Subjects with IVH Grades III–IV score significantly lower than those with IVH Grades I–II in verbal learning, everyday memory, visuoconstructive and visuospatial abilities.
- Sensory deficits (agnosia, tactile hypersensitivity, tactile hyposensitivity, dyspraxia) may also be associated with IVH.
- Risk of visual impairments (strabismus, optic atrophy, retinopathy of prematurity) is increased in the presence of IVH, particularly with PHI.
- PVD increases the likelihood of neurologic impairments and disabilities.
- There are only a few small reports of neurologic sequelae of IVH with/without PVD in term newborns[8,9]; alloimmune thrombocytopenia appears to be a poor prognostic factor (may be related to size of IVH).

Management of PVD

- Daily monitoring of head circumference, fontanelle, and serial head US examinations.
- Approximately 38% of preterm newborns without treatment will have spontaneous arrest/and or resolution of PVD without treatment.[6]
- Serial lumbar punctures (LPs) can be used to decrease ventricular volume ± increased intracranial pressure when there is evidence of rapidly progressive and/or persistent ventricular enlargement.
  - Sufficient CSF should be removed to decrease ventricular volume and/or ICP (10–15 mL/kg body weight at each lumbar puncture).
  - LPs should be continued until the ventricles stabilize or decrease in size on serial US studies or until surgical treatment deemed necessary and is feasible.
  - Consider ventricular tap if LPs are unsuccessful (PVD may not be communicating).
- Trials of fibrinolytics.
  - Five randomized trials evaluated intraventricular administration of fibrinolytics in newborns with IVH and PVD, with no significant effect on rate of death or shunt dependence. Risks of treatment included meningitis and secondary IVH.
  - A high-risk therapy called DRIFT (drainage, irrigation, and fibrinolytic therapy) was tested in an international randomized clinical trial. Although it did not significantly lower the need for shunt surgery, there was decreased mortality or risk of severe disability (54% vs. 71%) and decreased severe cognitive disability

(31% vs. 59%) at 2 y.[10] Due to high risks (e.g., secondary IVH), this therapy has not been widely adopted.

Intraparenchymal Hemorrhage

- Intraparenchymal hemorrhage (IPH) refers to bleeding into the brain parenchyma.

Causes

- Trauma (including nonaccidental trauma)
- Coagulation abnormalities
- Arteriovenous malformation (AVM), aneurysm, e.g., vein of Galen
- Venous infarction
  - Venous congestion or obstruction following large IVH.
  - Venous congestion or obstruction following sinovenous thrombosis (SVT).

Neurologic Outcome

- Depends on the location and size of parenchymal injury
- Could include epilepsy and motor, cognitive, and/or sensory impairments

Extra-axial Hemorrhage

Subpial Hemorrhage (a type of subarachnoid hemorrhage—see below)

- Hemorrhage between the pial layer and cortical surface, most often around temporal lobe.
- Appears to be related to local trauma, e.g., with instrumented delivery.[11]
- On CT or MRI, appears as ribbon-like collections of blood following contours of gyri and sulci.
- Seizures most frequent presenting sign, babies often otherwise well-appearing.

Subarachnoid Hemorrhage (SAH)

- SAH is more commonly seen in conjugation with other types of intracranial hemorrhage, e.g., IVH, subdural hematoma, etc.
- Primary SAH rarely leads to significant clinical signs unless large.
- Small SAH may cause seizures in an otherwise well baby (see also subpial hemorrhage above).
- Large SAH may result in hydrocephalus ± seizures.

Subdural Hematoma (SDH) & Epidural Hematoma

- SDH and epidural hematoma most frequently related to trauma (e.g., birth trauma or nonaccidental injury) but epidural hematoma much less common.
- Small SDH related to birth: common and inconsequential.
- Rare causes of SDH are coagulation abnormalities and glutaric aciduria type 1.
- Both large SDH and epidural hematoma may present with signs of raised intracranial pressure.
  - Lethargy, vomiting, bulging fontanel, increased head size, high-pitched cry, irritability, feeding difficulties, seizures, or loss of consciousness.
- Characterized based on size, location, and age (i.e., acute, subacute, or chronic).

- Early surgical evacuation may be lifesaving for large hematomas with signs of raised intracranial pressure and significant neurologic compromise.
- Size, location, and age of SDH/epidural hematoma as well as the neurologic and medical condition of the patient determine the course of treatment and outcome.

Subgaleal Hematoma (SGH)

- Prevalence of moderate-to-severe SGH is ~1.5 per 10,000 births.[12]
- SGH may form because of preexisting risk factors (e.g., coagulopathy).
- Vacuum extraction predisposes a newborn toward subgaleal hemorrhage.
- SGH must be considered in any newborn with a scalp swelling and a falling hematocrit.
- In term babies, this subaponeurotic space may hold as much as 260 mL of blood.
- Death can result from exsanguination and hypovolemic shock, caused by massive bleeding into the subgaleal space.
- Close monitoring of vital signs, level of consciousness, hematocrit, blood gases, head circumference, and signs of tissue hypoperfusion is recommended.
- Coagulation studies should be performed in all newborns with a diagnosis of SGH.

Cephalohematoma

- Very common, usually does not require treatment or diagnostic testing.
- Collection of blood beneath the periosteum.
- Limited by suture lines (if no associated skull fracture).
- Due to sliding/tearing forces during the birth process.
- More common with forceps and vacuum extraction.
- Generally benign, but if large, may exacerbate jaundice.
- Takes weeks to months to resolve (outer edges may calcify, so center may resolve initially, leaving a "crater"-like appearance).
- Large cephalohematomas may occur with coagulation abnormalities (vitamin K deficiency, factor 8 deficiency, etc.).

ENCEPHALOPATHY OF PREMATURITY/WHITE MATTER INJURY/PVL

- Classical PVL consists of focal necrotic lesions and surrounding areas of gliosis, with cyst formation detectable typically 2 to 4 wk after birth.
- Recent MRI studies have demonstrated a more diffuse form of non-cystic white matter injury.[13]
- Both cystic and non-cystic forms are usually bilateral and symmetric.
- Histology shows microglial activation and loss of premyelinating oligodendrocytes.
- The periventricular white matter dorsolateral to the trigones and frontal horns of the lateral ventricles are areas most commonly affected by PVL.
- Recent MRI and neuropathology studies strongly suggest that cerebral neuronal structures, as well as cerebellum, are also frequently injured.[14,15]

- Gray matter injury may reflect damage to subplate neurons, which appears early in cortical development and directs projections of afferent and efferent thalamocortical neurons.[16]
- Diffuse loss of brain tissue in PVL results in ventriculomegaly, enlarged extra-axial CSF spaces, and immature gyral development.

Incidence

- The reported incidence of cystic PVL has decreased over the past several years to ~5% of very low birth weight newborns.
- Diffuse non-cystic PVL is now recognized as the most common form of brain injury in preterm newborns; MRI studies at term show an incidence of up to 70%.[17]

Pathophysiology

Hypoxia, ischemia, and inflammation may all injure oligodendrocyte progenitor cells (preOL) in the periventricular white matter.

- Hypoxia–ischemia
  - "Border zone" in the white matter between penetrating cortical arteries and deep lenticulostriate arteries is susceptible to ischemia during periods of hypotension.
  - Hypocarbia (a potent vasoconstrictor) is independently associated with PVL.[18]
- Inflammation
  - Free radical formation associated with hypoxia–ischemia and breakdown of red blood cells, e.g., with an associated IVH.
  - Infection: PVL associated with premature rupture of membranes, maternal chorioamnionitis, postnatal infection, neonatal surgery, and necrotizing enterocolitis.

Diagnosis

- Cranial US remains the preferred method of screening for and monitoring PVL due to safety, availability of bedside US, and reduced access, cost, and difficulty of performing MRI.
- MRI, especially DTI, is more sensitive than US in detecting diffuse PVL.[19] However, detection of more subtle PVL rarely alters management as all infants born preterm should receive close developmental follow-up and developmental services as indicated by physical findings and developmental progress.
- Cystic PVL may be seen in the first postnatal week; however, cysts usually appear 2 to 4 wk after birth and are easily detected by US.
- Diffuse PVL.
  - Identified on cranial US or MRI by ex vacuo dilation of the ventricles (often associated with an abnormal shape of the lateral ventricles) and enlarged extra-axial spaces.
  - The importance of diffuse excessive high signal intensity (DEHSI) is unclear.
    - Because of its high incidence in preterm newborns at term age, its absence after postmenstrual age of 50 weeks, and the sometimes normal neurologic outcome at a corrected age of 2 y, DEHSI may not be part of the spectrum of white matter injury, but rather a prematurity-related developmental phenomenon.[20]

- Punctate white matter lesions appear to be another form of white matter injury, but the neuropathology and clinical significance are currently unclear.[19,21]
- Recommended screening protocols suggest an initial cranial US within 3 to 5 d after birth, repeated at 7 to 10 & ~30 days of age, and at 36-wk corrected gestational age and/or pre-discharge or term age equivalent.

Outcome—Encephalopathy of Prematurity

- Depends on the severity and extent of PVL; however, rates of cognitive impairments, cerebral palsy or milder motor impairments, and visual perceptual or other sensory dysfunction are high.
- Cystic PVL tends to damage more medial fiber tracts that control lower extremity function, leading to spastic diplegia, where upper extremity spasticity/dysfunction is less severe.
- Extensive white matter involvement may result in quadriplegia and include facial weakness.
- High incidence of subsequent cognitive deficits without prominent motor deficits may be explained in part by a reduction in the density of cerebral cortical neurons overlying areas of PVL.[14]
- Cognitive and/or behavioral deficits may be very specific, such as visuomotor and perceptual disabilities, constructional dyspraxia, or attention-deficit disorders.
- Attention deficits and impaired working memory may be associated with injury to the mediodorsal and reticular thalamic nuclei.[15]
- Visual impairments: children with PVL may have visual perception difficulties or, with severe PVL, bilateral inferior visual field deficit.
- Punctate white matter lesions and ventricular dilatation are significantly associated with cognitive and psychomotor developmental delay, motor delay, and cerebral palsy.[20]

NEONATAL ENCEPHALOPATHY

Definition

"A clinically defined syndrome of disturbed neurological function in the earliest days of life in the term newborn, manifested by difficulty with initiating and maintaining respiration, depression of tone and reflexes, subnormal level of consciousness and often seizures."[22]

- Divided into three grades depending on severity[23] (see Table 19.2).

Etiology

- Intrapartum asphyxia with resultant hypoxic-ischemic encephalopathy
- Infection
- Drug exposure
- Perinatal arterial ischemic stroke
- Metabolic or other genetic disorders
- Brain malformation, epileptic encephalopathy

The clinical history will determine the need for investigation to exclude these disorders.

TABLE 19.2 Distinguishing Features of the Three Clinical Stages of Hypoxic-Ischemic Encephalopathy in the Full-Term Newborn

	Stage 1	Stage 2	Stage 3
Level of consciousness	Hyperalert	Lethargic or obtunded	Stuporous
Neuromuscular control			
Muscle tone	Normal	Mild hypotonia	Flaccid
Posture	Mild distal flexion	Strong distal flexion	Intermittent decerebration
Stretch reflexes	Overactive	Overactive	Decreased or absent
Segmental myoclonus	Present	Present	Absent
Complex reflexes			
Suck	Weak	Weak or absent	Absent
Moro	Strong: low threshold	Weak, incomplete, high threshold	Absent
Oculovestibular	Normal	Overactive	Weak or absent
Tonic neck	Slight	Strong	Absent
Autonomic function	Generalized sympathetic	Generalized parasympathetic	Both systems depressed
Pupils	Mydriasis	Miosis	Variable; often unequal; poor light reflex
Heart rate	Tachycardia	Bradycardia	Variable
Bronchial and salivary secretions	Sparse	Profuse	Variable
Gastrointestinal motility	Normal or decreased	Increased; diarrhea	Variable
Seizures	None	Common; focal or multifocal	Uncommon (excluding decerebration)
Electroencephalogram findings	Normal (awake)	Early: low-voltage continuous delta and theta Later: periodic pattern (awake) Seizures: focal 1–1½-hz spike-and-wave	Early: periodic pattern with isopotential phases Later: totally isopotential
Duration	<24 h	2–14 d	Hours to weeks

Sarnat HB, Sarnat MS. Neonatal encephalopathy following fetal distress. A clinical and electroencephalographic study. *Arch Neurol.* 1976;33(10):696–705.

HYPOXIC-ISCHEMIC ENCEPHALOPATHY (HIE)

Incidence

- Wide variation in incidence of HIE by country/region.
- One broad review concluded that the incidence of HIE at term is 2.5/1,000 live births (range 1.2–7.7/1,000) in developed countries.[24]

Definition

An acute, evolving encephalopathy caused by intrapartum or late antepartum brain hypoxia and ischemia.

Eligibility for trials of therapeutic hypothermia required three sets of criteria (A, B, and C) to be satisfied, which are often used as clinical guidelines to assess eligibility for therapeutic hypothermia treatment.

- Criteria A. Newborns >36-wk gestation admitted to the NICU with at least one of the following:
  - Apgar score of <5 at 10 min after birth.
  - Continued need for resuscitation, including endotracheal or mask ventilation, at 10 min after birth.
  - Acidosis within 60 min of birth (defined as any occurrence of umbilical cord, arterial, or capillary pH <7.00).
  - Base deficit >16mmol/L in any blood sample (arterial, venous, or capillary) within 60 min of birth.

Newborns that met these criteria are assessed using criteria B:

- Criteria B. Moderate to severe encephalopathy, consisting of altered state of consciousness (lethargy, stupor, or coma) *and* at least one of the following:
  - Hypotonia
  - Abnormal reflexes including oculomotor or pupillary abnormalities
  - Absent or weak suck
  - Clinical seizures

Newborns meeting criteria A & B assessed by criterion C (amplitude-integrated electroencephalogram [aEEG] not used in all trials).

- Criteria C. At least 30 min duration of aEEG recording that shows the following:
  - Normal background with some seizure activity
  - Moderately abnormal activity
  - Suppressed activity
  - Continuous seizure activity

Management of the Newborn with HIE

General Considerations

- Stabilize the newborn (ventilation, oxygenation, and circulation).
- Consider passive cooling early (see Temperature below).
- Full septic workup, cover with antibiotic therapy while waiting for results.
- *Careful management of glucose*—hypoglycemia is common and may worsen hypoxic-ischemic brain damage.
- Careful fluid and electrolyte (sodium, magnesium) management is important, and fluid restriction usually required, especially with evidence of renal dysfunction.

Specific Considerations

Temperature Control

- Ambient heating should be switched off *as soon as HIE is suspected,* e.g., during resuscitation.
- Passive cooling should continue until a decision regarding active therapeutic hypothermia therapy has been made.
- If a newborn meets eligibility criteria for therapeutic hypothermia, then this should be initiated ASAP, and should be **within 6 h** after birth.
- Therapeutic hypothermia should only be performed in a unit with a protocol for neurologic assessment, monitoring, and follow-up.

A servo-controlled cooling blanket or cap is needed. If not available, then the baby should be transferred to a unit with such facilities and experience.

- Core (rectal or esophageal) temperature should be checked frequently or preferably monitored continuously to ensure the newborn's temperature remains within the range of 33.5 ± 1°C.
- Cooling should be continued for a total of 72 h unless an exclusion criterion (lethal chromosomal anomaly, severe congenital anomalies, symptomatic systemic congenital viral infection, symptomatic systemic bacterial infection, bleeding diathesis, or major intracranial hemorrhage) is identified, in which case early rewarming may be required.
- The target core temperature goal during cooling is 33.5°C (33°C–34°C), with acceptable range of 32.5°C to 34.5°C (esophageal or rectal probe).

Seizure Management

- Early treatment of seizures, including subclinical seizures, is important and may improve outcome.[25] (See section on seizures for management details.)
- Conventional EEG is superior to aEEG monitoring for the detection of neonatal seizures.[26] Current guidelines recommend 24 h of EEG monitoring for newborns with encephalopathy and/or suspected seizures.[27]

Imaging in Neonatal HIE

General Considerations

- Magnetic resonance (MR) techniques are best for HIE.
- Early head US is useful to rule out intracranial hemorrhage, which could be a contraindication to therapeutic hypothermia, if large.
- A combination of T1- and T2-weighted MR imaging, diffusion-weighted imaging, and MR spectroscopy is best if early imaging is being obtained.
- MR parameters, such as T1 and T2 characteristics, metabolic ratios, and diffusivity vary with the time after insult.
  - Apparent diffusion coefficient (ADC)
    - Decreased as early as 6 h following an acute hypoxic-ischemic insult even with normal conventional MRI.[28]
    - Shows a biphasic pattern of change: reaches nadir at day ~2 to 3, pseudonormalizes at day ~7 to 10, then increases to above-normal values.[29]
    - Therapeutic hypothermia results in lower diffusivity and longer duration of restricted diffusion, prolonging time to pseudonormalization.[30]
- Imaging between 1 and 4 wk (before atrophy becomes apparent) has been reported as the best time for predicting severity of neurologic outcome.[31,32]

Patterns of Injury in Term HIE

- Duration and severity of hypoxic-ischemic insult determines the pattern of brain injury.
- Acute, profound asphyxia:
  - Associated with injury to the deep gray nuclei (basal ganglia and thalamus) ± brainstem nuclei and perirolandic cortex.

- Extends to diffuse cerebral injury with loss of gray/white matter differentiation of the cortex and involvement of the hippocampi and brainstem when severe.
- Predilection for the posterior limb of the internal capsule (PLIC), brainstem, hippocampal region, and cortex in severe acute hypoxia–ischemia probably reflects vulnerability of certain neuronal populations to hypoxia–ischemia, e.g., due to the high metabolic rate of gray matter neurons and early myelination.
- Cortical highlighting is associated with a less profound acute insult (Figs. 19.1A–C, 19.2).

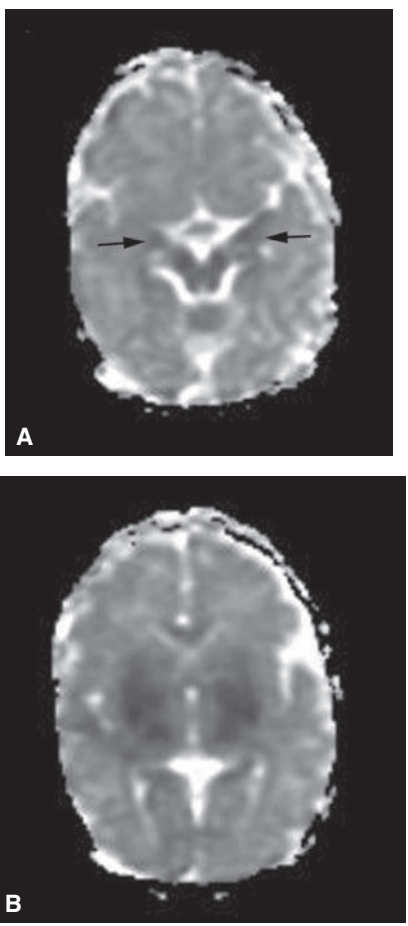


FIGURE 19.1 Basal Ganglia/Thalamic Pattern of Injury, MRI Day 5. ADC image shows darker area consistent with restricted diffusion. **A:** In midbrain and in both hippocampal areas (*arrows*). **B:** In thalami and basal ganglia bilaterally. **C:** In cortex of central sulcus area bilaterally.

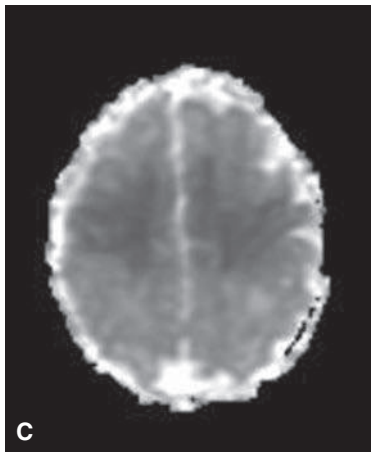


FIGURE 19.1 *(Continued)*

- Prolonged partial asphyxia:
  - Associated with watershed predominant pattern involving the vascular watershed zones (anterior–middle cerebral artery and posterior–middle cerebral artery).

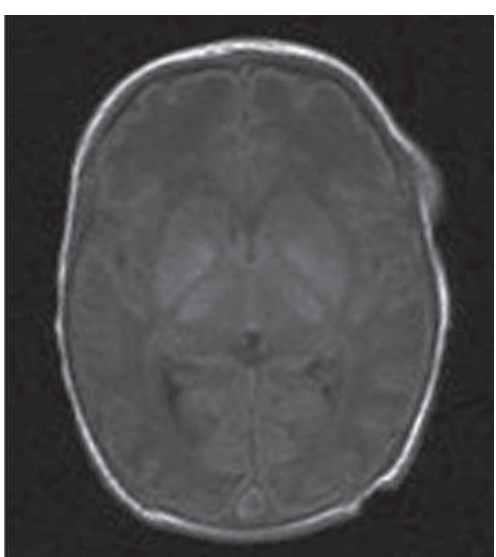


FIGURE 19.2 Basal Ganglia/Thalamic Pattern of Injury, MRI Day 6. T1 image shows abnormally high T1 signal in both lentiform nuclei and in the lateral nuclei of the thalami bilaterally. There is loss of the normal high signal of the PLIC bilaterally.

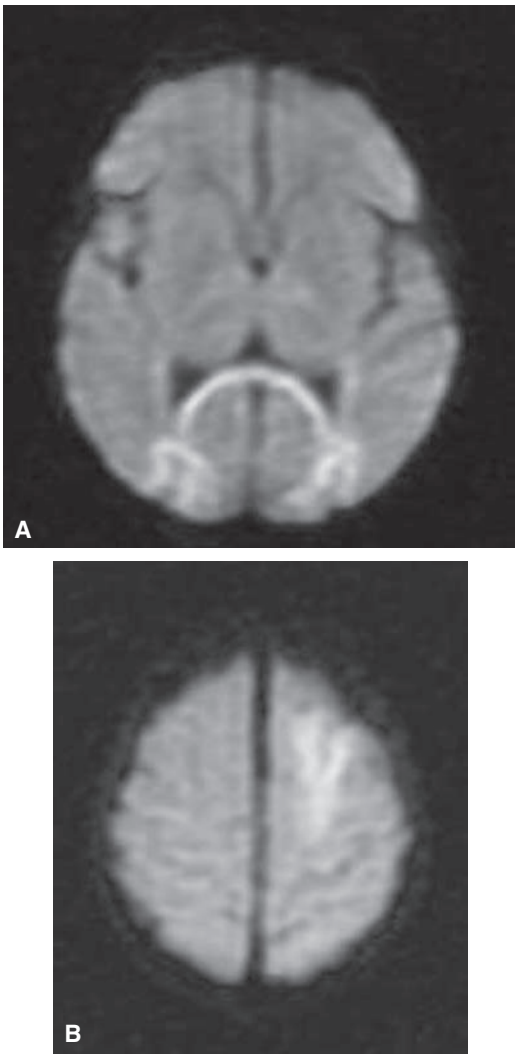


FIGURE 19.3 Watershed Pattern of Injury, MRI Day 4. Diffusion-weighted images show abnormally high signal in **(A)** posterior watershed areas bilaterally, **(B)** anterior watershed area anteriorly.

- Affects mainly the white matter and extends to the cortical gray matter when severe.
- Common after hypotension, infection, and hypoglycemia (Fig. 19.3A,B).

■ Small punctate hemorrhagic lesions scattered in the white matter are occasionally seen and areas of focal hemorrhage occur in around 5% of cases[33] (Fig. 19.4).

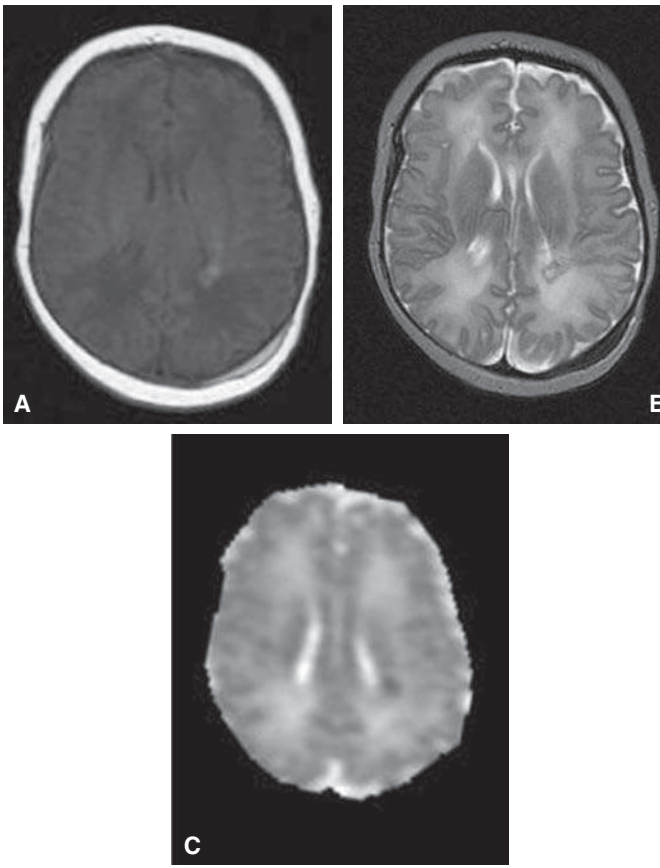


FIGURE 19.4 Punctate Hemorrhagic Lesions, MRI Day 7. Images show abnormal signal in deep white matter adjacent to body of left lateral ventricle. **A:** High T1 signal. **B:** Focus of high T2 signal with surrounding low signal. **C:** ADC image shows low signal in the affected area consistent with restricted diffusion.

- For any insult, a spectrum of brain injuries is possible,[34] and prolongation of either type of asphyxial insult results in more diffuse brain injury.

Outcome of Neonatal HIE

General Considerations

- A strong relationship exists between the severity of encephalopathy and neurologic outcome.
- In general, few children with mild encephalopathy show neurologic impairments; however, some studies report newborns with mild encephalopathy performing at a level between healthy controls and those with moderate NE.[33]

- Children who have suffered moderate encephalopathy form a heterogeneous group, with varying degrees of childhood morbidity, depending on the distribution and extent of brain injury (e.g., predominantly subcortical or watershed; see "Imaging and Outcome" below).
  - Investigations such as EEG (conventional and/or amplitude-integrated) and brain MRI aid prediction of outcome within this group.
- Outcome of severe, diffuse brain injury is generally poor.
  - Almost all die or have severe disabilities (cerebral palsy [spastic ± dystonic quadriplegia], intellectual disability ± sensory disabilities and epilepsy).
- Prolonged and/or frequent seizure activity is independently associated with brain injury and poor neurologic outcome.
- Studies have reported ~10% rate of epilepsy by the age of 3.5 y,[35] likely higher at older ages.
- Visual impairment has being found in ~9% of survivors of HIE.[36] Isolated visual impairment is rare following HIE; when present, it usually coexists with motor problems, mainly due to lesions in the basal ganglia.

EEG and Outcome in HIE

- An abnormal background on early aEEG is shown to be highly sensitive (0.93) in predicting poor neurologic outcome.
- A normal background is highly specific (0.93) in predicting favorable neurologic outcome ($n = 56$; median age of 5 h).[37]
- The predictive value of an early abnormal aEEG background may be altered by treatment with therapeutic hypothermia.
  - Positive predictive value (PPV) of an abnormal aEEG at 3 to 6 h was 84% in non-cooled newborns versus 59% in cooled newborns.[38–40]
- Conventional EEG in newborns with severe HIE treated with hypothermia remains a strong predictor of long-term neurodevelopmental outcome.[41–43]
- Normalization of EEG background by day 7 is predictive of favorable outcome.
- The predictive value of EEG background increases when early EEG findings are combined with neuroimaging findings.

Imaging and Outcome in HIE

Predominant *pattern* of brain injury has greater value in prediction of neurodevelopmental outcome than the severity of injury in a specific region.

- Isolated basal ganglia/thalamic injury—depends on the extent of injury.
  - Loss of the normal signal intensity from the PLIC is strongly associated with adjacent basal ganglia and thalami (BGT) injury and is a reliable predictor of abnormal motor outcome (predominantly spastic ± dystonic quadriplegia).[31,34,44]
  - Cognition may be preserved with small, discrete areas of BGT injury.
  - Involvement of the perirolandic cortex and hippocampus predict a greater degree of cognitive and motor deficits.
  - Hippocampal atrophy is associated with memory impairments. Deficits are more evident in subdomains of narrative memory and sentence repetition compared to semantic memory.

- Watershed pattern of injury appears to be associated with cognitive deficits.[34,45,46]
  - Mild forms of watershed injury (predominantly white matter) may have relatively mild motor impairments (e.g., proximal weakness) and preserved cognition, but extensive injury can cause motor, cognitive, and sensory (especially visual) impairments or disabilities.
  - Isolated cognitive deficits may occur in the absence of functional motor deficits. In addition, cognitive defects may not be detected at early assessment, highlighting the need for long-term follow-up.[47]
  - The long-term outcome of mild white matter injury is variable, often being associated with subtle cognitive and behavioral deficits.[33]
  - Severe white matter injury is associated with cerebral palsy (commonly spastic quadriplegia), microcephaly, and cognitive ± sensory disability.
  - Severity of outcome also depends on the extent of basal ganglia/thalamic injury.

Biochemical Tests

- Results of biochemical tests (LDH, CPK, renal and hepatic functions) reflect systemic asphyxia, vary widely in the first 96 h of life and should not be used for neurologic prognosis.
- The main value of these investigations is to complement other assessments (clinical/neuroimaging) in the diagnosis of HIE.

NEONATAL ISCHEMIC STROKE

Neonatal ischemic stroke includes perinatal arterial ischemic stroke (PAS), presumed pre- or perinatal stroke, and cerebral SVT.[48]

Associations

- Many risk factors have been identified, but the precise pathophysiology of neonatal stroke is not completely understood.
- Neonates with SVT may have a history of obstetrical and/or perinatal complications and often show signs of encephalopathy ± seizures.
  - Traumatic delivery
  - Diffuse hypoxic-ischemic injury
  - Septicemia/meningitis
  - Dehydration
  - Congenital heart disease
- The majority of neonates with arterial ischemic stroke present with seizures, with less severe encephalopathy than with SVT.
- A history of perinatal depression or other perinatal complications may also occur with PAS (Fig. 19.5).

Perinatal Arterial Ischemic Stroke (PAS)

Term Newborn

- PAS is defined as a thromboembolic event occurring before age 28 d.[49]
- The incidence of PAS is 1/2,800 to 1/5,000 live births; it is the most common known cause of cerebral palsy in term and near-term newborns.

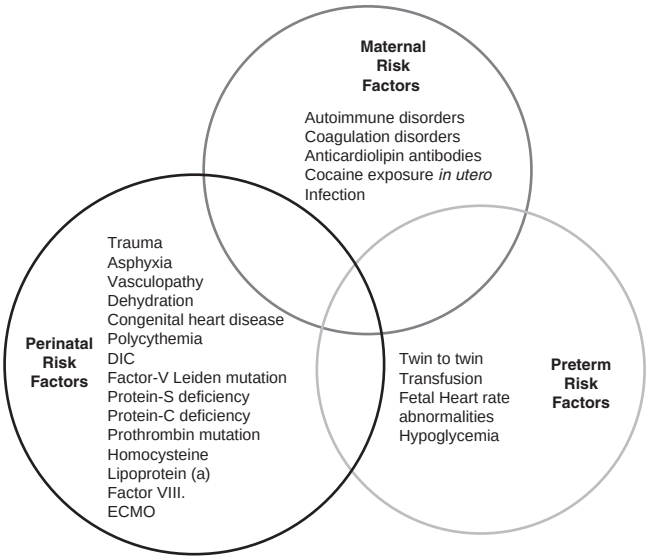


FIGURE 19.5 Associated Risk Factors for Neonatal Stroke. Adapted from Raju TNK, et al. NICHD-NINDS Perinatal Stroke Workshop Participants. Ischaemic perinatal stroke: summary of a workshop sponsored by the National Institute of Child Health and Human Development and the National Institute of Neurological Disorders and Stroke. *Pediatrics* 2007;120:609–616.

- Perinatal stroke is 17 times more common than pediatric stroke beyond the newborn period.
- Newborns with PAS may present either acutely (commonly with recurrent focal seizures in the first 3 d after birth) or remain asymptomatic until age 4 to 8 mo when a hemiparesis is noted.[50]

Preterm Newborn

- PAS may be more common in the preterm newborns, with an incidence of 7 in 1,000 reported in newborns <35 completed weeks gestation.[51]
- Risk factors identified in the preterm population are twin-to-twin transfusion syndrome, decreased fetal movements, and hypoglycemia.[52]
- Preterm newborns often do not present with clinical signs; therefore, the diagnosis can be missed or delayed.
- Lenticulostriate infarction appears to be especially common in the preterm population, whereas cortical infarction is uncommon.[51]
- A different predilection of the lenticulostriate branches of the MCA in the preterm group, compared to cortical branches of the MCA in the full-term newborn, favors diagnosis by US in preterm newborns.

Outcome Post PAS

Term Newborn

- Overall morbidity reported in 60%[53] to 81%.[49]
- Delayed presentation associated with a worse motor outcome, likely because hemiparesis is presenting sign and internal capsule commonly involved.[49]

- Cerebral palsy reported in ~60%.
  - The degree of Wallerian degeneration (WD) in the corticospinal tracts seen with MRI was correlated with the distribution and severity of congenital hemiplegia in 20 children aged 9 mo to 9 y.[54]
- One report showed involvement of basal ganglia, internal capsule, and cerebral cortex is necessary for the development of hemiparesis.[55]
  - Epilepsy ~39%[49]
  - Cognitive/language impairments in ~25%
  - Behavioral abnormalities in ~25%

Preterm Newborn

- Outcome poorer in preterm than in term group.
  - Especially in language development.
  - Interhemispheric reorganization in the preterm newborn is less than that in full-term newborns.[56]
  - Border-zone infarction in the preterm newborn has a more favorable outcome compared to involvement of main branches or posterior limb of internal capsule.[56]
- Given a very low recurrence rate in the absence of underlying disease, long-term prophylaxis with anticoagulant or antiplatelet agents after PAS is unwarranted.[57]

Cerebral Venous Infarction

- SVT in the term or preterm newborn can result in cerebral venous infarction (see notes on SVT).
- In the preterm newborn, germinal layer hemorrhage may obstruct venous drainage of the periventricular tissues, leading to venous infarction.

Sinovenous Thrombosis

- The incidence in neonates is estimated at 1 to 12 per 100,000.
- Extensive white matter damage is the predominant pattern of injury in the preterm newborn.
- Cerebral venous infarction may occur secondary to SVT; however, it likely represents the more severe end of the spectrum of outcome with SVT.
- High index of suspicion for SVT is needed for
  - neonates paralyzed on ECMO.
  - term newborns presenting with intraventricular or thalamic infarcts (especially if unilateral).
  - preterm newborns with unexpected late onset of bilateral white matter involvement $\pm$ associated IVH following an otherwise uncomplicated neonatal course.
- The most frequently involved sinuses in neonates are the superior sagittal sinus and lateral sinuses.
- In newborns with extensive sinovenous occlusion, dilated scalp veins and bulging fontanels with splayed cranial sutures may accompany the neurologic signs.
- The diagnosis is dependent on demonstrating decreased flow in the sinuses or the presence of a large thrombus or absent flow by MR venogram or Doppler imaging (US).
- Anticoagulant therapy for neonatal SVT is controversial.
  - Absence of anticoagulant therapy was an independent risk factor of poor outcome in multivariate analysis.[58]

- Propagation of clot has been reported in 25% of affected newborns.[59]
- Although not based on clinical trials, unfractionated heparin or low-molecular-weight heparin administration is advised in patients with SVT for a minimum period of 6 wk and no longer than 3 mo.
- It is probably not recommended in the presence of a large infarct or significant hemorrhage.

- Radiographic follow-up (US ± MRI) is required.
- If anticoagulants not used, US or MRI could detect subclinical progression, which would indicate need for anticoagulation.
- If anticoagulant is used, US or MRI could detect severe intracranial hemorrhage, which could indicate a need to stop the anticoagulant.

Outcome Post SVT

- Reported outcome varies widely—recent studies report better outcomes, reflecting improved diagnosis of less severely affected newborns and/or improved treatment.[60]
- The presence of venous infarction predicts a worse outcome.[61,62]
- Mortality varies between 2% and 19%.
- Moderate to severe impairments are reported in 40% to 45% of survivors.
- Postneonatal epilepsy is reported in 16% to 41% of survivors.
- Outcome in the preterm population is poorer.[51]

NEONATAL SEIZURES

- The neonatal period is the most vulnerable of all periods of life for developing seizures, particularly in the first week after birth.
- Incidence—term newborns 0.7 to 2.7 per 1,000 live births.
  - Higher incidence in preterm newborns.

Definition

Clinical

- Abnormal, stereotyped, paroxysmal alterations in neurologic function (i.e., motor, behavioral, or autonomic), occurring in the first 28 d after birth in a term newborn or before 44 wk of gestational age in a preterm newborn.[63]

Electrographic

- 10 s or greater of repetitive, evolving electrical discharges or rhythmic slowing.

Classification (Volpe)

- Subtle seizures (50%)
- Clonic seizures (25%)
- Myoclonic seizures (20%)
- Tonic seizures (5%)
- Nonparoxysmal repetitive behaviors

Generalized tonic–clonic seizures are rare in neonates due to incomplete myelination.

Etiology

- Hypoxia–ischemia, global or focal/multifocal infarction (e.g., perinatal [fetal distress, maternal hemorrhage], postnatal [cardiac arrest]).
- Hemorrhage, e.g., IVH, IPH, SAH, SDH, cerebral artery and vein infarction, etc.
- Malformations of cerebral development, e.g., polymicrogyria, neuronal heterotopias, lissencephaly, etc.
- Metabolic, e.g., hypoglycemia, hypocalcemia, hyponatremia, inborn errors of metabolism, pyridoxine dependency, etc.
- Infections, e.g., encephalitis, meningitis, brain abscess, intrauterine/congenital (rubella, toxoplasmosis, cytomegalovirus, herpes simplex virus).
- Trauma, including nonaccidental trauma.
- Drug withdrawal, e.g., narcotics, sedatives, barbiturates, etc.

Management

General Principles

- Stabilize the newborn (ventilation, oxygenation, and circulation).
- Identify underlying cause and treat appropriately, especially metabolic abnormalities.
- Commence antibiotic therapy while awaiting results of infectious workup.

Neurologic Management

- If prolonged or recurrent, start anticonvulsant therapy (see anticonvulsant management below) and obtain EEG.
- If refractory to multiple anticonvulsants and no apparent etiology identified, consider trials of pyridoxine, pyridoxal-5′-phosphate (PLP) ± folinic acid.

Investigations

- Blood gas
- Complete sepsis workup, including lumbar puncture
- Serum electrolytes, including calcium, magnesium, and phosphate
- Neuroimaging (MRI best, US if preterm/unstable, CT only for emergencies)
- EEG
- As indicated
  - Toxoplasmosis, rubella, cytomegalovirus, herpes simplex virus titers
  - Toxicology screen
  - Metabolic screen, e.g., lactate/pyruvate, amino acids (serum and CSF), urine organic acids, CSF neurotransmitters
  - Chromosomes ± genetic review
  - Ophthalmology

Anticonvulsant Management

- First-line anticonvulsant in most centers worldwide is **phenobarbital**.
  - Loading dose is 15 to 20 mg/kg.
  - Further boluses of 5 to 10 mg/kg can be given, up to a maximum of 40 mg/kg.

- Maintenance dose is 5 mg/kg/d (has a long half-life and so may be given as a single dose).
- Seizure response rates after loading doses of 15 to 20 mg/kg are reported at around 40%.
- With bolus doses, up to a total dose of 40 mg/kg, responsiveness can be around 70%.[64]
- Therapeutic drug monitoring—therapeutic window 20 to 40 mg/L.

■ Choice of second-line anticonvulsant therapy varies from center to center.

- **Phenytoin/fosphenytoin** has response rates similar to phenobarbital.[65]
  - Loading dose of phenytoin is 15 to 20 mg/kg.
  - Maintenance dose is 5 to 8 mg/kg/d divided t.i.d.–q.i.d.
  - Risk of increased toxicity in renal impairment and hypoalbuminemia.
  - Therapeutic drug monitoring—therapeutic window 10 to 20 μg/mL.
  - Risk of local reactions (high alkalinity); therefore, less alkaline prodrug **fosphenytoin** preferred (1.5 mg/kg of fosphenytoin is equivalent to 1 mg/kg of phenytoin).
- **Benzodiazepines** (cause sedation and may be associated with pooling of secretions)
  - **Lorazepam:** 0.05 to 0.1 mg/kg IV bolus over 2 to 5 min; may be repeated.
  - **Midazolam:** 0.06 to 0.15 mg/kg IV bolus, followed by infusion of 0.1 to 0.4 mg/kg/h. Short half-life. May cause involuntary movements in preterm newborns.
  - **Clonazepam:** 0.1 to 0.2 mg/kg bolus by slow IV infusion or po/pg bolus.
- **Lidocaine**
  - Not in widespread use—some centers in Europe.
  - Adverse cardiac effects, such as ventricular tachycardia or fibrillation, should be closely monitored but are not frequently observed.
  - Should not be administered with phenytoin.
  - Typical regimen (term newborn): 2 mg/kg in 10 min, followed by a continuous infusion of 6 mg/kg/h for 12 h, 4 mg/kg/h for 12 h and finally 2 mg/kg/h for 12 h, then stop.
  - In most cases, loading dose is sufficient without a need to start maintenance infusion.
  - Maintenance dose in newborns receiving therapeutic hypothermia may need to be reduced.
- **Newer antiepileptics for neonatal seizures.**
- Limited experience and data on safety and efficacy in newborns.
  - **Bumetanide**
    - Loop diuretic which inhibits Na(+)-K(+)-2Cl(−) cotransporter NKCC1.
    - In rat studies, inhibition of NKCC1 in cortical neurons with resultant elevation of intracellular chloride resulted in a depression of epileptiform activity.
    - Currently in clinical trials; only one published case report.
  - **Levetiracetam**
    - Unclear mechanism(s) of action.
    - Enhances the GABA inhibitory pathway and inhibits N-type calcium channels, reversal of inhibitory glycine currents, reduced K^+ rectifier current, modulation of neurotransmitter release.

- Several reports of pharmacokinetic data, use in newborns, but no randomized clinical trials or studies with prolonged continuous EEG monitoring to demonstrate efficacy.

- **Topiramate**
  - Enhances GABA activity, inhibits kainite-mediated conductance at glutamate receptors, and modifies Na^+- and Ca^{2+}-dependent action potentials.
  - May be useful for refractory seizures but lack of IV formulation limits use for many etiologies of acute neonatal seizures.

Pyridoxine-Dependent Epilepsy & PLP-Responsive Epilepsy

- Rare causes of neonatal seizures.
- The classic presentation consists of intractable seizures that appear within hours of birth and are resistant to conventional anticonvulsants.
- May present with episodes of restlessness, irritability, and occasionally hypotonia or poor feeding.
- The seizures rapidly respond to administration of parenteral pyridoxine.
- Diagnosis is by therapeutic trial, CSF neurotransmitter analysis, and specific genetic testing, where available.
  - Pyridoxine 50 to 100 mg IV while EEG is running. EEG normalization confirms pyridoxine-dependent epilepsy.
  - PLP 10 mg/kg/dose $\times$3 doses in 1 day as minimum trial, or trial of PLP 30 to 50 mg/kg/d divided into 4 to 6 doses/d.
    - Cessation of seizures indicates either pyridoxine-dependent epilepsy or PLP-responsive epilepsy.

Folinic Acid–Responsive Seizures

- Presentation similar to that of pyridoxine dependency/deficiency.
- Empiric trial of folinic acid 5 mg per dose for two doses 6 h apart, or trial of 3 to 5 mg/kg/d for 2 to 3 d.
- Characteristic peaks on CSF monoamine metabolite analysis.

GLUT-1 Deficiency

- Defect of glucose transport.
- Treatable cause of early-onset seizures, hypotonia, movement disorders, learning difficulties, and microcephaly, but typically presents in infancy after newborn period.
- CSF/blood glucose ratio mean 0.35 (range 0.19–0.49).
- Treat with ketogenic diet.
- Phenobarbital may exacerbate seizures.

Benign Sleep Myoclonus

- Commonly mistaken for seizures.
- Normal newborn examination and development.
- Characterized by myoclonic "lightning"-like jerks of the extremities that occur exclusively during sleep with chaotic pattern, i.e., nonrhythmic.
- Observation of an episode to confirm typical appearance may be sufficient (e.g., home video).
- Recognition is crucial to avoid unnecessary testing.
- Common in association with neonatal abstinence syndrome.

Jitteriness

- It is stimulus-sensitive and is easily stopped with passive movement of the limb.
- The movement resembles a high-frequency, low-amplitude tremor.
- No associated autonomic changes.
- Not associated with ocular deviation.
- Check calcium and glucose.
- Consider exposure to maternal drugs (e.g., heroin/opiates, cocaine, SSRIs).

CONGENITAL INFECTIONS

Early diagnosis and prompt treatment is essential.

In general, the later the infection occurs in the gestation, the less severe the disease.

Cytomegalovirus (CMV)

- Most common congenital viral infection.
  - ~1% of all children born each year in the United States, or 40,000 newborns, are congenitally infected with CMV.
  - Only 10% of these newborns are born symptomatic.
    - Neurologic manifestations (depend on timing of transmission)
      - Microcephaly, intracranial calcifications, and migrational central nervous system defects (polymicrogyria, cortical dysplasia, lissencephaly, if transmission occurred in 2nd trimester).
    - Nonneurologic manifestations
      - Thrombocytopenia, intrauterine growth restriction, hepatosplenomegaly, conjugated hyperbilirubinemia, and chorioretinitis.
  - 5% to 17% will develop progressive sensorineural hearing loss and/or other neurodevelopmental difficulties within the first 4 y of life.
  - Need audiologic follow-up testing in early childhood.
- Most common cause of nonhereditary sensorineural hearing loss in children.
- Transmission can be prenatal (placenta, cervical), natal, or postnatal (breast milk, blood transfusion, e.g., preterm).

Diagnosis

Prenatal Diagnosis

- Maternal serum antibodies IgM and IgG—nonspecific.
- Viral culture of amniotic fluid.
  - 100% specific
  - High false-negative rate
  - PCR of amniotic fluid
  - Sensitive and specific after 21 wk gestation

Postnatal Diagnosis

- Urine CMV.
  - High incidence of asymptomatic newborns (>70%) who will never develop complications—limits screening.
- CMV-specific immunoglobulin (IgM).
- Serum PCR to detect CMV DNA.
- MRI is best for the detection of associated cerebral abnormalities.

- Gradient-echo or susceptibility-weighted sequences and US can be used to detect calcification (avoid CT in view of risks associated with high radiation exposure).
- All infants should have formal ophthalmological examination and audiology testing.

Treatment

- CMV IgG should be considered in pregnant women with active fetal infection.
- Intravenous ganciclovir or oral valganciclovir
  - can be given to pregnant women or infants.
  - requires close monitoring for evidence of bone marrow suppression, nephrotoxicity, and hepatotoxicity.
- Increases the likelihood of improvement and reduces the likelihood of deterioration in hearing.
- Other benefits of treatment less clear.

Toxoplasmosis

- Most common congenital parasitic infection.
  - Incidence 0.1 to 1 in 1,000 live births, resulting in 400 to 4,000 cases each year.
- Domestic cat (or commonly kitten) is the primary host of *T. gondii*.
- Oocysts present in soil, cat litter, garden vegetables, and water.
- Pseudocysts present in undercooked meats.
- Symptoms and signs include meningoencephalitis, intracranial calcifications, hydrocephalus, seizures, microcephaly (less common), chorioretinitis, and deafness.

Diagnosis

Antenatal Diagnosis

- PCR of parasite DNA (amniotic fluid or fetal blood)
- Maternal *T. gondii* antibodies

Postnatal Diagnosis

- Placental culture
- T. *gondii*–specific IgG antibodies
  - Positive IgG titer indicates infection with the organism sometime in the past.
- IgM antibodies
  - High false-positive and false-negative results
  - Negative IgM result essentially excludes recent infection
  - Positive IgM result—difficult to interpret
    - May be detected by EIA for as long as 18 mo after acute acquired infection
- All children with *T. gondii* infection should undergo ophthalmological examination.

Treatment

- Pyrimethamine–sulfadiazine and folinic acid for about 1 y is recommended.
- Requires close monitoring for evidence of possible bone marrow suppression and hepatotoxicity.
- Consider prednisone 1 mg/kg when CSF protein is >1 g/dL and chorioretinitis threatens vision.

Rubella

- Rare in countries with high rates of rubella vaccination.
- Symptoms and signs in newborns include
  - Neurologic manifestations
    - Meningoencephalitis
  - Nonneurologic manifestations
    - Adenopathy, radiolucencies of long bones, cardiac defects (pulmonary arterial hypoplasia and patent ductus arteriosus), cataracts, salt-and-pepper chorioretinitis, microphthalmia, growth restriction, hepatosplenomegaly, thrombocytopenia, and purpura.
- Onset of symptoms usually within the first year of life.

Diagnosis

Antenatal Diagnosis

- Cord blood rubella-specific IgM
- PCR of amniotic fluid

Postnatal Diagnosis

- Serum rubella-specific IgM (newborn period)
- Rubella viral cultures (pharyngeal secretions, eye, throat, CSF, stool, and urine)

Treatment

- No specific treatment available, supportive care only

Herpes Simplex Virus (HSV)

- Usually due to transmission of HSV-2.
- Chance of shedding virus at the time of delivery if a woman has a past history of HSV-2 is ~1%.
- Current active infection is not necessary for transmission.
- Risk of transmission is
  - 50% with primary maternal infection.
  - 25% when mother has antibodies to HSV-1 only.
  - <2% in recurrent infection in a seropositive mother.

Symptoms and Signs

- Typically presents 1 to 3 wk after birth (presentation may be delayed up to 6 wk after birth)
- Neurologic manifestations
  - Poor feeding, lethargy, apnea, bulging fontanels, irritability, seizures
- Nonneurologic manifestations
  - Fever, respiratory distress, hepatomegaly, jaundice, and disseminated intravascular coagulation
- ~30% of neonates present with CNS disease, one-third of cases without skin findings

Diagnosis

- Viral culture (mouth, nasopharynx, conjunctivae, rectum, skin vesicles, urine, stool, blood, and CSF).
- CSF HSV-PCR testing (false-negatives occur; therefore, may have to be repeated).

- Formal ophthalmological evaluation required in all cases.
- EEG/MRI brain may aid diagnosis.

Treatment

- IV acyclovir
  - Outcome is often poor, with significant central nervous system involvement despite high-dose acyclovir treatment.
  - Even with systemic treatment, disseminated disease is associated with mortality rates between 50% (HSV-2) and 70% (HSV-1).
  - Seizures at or before initiation of antiviral therapy are associated with an increased risk for neurologic morbidity.

ABNORMAL HEAD SIZE

Normal head circumference at term ranges from 32 to 38 cm.

Macrocephaly

- Most common cause is familial macrocephaly.
  - Very low risk for serious neurologic problems.
  - Measure parental head size.
- Head US will indicate which structures or fluid spaces are enlarged. Brain MRI may be performed in an older infant where fontanels are closed or if neurologic exam abnormal.

Investigations

Hydrocephalus

- MRI identifies aqueductal stenosis, communicating hydrocephalus, benign external hydrocephalus, and also congenital or acquired abnormalities of brain parenchyma to indicate etiology.
- Toxoplasmosis titer (if indicated by MRI brain).
- Ophthalmology, as needed.
- Genetics as clinically indicated.
  - Dysmorphism, specific ocular or family history.

No Hydrocephalus

- Consider urine organic acids, serum glutaric acid (glutaric aciduria type 1), especially if wide Sylvian fissures by MRI.
- Genetics as clinically indicated.

Microcephaly

- Defined as head circumference >3 standard deviations below the mean.[66]

Investigations

- Viral cultures (throat swab), serum titers, and urine culture/PCR for congenital infections such as CMV.
- Brain MRI (MRI preferable to CT as it is more sensitive in the detection of structural abnormalities and avoids radiation), or cranial US as screen or if cannot obtain MRI.
- 3-view skull radiograph for detection of craniosynostosis if MR/CT is not readily available.
- Karyotype, chromosomal microarray, other specific genetic tests (e.g., ASPM gene) should be considered.

- Metabolic investigations—if other features such as seizures, abnormal tone, or cranial nerve exam.
- Maternal phenylalanine levels.
- Placental examination, especially with intrauterine growth restriction.

ABNORMALITIES OF TONE

Floppy Infant

It is important to distinguish weakness from hypotonia.

- Hypotonia is reduced resistance to passive range of motion in joints.
- Weakness is reduction in the maximum power that can be generated.
- Hypotonia may exist without weakness.

Axial Hypotonia

- Central causes (~80% of cases)
  - Hypoxic-ischemic encephalopathy.
  - Other acute causes of encephalopathy (e.g., infection, inborn error of metabolism, intracranial hemorrhage, etc.).
  - Brain malformations.
  - Genetic disorders—chromosomal disorders (e.g., trisomy 21), congenital syndromes (e.g., Prader–Willi—poor feeding, undescended testes, sticky saliva).
- Maternal drugs
- Benign congenital hypotonia (diagnosis of exclusion)

Generalized Weakness with Depressed or Absent Deep Tendon Reflexes

- Congenital muscular dystrophies and myopathies
  - Congenital myotonic dystrophy: Maternal history suggestive of uterine dystonia, difficult delivery, examining mother may reveal myotonia with handshake, percussion of thenar eminence.
- Congenital myasthenic syndromes
- Neonatal botulism (onset 10 d of age or later)

Weakness Sparing the Face

- Spinal muscular atrophy (SMA/Werdnig–Hoffmann disease)
  - Alert, inquisitive face but profound distal weakness, absent DTRs, tongue fasciculations
- Cervical cord damage (rare)
- Peripheral neuropathy (rare)

Evaluation of Weakness

Clinical

- Detailed family and past medical history (prenatal, perinatal, and neonatal).
  - Fetal movement in utero, fetal presentation, and the amount of amniotic fluid present.
  - Maternal exposures to toxins or infections.
  - Apgar scores, need for resuscitation (indication of whether hypotonia has been present since birth).
  - Onset after 12 to 24 h may indicate an inborn error of metabolism.

- Detailed neurologic assessment examining tone, strength, reflexes, and mental status.
- General examination may reveal dysmorphism or other signs of genetic disorders.

Laboratory

- Full septic workup, including lumbar puncture
- Liver function tests
- Ammonia
- Electrolytes—glucose, calcium, magnesium
- *Creatine phosphokinase* (best performed at least 7 to 10 d after delivery as often elevated in the initial postpartum period due to muscle injury sustained in birthing process)

Neuroimaging

- MRI, including spectroscopy, can delineate structural malformations or display findings typical of metabolic/genetic disorders, e.g.,
  - heterotopias, lissencephaly, polymicrogyria (isolated or with congenital muscular dystrophy).
  - posterior fossa structural abnormalities (Dandy–Walker, Joubert syndromes).
  - abnormalities in the corpus callosum (Smith–Lemli–Opitz syndrome).
  - abnormal signal in the basal ganglia (mitochondrial abnormalities).
  - deep white matter abnormalities (Lowe syndrome).

Additional Studies

- Electrophysiologic studies
  - Nerve conduction velocity (NCV)/electromyography (EMG) most useful for anterior horn (SMA) or spinal cord disorders, neuromuscular junction disorders (congenital myasthenia), sometimes muscular dystrophy or myopathy.
- Muscle biopsy with immunohistochemical staining and electron microscopy, possible enzyme studies on frozen muscle tissue for metabolic myopathies.
  - DNA studies for CMD, SMA should be sent before muscle biopsy is performed if clinical presentation indicates.
  - Method of choice for diagnosing myopathies and muscular dystrophies for which no genetic testing is available.
- Genetic and metabolic studies should be chosen according to the clinical presentation of the infant.

Arthrogryposis

- Characterized by multiple joint contractures.
- There are many known subgroups with differing signs, symptoms, and causes.
- Careful family and pregnancy histories are needed.
  - Extrinsic (improves gradually in the postnatal period)
    - Oligohydramnios
    - Fetal crowding
  - Intrinsic
    - May be related to abnormalities in
      - muscle
      - central nervous system

- spinal cord
- connective tissue

- Genetic causes most common

Stiff Infant

Hyperekplexia

- Stiffness increased on stimulation and decreased or abolished on sleep.
- Startle disease in the parent and nonhabituating head retraction on tapping the tip of the nose and/or auditory startle support the diagnosis.
- Characteristic CMAP "spikes" during syncope on EEG, ECG, and EMG.
- Gene analysis may confirm diagnosis.

Other Causes of Congenital Hypertonia

- Brain malformation.
- Prenatal subcortical injury.
- Often no significant antenatal history.
- Rarely may be primary manifestation of a mitochondrial disorder.
- Many other potential genetic or other causes (e.g., congenital infection) that cause in utero injury or abnormal brain development.
- Need brain MRI ± MRS.
- Consider appropriate genetic studies.

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20 Sleep Disorders in Child Neurology

Mandeep Rana, Umakanth Khatwa, and Sanjeev V. Kothare

NORMAL SLEEP IN CHILDREN

DEFINITION: Reversible behavioral state of perceptual disengagement and unresponsiveness to and from the environment.

PHYSIOLOGY: Complex amalgam of physiologic and behavioral processes.[1] Two separate states are defined on the basis of physiologic parameters: **rapid eye movement (REM) sleep** and **non-REM sleep** (Table 20.1).

MATURATIONAL CHANGES: Sleep architecture changes occur across entire life span (Figs. 20.1 and 20.2), but most significant changes occur within the 1st few years of life. For the 1st 3 mo of life, transition from wake to sleep is through REM sleep (called active sleep in newborns). Cyclic alternation of REM and NREM sleep occurs every 50 to 60 min at birth transitioning to every 90 min in adults. REM sleep decreases from birth (50% of sleep) through early childhood into adulthood (20%–25%). Slow-wave sleep peaks in early childhood and starts reducing at puberty, continuing to reduce through adulthood.

MECHANISM OF WAKE SLEEP REGULATION: "Two-process model" (Fig. 20.3): interaction between homeostatic sleep drive ("process S") and endogenous circadian timing ("process C").[2,3] S accrues during wakefulness and is dissipated during sleep; C oscillates with near perfect 24-h periodicity.[4,5]

EVALUATION OF CHILDHOOD SLEEP DISORDERS[63]

HISTORY:(1) Bedtime routine: Sleep associations and behaviors, sleep environment and sleep schedules, including that on weekdays and weekends, late evening activities such as watching TV, internet access, texting, emailing. **(2) Nighttime Sx:** Snoring, arousals, restlessness, leg movements, pauses in breathing, sweating, dry mouth, mouth breathing; **(3) Daytime Sx:** Sleepiness, fatigue, naps. **(4) Medical and psychiatric history:** Asthma, GERD, allergies, chronic lung disease, sickle cell disease, pain, neurologic problems such as epilepsy, HA, CP, DD, ADHD, ASD, depression, anxiety, and bipolar disorder. **(5) FHx:** Sleep apnea, narcolepsy, restless leg syndrome (RLS), long sleep requirements. **(6) Meds:** Caffeine, alcohol, sedatives, and stimulants.

PHYSICAL EXAMINATION: (1) Growth parameters: Height, weight, BMI, neck circumference. **(2) ENT exam:** Deviated nasal septum, turbinate hypertrophy, adenotonsillar hypertrophy, oropharyngeal crowding, large tongue. **(3) Craniofacial features:** Adenoid facies, high arched palate, midfacial hypoplasia, retrognathia, crossbite. **(4) Neurologic exam:** Especially in children with restless leg Sx, EDS, atypical parasomnias, and seizures.

TABLE 20.1 Sleep Staging: Classic vs. Updated Stage Definitions

Sleep Type	Describe Type	Classic Stage Definition	Updated Stage Definition
NREM	"Light sleep"	1, 2	N1, N2
	"Deep sleep" or SWS	3, 4	N3
REM	Dreaming sleep, Paradoxical sleep	REM	R

TOOLS

Polysomnography (PSG)

Continuous recording of several physiologic parameters during sleep, including electroencephalogram (EEG), electrocardiogram (EKG), electro-oculogram (EOG), respiratory effort using chest and abdominal belts, airflow, gas exchange using pulse oximetry and end tidal CO_2, EMG for legs and chin activity, snore, and microphone. PSG is indicated to evaluate: **(1) Sleep-disordered breathing (SDB):** OSA, central sleep apnea, and hypoventilation. **(2) Nocturnal events:** Parasomnia vs. nocturnal seizure (see also Tables 3.2 and 6.16, and note parasomnias by themselves are not an indication for performing a PSG), REM behavior disorder, periodic limb movements disorder (PLMD). **(3) Unexplained hypersomnia; (4) Narcolepsy:** Usually PSG is done prior to multiple sleep latency test (MSLT) to rule out OSA and assess adequate duration of sleep. **(5) Sleep state misperception (6) CPAP/Bi-level positive airway pressure titration. (7) SDB in special populations:**

1. Neuromuscular weakness: hypoventilation and OSA
2. Chiari 1 and 2 malformation: central sleep apnea, OSA, and hypoventilation
3. Chronic respiratory disease: gas exchange abnormalities

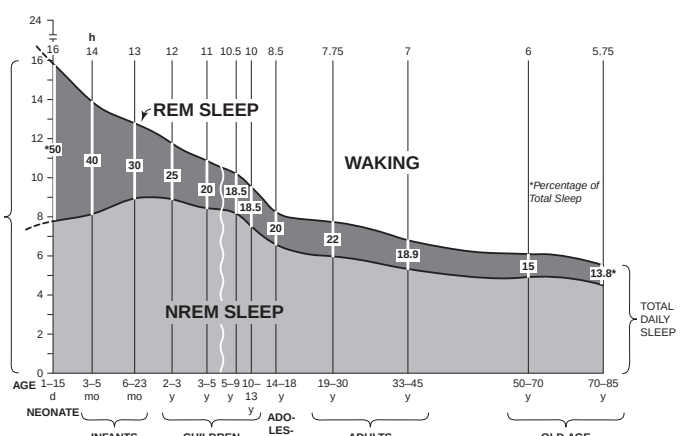


FIGURE 20.1 Changes in Total Daily Sleep Time, and REM and NREM Distribution over Ages. Note the large amount of REM in neonates and infants.[61] Total sleep time decreases with age. (From Roffwarg HP, Muzio JN, Dement WC. Ontogenetic development of the human sleep-dream cycle. *Science.* 1966;152(3722):604–619, with permission.)

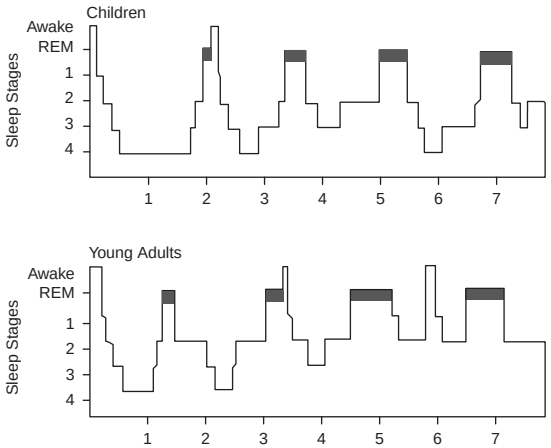


FIGURE 20.2 NREM and REM Sleep Cycles through Age: Sleep Maturation from Childhood to the Adult Period. Slow-wave sleep is maximal in childhood and decreases with age. REM sleep gradually decreases from childhood to adulthood. The first NREM cycle in children is over 90 min, unlike in adults where it is around 60 min. Also note REM sleep increases in the latter half of the night. These may be physiological mechanisms why night terrors occur in the first half of the night and nightmares in the second half.[62] (From Mindell JA, Owens JA. Biology of Sleep. In: *Clinical Guide to Pediatric Sleep: Diagnosis and Management of Sleep Problems*. Philadelphia, PA: LWW; 2003, with permission.)

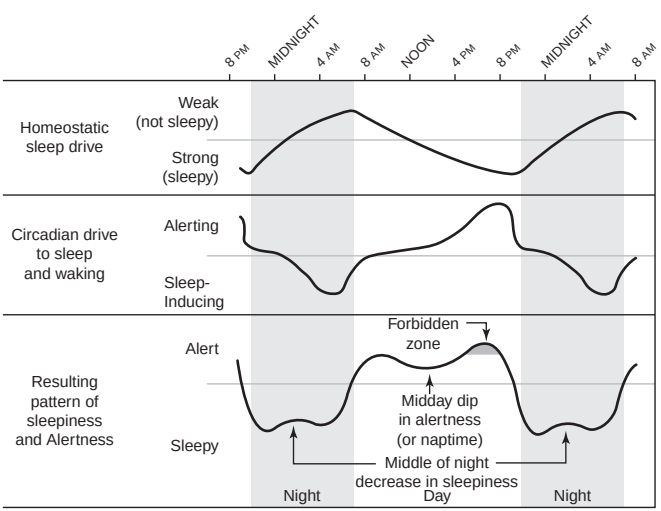


FIGURE 20.3 The Two-Process Model (Homeostatic and Circadian Drive) for Control of Sleep and Arousal. Homeostatic drive accumulates during wake period and dissipates in sleep, whereas the circadian drive oscillates with a 24-h periodicity. The *forbidden zone* is the period where these drives are maximal and is a poor time to expect a child to sleep.[3] (From Ferber R. *How to Solve Your Child's Sleep Problems*. New York, NY: Simon and Schuster; 2009, with permission.)

4. Sickle cell disease: OSA
5. Down syndrome, Prader–Willi syndrome: OSA

Multiple Sleep Latency Test (MSLT)

Validated measure to assess the tendency to fall asleep during daytime.

CSF Studies

CSF hypocretin/orexin levels are occasionally used to confirm the diagnosis of narcolepsy/cataplexy. Levels $<$110 pg/mL have $>$95% specificity in diagnosing narcolepsy with cataplexy and $>$50% specificity in diagnosing narcolepsy without cataplexy.[6,7]

Miscellaneous

(a) Pediatric **sleep questionnaires** such as "BEARS" algorithm (Table 20.2).[8] **Sleep Logs** assess sleep–wake behaviors over 24-h period. **Actigraphy** is a viable tool for assessing insomnia/circadian rhythm disorders. It is based on the premise that presence of movements indicates wakefulness and absence of movements indicates sleep.[9]

INSOMNIA IN CHILDHOOD

Behavioral Insomnia of Childhood (Table 20.3)

DEFINITION: Difficulty falling asleep, staying asleep, or both, related to an identified behavioral etiology.[10,64]

PATHOPHYSIOLOGY: (1) Limit-setting type is characterized by bedtime stalling or refusal that is the result of inadequate limit setting by the caregiver. **(2) Sleep onset association type** is characterized by the child's dependency on specific stimulation, objects, or settings for initiating sleep or returning to sleep following awakening. In the absence of these conditions, sleep onset is significantly delayed. **Nighttime awakenings** are actually the norm in early childhood (Table 20.4). They occur in between normal sleep cycle, so that brief awakenings occur every 90 to 120 min. The response to this waking is variable: *Self-soothers* go back to sleep without parental intervention, *signalers* alert their parents with crying or getting out of bed and typically have developed this pattern as a result of reinforcement by the caregiver.

TREATMENT: (1) Promoting good night sleep with good sleep hygiene, regular bedtimes and nap times, and positive reinforcement. **(2)** Putting the child into the bed **drowsy but still while awake** is helpful. **(3) Pharmacotherapy** (Table 20.5) not typically for mild behavioral insomnia. No FDA-approved medications for pediatric insomnia exist.[11,12] Indications: failure of behavioral interventions, medical illness, neurodevelopmental disabilities, and psychiatric and genetic disorders. Contraindications: substance abuse, drug–drug interactions, associated OSA.

SLEEP-RELATED BREATHING DISORDERS IN CHILDREN

Obstructive Sleep Apnea (OSA)

PATHOPHYSIOLOGY: OSA results from increased upper airway resistance during sleep, resulting in intermittent partial or complete airway closure, a/w snoring, increased respiratory effort, resulting in sleep fragmentation and/or gas exchange abnormalities.[13]

EPIDEMIOLOGY: OSA occurs in children of all ages, from neonate to adolescents, but peaks between ages of 2 and 6 y, which coincides with the peak age of lymphoid hyperplasia and adenotonsillar hypertrophy. Second peak

TABLE 20.2 BEARS Sleep Screening Algorithm

	Toddlers/Preschool (2–5 y)	School-aged (6–12 y)	Adolescents (13–18 y)
Bedtime problems	Does your child have any problems going to bed? falling asleep?	Does your child have any problems at bedtime? (P) Do you have any problems going to bed? (C)	Do you have any problems falling asleep at bedtime? (C)
Excessive daytime sleepiness	Does your child seem overtired or sleep a lot during the day? Does he or she still take naps?	Does your child have difficulty waking in the morning, seem sleepy during the day, or take naps? (P) Do you feel tired a lot? (C)	Do you feel sleepy a lot during the day? In school? While driving? (C)
Awakenings during the night	Does your child wake up a lot at night?	Does your child seem to wake up a lot at night? Any sleepwalking or nightmares? (P) Do you wake up a lot at night? Have trouble getting back to sleep? (C)	Do you wake up a lot at night? Have trouble getting back to sleep? (C)
Regularity and duration of sleep	Does your child have a regular bedtime and wake time? What are they?	What time does your child go to bed and get up on schooldays? Weekends? Do you think he or she is getting enough sleep? (P)	What time do you usually go to bed on school nights? Weekends? How much sleep do you usually get? (C)
Snoring	Does your child snore a lot or have difficulty breathing at night?	Does your child have loud or nightly snoring or any breathing difficulties at night? (P)	Does your teenager snore loudly or nightly?

Owens JA, Dalzell V. Use of 'BEARS' sleep screening tool in a pediatric residents' continuity clinic: a pilot study. *Sleep Med*. 2005;6(1):63–69.
Note: For school-aged children and adolescents: (P) Parent-directed question, (C) child-directed question. The BEARS is designed to provide practical guidance of how to incorporate a pediatric sleep history into the standard history. Each sleep domain has a set of age-appropriate "trigger questions" for use in the clinical interview.

TABLE 20.3 Behavioral Insomnia of Childhood

A. A child's Sx meet the criteria for insomnia based upon reports of parents or other adult caregivers.
B. The child shows a pattern consistent with either the sleep-onset association or limit-setting type of insomnia described below.
   i. **Sleep-onset association type** includes each of the following:
      1. Falling asleep is an extended process that requires special conditions.
      2. Sleep-onset associations are highly problematic or demanding.
      3. In the absence of the associated conditions, sleep onset is significantly delayed or sleep is otherwise disrupted.
      4. Nighttime awakenings require caregiver intervention for the child to return to sleep.
   ii. **Limit-setting type** includes each of the following:
      1. The individual has difficulty initiating or maintaining sleep.
      2. The individual stalls or refuses to go to bed at an appropriate time or refuses to return to bed following a nighttime awakening.
      3. The caregiver demonstrates insufficient or inappropriate limit setting to establish appropriate sleeping behavior in the child.
C. The sleep disturbance is not better explained by another sleep disorder, medical or neurological disorder, or medication use.

ICSD: Diagnostic and Coding Manual. 2nd ed.; 2005:23.

occurs in adolescence and is most likely secondary to obesity. Overall prevalence is 2.2% to 3.8%[14,15] and up to 36% in obese children.[16]

Risk factors: African Americans, male gender after puberty, obesity, prematurity, hypotonia, craniofacial syndromes, laryngomalacia, cerebral palsy, GE reflux, hypothyroidism, sickle cell disease, Prader–Willi, Down syndrome (most common, OSA from macroglossia, midfacial hypoplasia, micrognathia, and hypotonia).

TABLE 20.4 Causes of Night-Wakings

Inadequate sleep hygiene	**Parasomnias**
Inappropriate napping	**NREM parasomnias**
Inconsistent sleep schedule	Confusional arousals
Excess caffeine	Sleepwalking
Environmental factors	Sleep terrors
Child behavior/parent–child interaction	**REM parasomnias**
Sleep-onset association disorder	REM behavior disorder
Limit-setting sleep disorder	Nightmares
Nighttime fears	**Medical or psychiatric conditions**
Primary insomnia	Anxiety/depression
Fragmented sleep secondary to arousals	Pain
OSA	Substance abuse
PLMS	Psychoses
Narcolepsy	Epilepsy
Bruxism	HAs
Others	Asthma
Nocturnal seizures	GERD
	Medications

TABLE 20.5 Pharmacotherapy of Insomnia in Children

Drug	Dose	Half-life (h)	Side Effects	Tolerance/Withdrawal	Safety Profile
Clonazepam	0.01 mg/kg	19–60	Daytime sedation, cognitive changes, anterograde amnesia	Yes	Abuse, respiratory depression
Flurazepam	15–30 mg	48–120			
Quazepam	7.5–30 mg	48–120			
Temazepam	15–30 mg	3–25			
Estazolam	1–2 mg	8–24			
Triazolam	0.125–0.25 mg	8–24			
Chloral Hydrate	50 mg/kg	10	Gastrointestinal, dizziness	Yes	Liver toxicity, respiratory depression
Clonidine	0.05–0.3 mg	6–24	Fluctuation with blood pressure		
Guanfacine	0.5–2 mg	24			Little experience in children
Zolpidem	5–10 mg	2–4		Ususally no	
Zaleplon	5–10 mg	1–2			
Eszopiclone	1–3 mg	4–6			
Trazodone	25–50 mg	30–120	Anticholinergic		Priapism
Amitryptiline	0.5 mg–2 mg/kg	4–8	Decreased REM		Cardiac
Melatonin	3–9 mg	3–9	Daytime sedation	No	Worsens seizures
Diphenhydramine	1 mg/kg	4–6	Daytime sedation	Possible	Anticholinergic
Hydoxyzine	0.6 mg/kg	6–24			

Selected herbal preprations used for insomnia in children

Name	Mechanism of action	Dosage	Sleep effect	Comments
Valerian	Binds BDZ receptors	2–3 g t.i.d.	Decreases sleep-onset latency SWS, improves sleep efficiency	Toxicity rare
Chamomile	Binds BDZ receptors	1–3 g t.i.d.	Decreases sleep-onset latency	Hypertensive effect
Kava	CNS depressant	60–120 mg/d	Improves SE	Weak anxiolytic
Lavender	CNS depressant	Oil inhalation	Improves SE	Potentiates effects of alcohol

Van der Heijden KB, Smits MG, Van Someren EJ, et al. Idiopathic chronic sleep onset insomnia in attention-deficit/hyperactivity disorder: a circadian rhythm sleep disorder. *Chronobiol Int*. 2005;22(3):559–570.

SYMPTOMS: Daytime Sx include mouth breathing, morning headaches (HAs), behavioral and mood changes, learning difficulties, poor attention span, hyperactivity, and EDS.[17–19] **Nocturnal Sx** include snoring, mouth breathing, apneic pauses, gasping, paradoxical breathing, sweating, labored breathing, enuresis, abnormal sleeping position (e.g., hyperextended neck).

DIAGNOSIS: PSG helps in confirming the diagnosis and assessing the severity of OSA. It is also an important baseline measure for children with OSA who may need additional PSGs after treatment to assess residual deficit.

TREATMENT: (1) Adenotonsillectomy: Recommended first-line therapy. Residual OSA may be present in PSG in up to 40% of cases postoperatively,[20] especially in obese children. **(2) Continuous positive air pressure (CPAP) therapy:** For children with moderate to severe OSA without surgically correctable obstruction. **(3) Leukotriene antagonists, nasal steroids** may reduce adenotonsillar size,[21] e.g., intranasal budesonide and fluticasone, in combination with montelukast, for mild OSA or mild residual OSA after surgery.[22] **(4) Surgical options:** Turbinectomy, deviated nasal septum repair, maxillary expansion, tongue reduction, and rarely tracheostomy. **(5) Weight reduction:** Important in all overweight children.

PROGNOSIS/COMPLICATIONS: Sequelae of pediatric OSA are listed in Table 20.6.

Central Sleep Apnea

DEFINITION: Respiratory pause lasting 20 s or at least 2 missed breaths with absent inspiratory effort, a/w an electrocortical arousal or oxygen desaturation of at least 3%.

PATHOPHYSIOLOGY: Central ventilatory drive may be reduced in some patients resulting in ventilatory control instability, which leads to central

TABLE 20.6 Sequelae of Pediatric Sleep Apnea

Metabolic
Elevated C-reactive protein
Insulin resistance
Hypercholesterolemia
Elevated transaminases
Decreased insulin-like growth factor
Decreased altered growth hormone secretion

Neurocognitive
Aggressive behavior
Poor school performance
Depression
Attention deficit
Hyperactivity
Moodiness

Cardiovascular
Autonomic dysfunction
Systemic hypertension
Absence of normal blood pressure dip during sleep
Left ventricular dysfunction
Pulmonary hypertension
Abnormal heart rate variability
Elevated vascular endothelial growth factor

sleep apnea. It is deemed clinically important when it results in chronic intermittent hypoxemia, bradycardia, or sleep fragmentation, which may adversely affect cardiovascular function or neurocognitive development.

ETIOLOGY: Congenital central hypoventilation syndrome (CCHS), Chiari malformation, Leigh syndrome, Joubert syndrome, brain/brainstem tumor, Rett syndrome, medications (narcotics, anesthetics), achondroplasia, post-CNS infection, respiratory syncytial virus (RSV) infection, and hypoxic-ischemic encephalopathy.

Periodic Breathing (PB)

DEFINITION/PATHOPHYSIOLOGY: A series of three or more respiratory pauses lasting 3 s or longer separated by 20 s or more of normal breathing. PB is minimal in the first week of life, peaks at 2 to 4 wk of age, and reduces by 4 mo. Rare after 6 mo of age.[23] PB as a percentage of total sleep time ranges from 0% to 5% in term infants. Excess PB persisting beyond early infancy may indicate CNS abnormalities.

CIRCADIAN RHYTHM SLEEP DISORDERS

Persistent or recurrent pattern of sleep disturbance due primarily to alterations of the circadian time-keeping system or misalignment between endogenous circadian rhythm and exogenous factors that affect the timing or duration of sleep (Fig. 20.4). The circadian-related sleep disruption leads to insomnia or EDS and is a/w impairment of social, occupational, or other areas of functioning.[24,65]

Delayed Sleep Phase Disorder (DSPD)

DEFINITION/PATHOPHYSIOLOGY: Habitual sleep shows difficulty falling asleep and waking up in the morning. The wake time is typically delayed, usually >2 h, relative to socially acceptable times.[23] Often a/w mood and personality changes.[25,26]

EPIDEMIOLOGY: Prevalent in 7% of adolescents and young adults,[27] it is the most common circadian rhythm sleep disorder.[28]

TREATMENT: (1) Adherence to good sleep hygiene. (2) Comorbid psychiatric disorder should be identified and treated. **(3) Regular wake-up schedule** both on weekdays and weekends. **(4) Melatonin** 0.5 to 1 mg given at least 4 to 6 h prior to *habitual* bedtime has been shown to advance sleep onset and improve quality of sleep. **(5) Light therapy:** Bright light exposure of 10,000 lux (commercially available light therapy equipment) for about 30 min in the morning will help to shift wake-up time earlier. **(6) Chronotherapy** (successive delay of sleep times by 1 to 2 h daily over

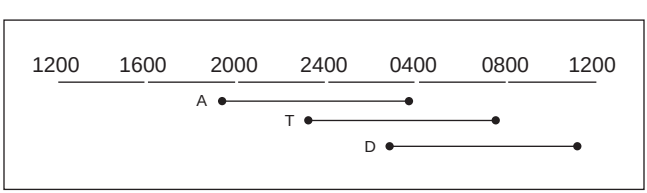


FIGURE 20.4 Temporal Distribution of Sleep and Wake in Patients with Circadian Rhythm Sleep Disorders.[1] *A*, advanced sleep phase disorder; *T*, typical sleep phase; *D*, delayed sleep phase disorder. (From Avidan A. Normal sleep. In: Kryger M, ed. *Principles and Practice of Sleep Medicine*. Philadelphia, PA: Saunders; 2010:61–68.)

5- to 6-d period until desired sleep time achieved) and maintaining the desired time consistently may be used if the above measures fail.[29]

Advanced Sleep Phase Disorder (ASPD)

DEFINITION: Habitual sleep onset and wake times that are several hours earlier relative to desired times.[24] Sleepiness early in the evening and quite early wakeup in the morning (early morning insomnia). The sleep duration by itself is normal for age.

EPIDEMIOLOGY: Unusual in children, but common in old age. Its prevalence is 1% in middle-aged and older adults and increases with age.

TREATMENT: Chronotherapeutic approach (advancing bedtime by 3 h every 2 d until desired bedtime reached) has been reported, although relapse occurs quickly.[30] The practice parameters established by American Academy of Sleep Medicine considered bright light therapy during early evening hours as treatment option for ASPD.[24]

Irregular Sleep–Wake Disorder

DEFINITION: Lack of clearly defined circadian rhythm of sleep and wake. Sleep–wake pattern temporally disorganized, so that sleep and wake periods are variable throughout 24-h period. Napping is prevalent throughout 24-h period. Total sleep time normal for age.[24] Sx of insomnia and excessive sleepiness depending on the time of day.

ETIOLOGY/PATHOPHYSIOLOGY: Anatomic or functional abnormalities of circadian clock are the likely cause. Seen in dementia, Alzheimer disease, brain injury, and children with intellectual disability, blindness, and operated craniopharyngiomas.

TREATMENT: Morning bright light, evening melatonin, and occasional use of hypnotics.[31,32]

Jet Lag

DEFINITION: Temporary mismatch between timing of sleep and wake cycle generated by endogenous circadian clock and sleep–wake pattern required by a change in time zone.[24]

SYMPTOMS: Disturbed sleep (eastward, insomnia; westward, daytime sleepiness), malaise, GI upset.

TREATMENT: Adjustment of the circadian system to a new time zone takes days, with ~1 d required for each time zone crossed. Proper timing of bright light exposure and dim light/darkness can quicken adaptation to new time zone.[33]

PARASOMNIAS

Undesirable physical events or experiences that occur during entry into sleep, within sleep, or during arousals from sleep, classified as: **Disorders of arousal (1) from NREM sleep, (2) from REM sleep, and (3) other parasomnias** (Table 20.7).[34]

Disorders of Arousal from NREM Sleep

DEFINITION: Tend to occur in the first half of night, when slow-wave sleep (SWS) is most prominent. In these disorders, the transition from SWS to lighter sleep, just prior to REM sleep onset is abnormal. The patient is neither awake nor fully asleep.

TABLE 20.7 Clinical Features of Most Common Parasomias

Characterstic	Disorder of Arousal from NREM Sleep	Nocturnal Seizure	REM Sleep Behavior Disorder
Age of onset	Usually childhood, tending to dimnish with increasing age	Any	Usually >50 y of age, mostly males
Time of sleep period	Usually within first third of night	Anytime during night stage 1 or 2 NREM sleep	First episode usually 1–2 h after sleep onset
Frequency	Rarely >1–2 per night, rare from daytime naps	Often multiple. May occur during daytime naps	May occur nightly, rarely from daytime naps
Stereotypy	Low	High	Low
Post-event confusion	Typical	Variable	Uncommon

Mahowald MS, Schenck CH. Parasomnias. In: Kryger MH, ed. *Atlas of Clinical Sleep Medicine.* 2010:206.

EPIDEMIOLOGY: Age of occurrence is generally between 2 and 12 y with resolution by adolescence. **Risk factors** include positive family history, sleep deprivation, irregular sleep schedule, fever and illness, medications (e.g., chloral hydrate), sleeping in a different environment, stress and anxiety, and conditions fragmenting sleep, such as OSA and periodic limb movements of sleep (PLMS).

SUBTYPES: **(1) Sleepwalking** in children shares features with sleep walking in adults. Children are usually calm and may walk in different parts of house. They are at risk of injury from falls, lacerations from broken windows, and even hypothermia. **(2) Confusional arousals** begin with moaning and evolve to confused and agitated behavior with crying and thrashing. The child cannot be fully aroused and may last 5 to 15 min before the child returns to sleep. **(3) Sleep terrors** are dramatic partial arousals from SWS. The child may sit up suddenly and scream, with intense blood-curdling cry. Autonomic activation occurs with diaphoresis, mydriasis, and tachycardia. There is no recollection of these events the following day.

DIFFERENTIAL Dx: Nightmares, nocturnal panic attacks, epileptic events, and cluster HAs.

DIAGNOSTIC WORKUP: Detailed history, regarding how soon after sleep onset these events are noted, and if they occur during nap and during wakefulness. In occasional cases, simultaneous video-EEG monitoring will help to differentiate them from seizure.

TREATMENT: Reassurance, use of safety measures (gates, locking outside doors and windows), and ensuring adequate sleep amount for age. Pharmacologic treatment including BDZ (CZP, OXA), TCA are indicated in cases of frequent or severe episodes and at high risk for injury.

Disorders of Arousal from REM Sleep

(1) NIGHTMARES: Vivid dreams with intense feelings of terror or dread that awaken a patient from sleep. Children can usually give a detailed description of the dream imagery. While infrequent nightmares do not require further evaluation, presence of frequent nightmares has been a/w

increased prevalence of generalized anxiety disorder and separation anxiety. It may also be a marker of sexual abuse.

EPIDEMIOLOGY: Common (30%–90% of children between 3 and 6 y).

(2) REM BEHAVIOR DISORDER: Lack of REM sleep atonia, and patients with this disorder present with dreams a/w complex movements that can be vigorous and violent.

EPIDEMIOLOGY: Uncommon in children. Can occur in setting of narcolepsy, BS tumors, juvenile PD, olivopontocerebellar degeneration, use of SSRIs, and some genetic syndromes like Smith–Magenis syndrome.

Other Parasomnias

Other parasomnias include nocturnal enuresis, sleep-related dissociative disorder, exploding head syndrome, and sleep-related eating or sexual disorder, catathrenia (nocturnal groaning).

HYPERSOMNIA/EXCESSIVE DAYTIME SLEEPINESS (EDS)

Inability to stay awake and alert during the major waking episodes of the day, resulting in unintended lapses into drowsiness or sleep.[35] As in adults, the most common cause of EDS is inadequate quantity of sleep. Other causes include narcolepsy, idiopathic hypersomnia (IH), and recurrent hypersomnia (Table 20.8).

Narcolepsy

DEFINITION: A lifelong neurological REM sleep disorder, characterized by EDS, disturbed nocturnal sleep, cataplexy (loss of postural tone, brought on by emotion, particularly laughter), hypnagogic/hypnopompic hallucinations, and sleep paralysis; the latter three are abnormal manifestations of REM sleep intrusion into wakefulness/sleep.[36] Narcolepsy may occur with or without cataplexy.

EPIDEMIOLOGY: Prevalence is 1 in 4,000 in North America and Europe. Male and female are equally affected. Symptoms usually appear in their teens or early twenties.

TABLE 20.8 Causes of Excessive Daytime Sleepiness (EDS) in Pediatric Population

Insufficient Sleep	Sleep Disorders a/w Mental or Medical Conditions
Sleep deprivation/sleep restriction	Anxiety/depression
Fragmented sleep	Substance abuse
Obstructive sleep apnea/sleep disordered breathing	Psychoses
Obesity hypoventilation syndrome	Epilepsy
PLMS	HAs
Bruxism	Asthma
Circadian rhythm disorders	GERD
DSPD	Pain
Primary disorders of EDS	Medications
Narcolepsy	
Idiopathic hypersomnia	
Recurrent hypersomnia	

PATHOPHYSIOLOGY: Loss of hypoceretin-1–secreting neurons in the lateral hypothalamus, possibly due to an autoimmune phenomenon. CSF hypocretin-1 levels are often normal in narcolepsy without cataplexy, but substantially decreased in narcolepsy with cataplexy. It is a/w HLA DR2 and DQ1. HLA DQB1*0602 is a more sensitive marker for narcolepsy, being positive in 95% of patients with narcolepsy with cataplexy, but also normally present in 25% of the population. Familial cases are also described.

DIAGNOSTIC WORKUP: Narcolepsy with cataplexy can be diagnosed clinically, but narcolepsy without cataplexy needs additional conformational test for diagnosis such as nocturnal PSG showing fragmented sleep and short REM latency w/o any other organic sleep pathology (OSA, PLMS). The MSLT criteria to diagnose narcolepsy include mean sleep latency ≤8 min with 2 or more sleep-onset REM periods in the five daytime nap trials.

TREATMENT: For medical management of narcolepsy, see Table 20.9.[37]

Idiopathic Hypersomnia (IH)

DEFINITION: EDS occurring almost daily for at least 3 mo, and not explained by another sleep disorder, medical, neurological or mental disorder, medication use, and substance use disorder. It may be mistaken for narcolepsy without cataplexy. Unlike narcolepsy, IH lacks REM intrusion in sleep and wakefulness and nocturnal sleep disruption. IH is further classified into **with or without long sleep hours** (>10 h) and naps are usually not refreshing.[36]

Recurrent Hypersomnias

(1) KLEINE–LEVIN SYNDROME: Recurrent episodes of extreme sleepiness lasting days to several weeks, but with normal sleep pattern and functioning between episodes of hypersomnia. The patient may sleep anywhere between 16 and 20 h during this period and may be accompanied by disturbances in mood, cognition, increased appetite, and hypersexual behavior. These

TABLE 20.9 Pharmacotherapy for Treatment of Narcolepsy

Drug	Adult Daily Dose (mg)	Pediatric Daily Dose (mg)
EDS		
Modafinil	100–600	50–200
Methylphenidate	10–60	10–30
Dextroamphetamine	5–50	5–30
Methamphetamine	5–40	5–40
Amphetamine/ Dextroamphetamine mix	10–60	10–30
Selegiline	20–40	no dose rec available
Cataplexy		
Imipramine	25–200	1.5–5 mg/kg/d
Cloimipramine	10–200	3 mg/kg/d
Desimipramine	25–200	25–200
Fluoxetine	20–60	5–30

Zarowski M, Dinar TA, Kothare SV. Narcolepsy. *Minerva Pneumol*. 2009;48:345–375.

episodes occur 1 to 10 times a year, often with gradual improvement over several years (median 4 y).[35] More common in boys; typical onset during early adolescence, at older age for women.

(2) MENSTRUAL-RELATED HYPERSOMNIA: Occurs within the first months after menarche. Episodes generally last for 1 wk, with rapid resolution at the time of the menstrual period.[34]

SLEEP-RELATED MOVEMENT DISORDERS

Restless Leg Syndrome (RLS)

DEFINITION: Presents with difficulty falling asleep and staying asleep. The diagnostic criteria are essential similar to that of adults and include: (1) urge to move or unpleasant sensation of the legs, (2) sensation worsens with inactivity, (3) sensation improves with activity, (4) occurs in the late evening[38] with some additional features in children (Table 20.10).[39]

EPIDEMIOLOGY: Common, 5% to 10% in adults and about 2% in 8 to 17 yo.[40]

DIAGNOSTIC WORKUP: While RLS is mainly a clinical diagnosis, **PLMS** is diagnosed by leg movements on PSG. **PLMD,** on the other hand, is characterized by periodic episodes of PLMS a/w disturbed sleep patterns and/or daytime fatigue and sleepiness not accounted by another sleep disorder.

PATHOPHYSIOLOGY: RLS is related to dopamine dysfunction. Other hypotheses speculate brain iron storage deficiency.[38] Primary RLS is idiopathic in nature. Genetic link is postulated to follow an autosomal dominant pattern. Secondary RLS can occur in relation to a number of different medical conditions including iron deficiency anemia, renal disease, pregnancy, and certain drugs. In adults, studies indicate that 70% of those with RLS also have PLMS; whereas only 20% of patients with PLMD have RLS. Similar studies have not been conducted in children. ADHD is associated with RLS and PLMD, unclear whether ADHD is cause or effect.[41]

DIFFERENTIAL DIAGNOSIS: Differential diagnosis of RLS includes peripheral neuropathy, chronic arthritis, dermatitis, akathisia, and growing pains.

TABLE 20.10 Diagnosis of RLS in Pediatric Patients (Age 2–12 y)

Four essential criteria: (1) Urge to move or unpleasant sensation of the legs. (2) Sensation worsens with inactivity. (3) Sensation improves with activity. (4) Occurs in the late evening.

A. The child meets all four essential criteria for RLS *and* relates a description in his or her own words that is consistent with leg discomfort.

or

B. The child meets all four essential criteria for RLS, but *does not* relate a description in his or her own words that is consistent with leg discomfort.

and

C. The child has at least two of the following three findings:
   1. A sleep disturbance for age
   2. A biological parent or sibling with definite RLS
   3. A polysomnographically documented periodic limb movement index of five or more per hour of sleep

Zarowski M, Dinar TA, Kothare SV. Narcolepsy. *Minerva Pneumol.* 2009;48:345–375.

TABLE 20.11 Approach to Treatment of Daily RLS in Pediatric Patients

Nonpharmacologic interventions
1. Mental alerting activities
2. Abstinence from caffeine, nicotine, and alcohol
3. Consider patient's use of medications that may worsen RLS
4. Iron suppletion, if appropriate

Pharmocologic therapy (FDA-approved for moderate to severe primary RLS)
1. Ropinerole
2. Pramipexole

TREATMENT: Replacement of iron if found deficient (serum ferritin < 50 ng/mL), good sleep hygiene, avoiding caffeine, antihistamines, cold/sinus preparations, and antiemetic (Table 20.11). Treatment medications include BDZ and dopamine agonists, started at the lowest possible dose and titrated upward. Data on their use in children are scant.

Rhythmic Movement Disorders of Sleep

Head banging and body rocking are common in young children and serve as self-soothing behaviors. These can occur at sleep onset and following normal nighttime arousals. Management includes evaluation for underlying sleep disrupters like OSA. Parents instructed about safety, desensitization of the behavior. Benzodiazepines may be considered in severe and extremely persistent cases.

SLEEP IN CHILDREN WITH SPECIAL NEEDS

Sleep disturbance is highly prevalent in children with neurodevelopmental disorders (Table 20.12).[42] It is included in the diagnostic criteria for disorders like Angelman syndrome, Prader–Willi syndrome, Smith–Magenis syndrome, and Williams syndrome. Causes of sleep disturbance could be due to medical or neurological disorders (e.g., seizures, GERD, nocturia), sleep disorder (sleep apnea, RLS, PLMD, circadian rhythm disorder), psychiatric disorder (e.g., anxiety, ADHD), medication use (e.g., antidepressants, stimulants), behavioral factors including difficulty understanding parental

TABLE 20.12 Sleep Problems in Children with Neurodevelopmental Disorders

Sleep Problem	Autism	Angelman Syndrome	Prader–Willi Syndrome	Williams Syndrome
Sleep-onset insomnia	++			
Sleep-maintenance insomnia	+	++	+	
OSA			+	
Daytime sleepiness			++	+
Nocturnal seizures	+	++		

Picchietti DL, Underwood DJ, Farris WA, et al. Further studies on periodic limb movement disorder and restless legs syndrome in children with attention-deficit hyperactivity disorder. *Mov Disord.* 1999;14(6):1000–1007.

expectations secondary to communication problems related to the disorder. Others factors a/w neurodevelopmental disorders include neurotransmitter abnormalities and increased sensitivity to environment.

Treatment approach includes behavioral modification, avoiding excessive daytime napping, nighttime melatonin, and use of other sleep-promoting medications. Maximizing sleep-promoting properties of the child's other medications when possible is also helpful.[41]

Attention Deficit Hyperactivity Disorder (ADHD) and Sleep

PATHOPHYSIOLOGY: Sleep problems are likely multifactorial, including a direct relationship to ADHD or comorbid conditions like OCD, mood disorder, anxiety, PLMD, and SDB (Table 20.13).[43]

EPIDEMIOLOGY: Prevalence of sleep problems in children with ADHD is 5-fold that of healthy controls.[44,45]

TREATMENT: Treatment of underlying SDB, PLMD, and RLS (Table 20.14) leads to improved neurobehavioral functioning in children with ADHD and reduces both inattention and hyperactive behavior.[41] Promotion of sleep hygiene and use of melatonin is effective in abating chronic sleep-onset insomnia (see Table 20.5).[46,47]

Epilepsy and Sleep

EPIDEMIOLOGY: Common comorbidity: 1% to 2% of sleep disorder patients have epilepsy and 20% of patients with epilepsy have seizures solely while asleep.[48] 30% of patients with nocturnal seizures have coexisting parasomnias.

PATHOPHYSIOLOGY: NREM sleep is considered a seizure promoter due to the synchrony of thalamocortical synaptic activity in this stage. This in turn leads to propagation of epileptiform discharges. On the other hand, REM sleep is seizure-protective, due to desynchronized neuronal discharge patterns.

DIAGNOSTIC CONSIDERATIONS: Sleep disruption in children with epilepsy is multifactorial due to: **(1) epilepsy** per se, **(2) AEDs** (e.g., benzodiazepine decreases SWS; phenytoin shortens sleep latency; and lamotrigine, ethosuximide, and felbamate may induce insomnia), **(3) coexistent treatable sleep disorders** such as SDB and PLMS in patients with epilepsy leading to sleep fragmentation with resulting EDS, which in turn could lead to poor seizure control.[49] **Sleep-related epilepsy syndromes** (see Chapter

TABLE 20.13 Subjective and Objective Reports of Sleep Problems in Children with ADHD

Subjective	Objective (Test Modality)
Bedtime resistance	Prolonged sleep-onset latency (ACT)
Sleep-onset difficulties	More stage shifts per hour of sleep (PSG)
Nocturnal awakenings	Higher apnea–hypopnea index (PSG)
Difficult morning awakenings	Lower sleep efficiency index (PSG)
Sleep disordered breathing	Less total sleep time (ACT)
Daytime sleepiness	Shorter sleep latency (MSLT)

Picchietti DL, Underwood DJ, Farris WA, et al. Further studies on periodic limb movement disorder and restless legs syndrome in children with attention-deficit hyperactivity disorder. *Mov Disord.* 1999;14(6):1000–1007.

TABLE 20.14 Pharmacotherapy of RLS/PLMS in Children

Drug	Mechanism of Action	Dosage	Adverse Effects	Safety Profile
Clonidine	Central α-2 adrenergic receptor agonist	0.05–0.3 mg	Hypotension, bradycardia, dry mouth	Rebound night terrors, REM suppression
Clonazepam	GABA-A receptor agonist	0.01 mg/kg	Daytime sedation, cognitive difficulties	Respiratory depression, tolerance, abuse
Levadopa/ carbidopa	Metabolic precursor of dopamine	25/100 mg (½) 3 tabs/d	Hallucinations, confusion, orthostatic hypotension	Augmentation
Pramipexole	Nonergot dopamine receptor agonist	0.125–0.75 mg	Headache (HA), hypotension, daytime somnolence	Impulse control behavior, gambline, augmentation
Ropinirole	Nonergot dopamine receptor agonist	0.5–4 mg	HA, hypotension, daytime somnolence	Impulse control behavior, gambline, augmentation
Gabapentin	May potentiate neuronal GABA synthesis	100–500 mg	Drowsiness, irritability, worsening behaviors	Blurred vison, tremors, weight gain, sleepiness

Pillar G, Shahar E, Peled N, et al. Melatonin improves sleep-wake patterns in psychomotor retarded children. *Pediatr Neurol.* 2000;23(3):225–228.

5) include autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE), juvenile myoclonic epilepsy (JME), benign epilepsy with centrotemporal spikes (BECTS), and Landau–Kleffner syndrome (LKS).

TREATMENT: Occurrence of seizures in relation to sleep/wake cycles has important therapeutic implications, such as use of higher doses of AEDs at night.

HEADACHE AND SLEEP

PATHOPHYSIOLOGY: Intimate but complex and incompletely understood relationship between some HA syndromes and sleep.[50] While sleep has a peculiar effect on terminating attacks of HA, many times patients awaken at night or early morning with a HA. Furthermore, HA may represent one of the Sx of sleep disorders such as OSA, PLMS, or narcolepsy, and disrupted sleep may be the consequence of a HA syndrome. HA clinics have noted 17% cases to report HA at night or early morning before the final awakening period.[51]

ASSOCIATED HA SYNDROMES: Recognized by the ICSD 2nd edition: **(1) Migraines:** May occur during the day or during sleep. 50% of migraine episodes occur between 4:00 and 9:00 AM. No fixed association with a particular sleep stage has been reported. **(2) Cluster HA:** Has a strong predilection to occur during sleep, especially during REM sleep. **(3) Chronic paroxysmal hemicrania:** Attacks of severe pain appear predominantly at night, in close linkage with REM sleep, leading to the term REM–sleep locked HA. **(4) Hypnic HAs** are a rare type of HA that typically awakens the patient from sleep. Headache is generalized or lateralized and lasts for 5 to 60 min, and can occur 1 to 3 times a night. These are not a/w cranial autonomic features. They can occur during REM sleep or SWS.

OTHER CONDITIONS: Hypertension, neurologic (e.g., brain tumor, arteriovenous malformation, and trauma), psychiatric (e.g., depression), and sleep disorders (snoring, OSA) can give rise to HAs during sleep or upon awakening from sleep.

TREATMENT: Pharmacological intervention is based on the type of HA.

SLEEP IN TRAUMATIC BRAIN INJURY

Sleep–wake disturbances, particularly EDS, fatigue, and hypersomnia, are common after traumatic brain injury (TBI) and this spectrum of problems significantly impair quality of life.

Sleep-Disordered Breathing

Disordered respiration during sleep including central sleep apnea, OSA, sleep-related hypoventilation, and hypoxia may be caused by injuries to brain and spinal cord and is worsened by accompanying injuries in other organs, most prominently in upper airway. Aggravation of SDB can occur with use of sedatives and hypnotics commonly administered to these patients.

Posttraumatic Hypersomnia

Common occurrence not only after severe brain injury but also seen after mild head injury not a/w loss of consciousness.

Posttraumatic Narcolepsy

Rare, only a few cases reported. Either narcolepsy preceded the episode of head trauma and the head injury served as a triggering factor,[52] or the head injury affected the hypothalamic orexin neurons.[53]

Other Sleep Disorders

Circadian rhythm disorders with reversal of circadian rhythm,[54] insomnia[55,56] likely due to pain, anxiety, depression, medications, or adverse sleep environment during period of rehabilitation[57] and occasional loss of dreaming, perhaps related to impairment of visual memory.[58]

TREATMENT: Sleep-related Sx should be treated as they might otherwise be. Hypersomnia may be treated with stimulant medications. OSA may require ENT management or positive airway pressure. Data evaluating the outcome of sleep disturbances following head trauma in children is scant. Prognosis often depends on the area and extent of brain damaged and if comorbid conditions are present.

SLEEP IN CHILDREN WITH BRAIN TUMORS

PATHOPHYSIOLOGY: The relationship between brain tumors and sleep is complex because sleep and wakefulness are both regulated by the brain. Three distinct processes may play a role: **(1) Same prevalence of sleep problems** in children with brain tumors as in healthy children, **(2) Psychological stress** on the child and family resulting from presence of a life-threatening disease, and **(3) Direct effects of brain injury** from tumor, surgery, chemotherapy, and medical complications of cancer including cancer-related fatigue, pain, seizures, obesity, endocrinopathies, heart failure, blindness, and medications. **OSA** can be related to obesity and hypothyroidism, while **central sleep apnea** may occur from injury to respiratory control center located in medulla oblongata or from damage to phrenic nerve, along with narcotic use.[59,60] **Insomnia** and **circadian rhythm disorders** are other problems seen in these children.

TREATMENT: Intervention is targeted to the sleep problem, to improve daytime functioning and decrease the effect of sleep disturbance on quality of life.

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ONLINE RESOURCES

www.aasmnet.org – American Academy of Sleep Medicine

www.nhlbi.nih.gov/about/ncsdr – NIH National Center on Sleep Disorders Research

www.sleepresearchsociety.org – Sleep Research Society

21 Neuro-ophthalmology

Kevin A. Shapiro and Gena Heidary

ASSESSMENT OF VISION IN CHILDREN

This initial section provides a schematic for a detailed neuro-ophthalmic assessment of visual function in pediatric patients. Attention has been given to milestones in visual development and age-appropriate methods of assessment to provide a framework for the clinical evaluation.

Visual Acuity

DEFINITION: Measurement of capacity for discrimination of fine details at high contrast.

EVALUATION: Distance vision is evaluated using age-appropriate methods of measurement that may be converted to a standard Snellen acuity; normal milestones of visual development are shown in Table 21.1.

Infants and Toddlers (0–3 y): Assess ability to fix and later follow a light or toy. Optokinetic nystagmus can confirm cortical vision and can be obtained by ~6 wk with large gratings across the entire visual field. Nystagmus may develop by 8 to 12 wk of age and may be the harbinger of visual impairment. Roving, non-purposeful eye movements may signal profound visual impairment. For quantification of acuity, *Teller acuity cards* that use gratings of alternating black and white stripes may be used.

Preschool-age children (3–5 y): For quantification, use symbol optotypes (Allen or Lea symbols) or letter optotypes when appropriate (HOTV letters, tumbling Es).

TABLE 21.1 Milestones in Visual Development

Age	Pupillary Light Reflex	Blink to Light Reflex	Fix and Follow	Smooth Pursuit	Color Vision	Stereopsis	Snellen Acuity
Term	Present	Present	—	—	—	—	20/400–20/1,600
3 mo	—	—	Present	Present	Present	—	20/400
6 mo	—	—	—	—	—	Present	20/400
1 y	—	—	—	—	—	—	20/50–20/100
4 y (Fovea mature)	—	—	—	—	—	—	20/32 or better

School-age children (>5 y): Usually able to use Snellen chart; otherwise use same methods as for preschool-age children.

Retinoscopy may be used to confirm that vision changes are not secondary to correctable refractive error.

Color Vision

Standard tests include pseudoisochromatic *Ishihara color plates* and Hardy–Rand–Rittler (HRR) plates. More detailed tests, including Farnsworth–Munsell 15- or 100-Hues tests, may be used to further characterize the type of color deficiency (i.e., trouble with distinguishing colors in the red–green spectrum: protanopia or deuteranopia, or trouble with distinguishing colors in the blue–yellow spectrum: tritanopia). Testing of color vision may be confounded by visual impairment (<20/200). Monocular dyschromatopsia is a characteristic of an ipsilateral optic neuropathy.

Visual Fields

EVALUATION: Infants and Toddlers (9 mo–3 y): Evaluate presence of saccade toward a toy or light brought into view in each quadrant of the visual field tested binocularly and if able, monocularly. **Preschool-age children (3–5 y):** Can assess by having the child fixate at a point between the examiner's eyes, ask child to point to fingers moving in the periphery. **School-age children (>5 y):** Use confrontation visual fields as described. Formal Goldmann visual field perimetry can be used reliably by age 8 to 9 y and automated Humphrey visual field perimetry in young teens and older.

Pupillary Examination

Examine pupillary size, shape, and symmetry in light and dark conditions.

SHAPE: Irregular pupillary shape may be caused by a variety of congenital conditions (aniridia, iris coloboma, isolated corectopia); it can also be caused by local trauma or inflammation.

SYMMETRY: In **physiologic anisocoria,** pupillary response is normal, and the relative asymmetry in size between the pupils is the same in light and dark; most often, this disparity is <1 mm in light and dark. Anisocoria being greater in light implies parasympathetic abnormality in larger pupil and may implicate dysfunction of the third cranial nerve (see "Third Nerve Palsy" below). Anisocoria greater in dark suggests sympathetic abnormality in smaller pupil (see "Horner Syndrome" below).

LIGHT REACTION: Direct and consensual pupillary light reaction is best examined with a bright light in a dimly lit room, while patient fixates on a distant target. Use *swinging flashlight* test to evaluate for **relative afferent pupillary defect**, which is characteristic of asymmetric compromise of optic nerve function. Constriction of the pupils in darkness indicates a **paradoxical pupillary response**. Differential diagnosis includes retinal disease, such as congenital stationary night blindness and achromatopsia (see "Retinal Dystrophy/Degenerative Disease" below).

Ocular Alignment and Motility

ALIGNMENT: Observe position of corneal light reflex in each eye at rest to detect misalignment (Hirschberg method). Observe head posture; large head turn toward the affected eye in a child with esotropia is suggestive of a 6th nerve palsy; a head tilt away from the affected eye may represent 4th nerve palsy.

MOTILITY: Test conjugate movement of both eyes together (versions) and then test movements of each eye separately with the other eye covered (ductions). In convergence spasm, there is a disparity between versions and ductions; versions show evidence of an abduction limitation but ductions will demonstrate full abduction in each eye helping to distinguish this process from a 6th nerve palsy.

EXTERNAL EXAM: Note abnormalities of the orbit (e.g., proptosis) and eyelids (e.g., ptosis or eyelid retraction).

ANTERIOR SEGMENT EXAM: Any anomalies of the anterior aspect of the eye are noted (i.e., anomalies of the conjunctiva, cornea, anterior chamber, iris, or lens) either with a handheld light or using slit-lamp biomicroscopy.

Funduscopic Exam

VITREOUS: Note the clarity and document whether abnormal cells are present.

OPTIC NERVE: Evaluate the size, color, and sharpness of the nerve border; note any peripapillary abnormalities.

FOVEA: Evaluate the contour of the foveal pit (in albinism, the pit may be absent or hypoplastic); note any pigmentary changes of the macular region.

VASCULATURE: Note the course and caliber of the retinal arterioles and venules.

PERIPHERAL RETINA: May be visualized with pupillary dilation; particular attention is paid to any peripheral retinal pigmentary changes.

DISORDERS OF AFFERENT PATHWAY FUNCTION

Retinal Dystrophy/Degenerative Disease

Diseases of the retina suspected in children with bilateral visual loss, light sensitivity, color vision deficiency, visual loss confined to nighttime or daytime. Patients with retinal disease often are referred to a neuro-ophthalmic practice in the setting of unexplained visual impairment, nystagmus, or roving eye movements secondary to subnormal vision or true vision loss misdiagnosed as psychogenic or nonorganic.

LEBER CONGENITAL AMAUROSIS: Congenital retinal dystrophy involving both rods and cones.[1] **Genetics:** Usually autosomal recessive, occasionally autosomal dominant. **Presentation:** Onset of visual impairment variable but may be present at birth with signs of roving, non-purposeful eye movements, positive oculodigital sign (pushing on the eyes or rubbing them with a finger), high hyperopia; retinal examination may be normal initially. **Evaluation:** ERG useful to establish the diagnosis.

ACHROMATOPSIA: Congenital, nonprogressive defect of cone receptors more common in males; children present with nystagmus, decreased vision, dyschromatopsia, and paradoxical pupillary response (constriction of pupils with dim light).[2] Complete achromatopsia: autosomal recessive with absent cone function; vision ranges from 20/200 to 20/400. Incomplete achromatopsia: commonest form of color vision deficiency; X-linked, vision ranges from 20/40 to 20/400; may have residual sensitivity to one or a combination of red, green, or blue light stimuli.

CONGENITAL STATIONARY NIGHT BLINDNESS: Characterized by impaired dark adaptation and often high myopia; vision ranges from 20/20 to 20/200 and does not deteriorate with time. **Genetics:** Various subtypes and genetic causes recognized. X-linked form is most common, due to mutations in *Nyx* gene (encoding nyctalopin).[3]

STARGARDT MACULAR DYSTROPHY: Hereditary syndrome of macular degeneration beginning in childhood; over time, atrophic macular degeneration with foveal pigmentary changes that may have bull's-eye configuration (bull's-eye maculopathy); yellow flecks in retinal periphery; dyschromatopsia; may be mistaken for psychogenic visual loss, as retina may appear normal initially in spite of vision loss. **Genetics:** Autosomal recessive secondary to mutations in *ABCA4* gene. **Evaluation:** ERG usually normal early in the disease; dark choroid on fluorescein angiography.

ALBINISM: Hereditary condition characterized by decreased pigmentation either specifically in ocular structures (ocular albinism) or ocular structures, skin, and hair (oculocutaneous albinism, OCA). **Genetics:** Most commonly **OCA** is autosomal recessive and ocular albinism is X-linked recessive; dominant forms of OCA have been reported but are rare. **Presentation:** Subnormal visual acuity, nystagmus, transillumination defects of the iris (seeing the red reflex through the pigmented iris), photophobia, foveal hypoplasia, blonde fundus, aberrant decussation of fibers of the anterior visual pathway at the optic chiasm. **Systemic associations:** Albinism and bleeding diathesis seen in Hermansky–Pudlak; more common in patients of Puerto Rican descent; albinism and increased susceptibility to infection in Chediak–Higashi. **Evaluation:** Genetic testing and workup for associated systemic disorders when indicated.

ACUTE IDIOPATHIC BLIND SPOT ENLARGEMENT: Unilateral enlarging paracentral scotoma, which may obscure central vision; believed to be a post-viral retinopathy; sometimes, but not always, improves spontaneously. **Evaluation:** multifocal ERG may reveal peripapillary areas of retinal dysfunction.[4]

Retinal Disease in Syndromic Disorders

Retinal degeneration is seen in a variety of syndromes and neurodegenerative disorders, including sphingolipidoses and neuronal ceroid lipofuscinoses.

JOUBERT SYNDROME: Episodic neonatal tachypnea and apnea, rhythmic protrusion of the tongue, ataxia, hypotonia, and gross motor delay; 50% have retinal dystrophy with visual acuity 20/60 to 20/200; genetically heterogeneous; MRI demonstrates characteristic dysgenesis or hypoplasia of the cerebellar vermis with associated brainstem cleft and altered morphology of superior cerebellar peduncles (*molar tooth sign*).[5]

Disorders of Optic Nerve Development

Congenital anomalies of the optic disc account for ~15% of severe visual impairment in children; thought to result from injury or maldevelopment early in gestation.[6] Unilateral anomalies typically present in the preschool period with strabismus (most commonly esotropia); bilateral anomalies present in infancy with poor vision and nystagmus. There is a high prevalence of associated CNS malformations and systemic disorders, often necessitating further workup.

EMBRYOGENESIS: After closure of the embryonic neural tube (~4 wk gestation), evaginations from the anterior part of the neural tube extend laterally, forming the optic stalk (proximally) and the optic cup (distally). Retinal ganglion cell axons project directly to the optic cup and enter the optic stalk, forming the optic nerve; all RGC axons enter the optic nerve by ~20 wk gestation. During development, ~2 million RGCs send projections into the optic nerve; programmed cell death eliminates about ½ of these, so that the adult optic nerve contains ~1.2 million axons. Myelination of the anterior visual pathways begins at the lateral geniculate body at ~20 wk

gestation, reaches the lamina cribrosa at term, and continues over the first 2 y of life; geniculostriate pathway begins around term and is fully mature about 4 mo postnatally.

OPTIC NERVE HYPOPLASIA: Most common congenital anomaly of the optic disc;[7] appears as an abnormally small, discolored (gray or pale) optic nerve head, reflecting loss of optic nerve axons often with peripapillary halo (double ring sign). **Epidemiology:** Risk increased by a variety of prenatal factors, including young maternal age, primiparity,[8] and exposure to teratogens (alcohol, cocaine, LSD, PCP, phenytoin, quinine);[9] segmental hypoplasia occurs in infants of diabetic mothers.[10] **Genetics:** Currently no strong genetic associations for isolated optic nerve hypoplasia. **Presentation:** Localized visual field defects and constriction of the visual fields; acuity ranges from normal (if macular fibers are spared) to no light perception; more commonly bilateral than unilateral; may be associated with other CNS malformations, ocular anomalies, and multisystem genetic disorders. **Evaluation:** (1) Neuroimaging with MRI. (2) Endocrine evaluation: Hormonal dysfunction may be present in spite of normal anatomic appearance of pituitary on MRI. Growth hormone deficiency resulting in pituitary dwarfism is most common; there may also be deficiencies in thyroid, adrenal, and gonadal axes, panhypopituitarism, or diabetes insipidus due to ADH deficiency; hyperprolactinemia is common. **Associated conditions:** Septo-optic dysplasia (de Morsier syndrome): optic nerve hypoplasia, absent septum pellucidum, and thinning or agenesis of the corpus callosum; associated with mutations in *HesX1* gene.[11]

OPTIC NERVE APLASIA: Complete absence of the optic nerve and disc, retinal ganglion and nerve fiber layers, and optic nerve vessels, sometimes with a whitish area or cavity in the site normally corresponding to the optic disc;[12] typically unilateral and frequently associated with other malformations in the same eye (microphthalmia, iris hypoplasia, cataracts, colobomas, retinal dysplasia); when bilateral, usually associated with CNS malformations.[12]

OPTIC NERVE COLOBOMA: Well-defined, bowl-shaped excavation centered in the inferotemporal part of the optic disc, often involving adjacent choroid and retina, due to faulty closure of embryonic fetal fissure of optic stalk and cup.[13,14] **Genetics:** Sporadic or inherited, with multiple modes of transmission (AR, AD, X-linked)[15]; associated with multisystem disorders, including CHARGE association (60% with *CHD7* mutation), Walker–Warburg syndrome, linear sebaceous nevus syndrome (see below). **Presentation:** May present with microphthalmos, microcornea, iris defects, or strabismus; acuity mildly to severely decreased; prone to serous retinal detachment. **Evaluation:** Consider genetics evaluation to exclude associated syndromes.

OPTIC NERVE PIT: Round or oval depression in the optic disc formed by herniation of dysplastic retina into a pocket formed by a defect in the lamina cribrosa. **Presentation:** Variable visual acuity and visual field defects if any; associated with serous retinal detachments.[16]

MORNING GLORY ANOMALY: Funnel-shaped excavation of the posterior fundus, involving the optic disc; the optic nerve appears enlarged with a central glial tuft (resembling the morning glory flower) and may be surrounded by a halo of chorioretinal pigmentary disruption; radial orientation of retinal vasculature as it emerges from the disc. **Presentation:** Decreased acuity (usually 20/200 to finger counting, although cases with 20/20 vision and no light perception have been reported), or discovered in workup for midline defects (see below). **Associations: (1) Transsphenoidal basal encephalocele:** Occult midline congenital malformation in which meningeal pouch protrudes into nasopharynx through round defect in sphenoid

bone; affected children may have other midline defects (hypertelorism, midline cleft lip, cleft palate, callosal agenesis, absence of the optic chiasm, panhypopituitarism) and may present with rhinorrhea or symptoms of airway obstruction. **(2) Vascular anomalies:** ~45% of patients with morning glory anomaly, including carotid hypoplasia and moyamoya syndrome.[17] **Evaluation:** MRI and MRA indicated to evaluate for associated anomalies.

TILTED DISC ANOMALY: Discs appear tilted bilaterally, with superonasal elevation; anomalous origin of retinal vessels; secondary to posterior ectasia of the inferonasal fundus and optic disc; may have bitemporal visual field defects that do not respect the vertical meridian.

MYELINATED RETINAL NERVE FIBERS: White, striated patches at the upper and lower poles of the optic disc (less often, discrete patches are seen separate from the disc), which may elevate the disc and obscure the disc margin; recognizable by irregular, fan-shaped appearance of distal border; can be associated with high myopia, amblyopia, and visual field loss; pathogenesis unclear, may be familial (autosomal dominant).

PAPILLORENAL SYNDROME: Centrally excavated discs, normal in size, with radial orientation of retinal vessels that emanate from the edge of the optic disc; associated with renal dysfunction. **Genetics:** Often caused by mutations in *PAX2* gene.[18] **Presentation:** Visual acuity typically normal, but may be diminished due to choroidal or retina hypoplasia, or serous retinal detachment; peripheral field defects due to areas of retinal hypoplasia. **Evaluation:** Renal workup, including renal ultrasound.

AICARDI SYNDROME: Constellation of *infantile spasms, agenesis of the corpus callosum*, and pathognomonic peripapillary *chorioretinal lacunae* or "punched out lesions" (defects in retinal pigment epithelium) surrounding an optic disc which is often anomalous. Considered to be X-linked lethal in males.

Optic Atrophy

End result of any of various insults to the anterior *visual* pathway leading to loss of retinal ganglion cell axons; appearance is of a pale optic disc of normal size, often with fewer-than-normal fine vessels; degree of optic atrophy on examination is not well-correlated with visual acuity.

COMPRESSIVE OPTIC NEUROPATHY: Optic atrophy may result from lesions resulting in chronically increased pressure on the optic pathways.

Optic nerve glioma: Tumor arising from astrocytes surrounding optic nerve axons, most often low grade and pathologically identical to juvenile pilocytic astrocytoma; may initially present with disc edema, but eventually result in optic atrophy. **Epidemiology:** 75% within the 1st decade of life, 90% within the 1st 2 decades. **Presentation:** Vision loss may occur although some optic nerve gliomas do not affect visual acuity; strabismus, painless proptosis, and monocular nystagmus may all be signs of an optic nerve glioma. **Associations:** 25% are associated with NF-1; frequency of optic gliomas in NF-1 patients varies from 10% to 70%; in NF-1 patients gliomas may be multifocal, affecting both optic nerves independently. **Evaluation:** MRI often shows homogeneous thickening and kinking of orbital optic nerve(s), enlargement of chiasm, infiltration of hypothalamus. **Prognosis:** Varies; may remain stable, enlarge, or regress spontaneously. **Treatment:** Controversial and dependent upon impact of tumor on visual function; observation, chemotherapy, surgical debulking may be pursued; radiation less commonly pursued given risk of secondary tumors in NF1 and secondary effects on vascular integrity (radiation induced moyamoya disease) and neurodevelopment.

Craniopharyngioma: Most common supratentorial tumor of childhood; location frequently causes anterior visual pathway compression and endocrine dysfunction; may present as seesaw nystagmus.

Congenital Hydrocephalus: Common cause of optic atrophy in children; optic atrophy is often coincident with cortical visual loss; major mechanism appears to be long-term increase in intracranial pressure.

TOXIC AND NUTRITIONAL OPTIC NEUROPATHY: Several nutritional deficiencies and drugs have been associated with symmetrical, usually insidious bilateral optic neuropathy with loss of acuity and centrocecal scotomas (Table 21.2).

TRAUMATIC OPTIC NEUROPATHY: Damage to one or both optic nerves may result from direct or indirect trauma, including contusion, avulsion, or laceration of the optic nerve, or hemorrhage into the optic nerve sheath; optic disc typically appears normal at first, with atrophy ensuing quickly after the inciting event[19]; high-dose steroids have been used but are not clearly beneficial and may be harmful.[20]

RADIATION OPTIC NEUROPATHY: Cumulative doses of 50 to 60 Gy or single doses of >10 Gy to the anterior pathway increase risk of radiation optic neuropathy[21] can occur within several weeks of radiation (early form) or years after treatment with a peak at 18 mo (late form).

HEREDITARY OPTIC NEUROPATHY: Heterogeneous group of disorders, many with evidence of mitochondrial dysfunction; systemic mitochondrial disorders may also produce optic atrophy.[22]

Dominant optic atrophy (Kjer): Most common form of hereditary optic atrophy; onset insidious, typically between ages 4 to 8 y. **Genetics:** Autosomal dominant with incomplete penetrance and variable phenotype; genetically heterogeneous, most mutations described in OPA1, with additional loci at OPA3 (dominant optic atrophy with cataract), OPA4, and OPA5.[23] **Presentation:** Often discovered during routine visual screening; visual acuity typically 20/70 to 20/100 (range 20/20 to count fingers), but may vary even between eyes in the same individual; mild photophobia and dyschromatopsia are also common. **Prognosis:** Visual function usually stabilizes after teenage years; 80% of patients over 45 y have acuity better than 20/200.

Leber Hereditary Optic Neuropathy (LHON): Mitochondrial disorder causing rapid loss of vision, more commonly affecting males; usually presents between ages 18 to 35 y (range: 1–80 y). Risk of females carrying this mutation is <10%. **Genetics:** Maternally inherited, associated with mitochondrial

TABLE 21.2 Toxic and Nutritional Optic Neuropathies

Vitamin Deficiencies	Toxic Exposures
Thiamine	Ethambutol
Pyridoxine	Chloramphenicol
Cobalamin	Rifampin
Riboflavin	Carmistine
Folic acid	Vincristine
	Methanol
	Lead
	Cobalt

Adapted from Brodsky MC. *Pediatric Neuro-ophthalmology.* 2nd ed. New York, NY: Springer; 2010 and Grant WM. *Toxicology of the Eye.* 3rd ed. Springfield, IL: Charles C. Thomas; 1986, with permission.

DNA mutations[23]; 3 most common mutations include m.11778 G>A (most common), m.3460 G>A, and m.14484 T>C of which spontaneous visual recovery is more likely in the m.14484 T>C mutation. In addition to primary causative mutations, many mitochondrial mutations/polymorphisms have been identified that are weakly associated but not sufficient for the onset of disease. **Presentation:** Rapidly progressive, painless unilateral vision loss, with involvement of the other eye usually within days to months; acutely may detect peripapillary telangiectasia of the vessels and swelling of the retinal nerve fiber layer without true optic nerve edema. **Prognosis:** Visual acuity usually stabilizes at ~20/200, with dyschromatopsia; central or centrocecal scotoma; most often permanent but some patients show visual recovery. **Evaluation:** Fluorescein angiography may be useful in distinguishing the pseudoswelling in LHON from true optic nerve edema. In LHON there is no evidence of leakage around the optic nerve, whereas in true optic nerve edema, there is leakage of fluorescein around the optic nerve.

Wolfram syndrome (DIDMOAD): Constellation of **D**iabetes **I**nsipidus, **D**iabetes **M**ellitus, **O**ptic **A**trophy, and sensorineural **D**eafness.[24] **Epidemiology:** Most patients under 25 y, with different manifestations presenting at different ages; mean age at diagnosis of diabetes mellitus at 9 y, optic atrophy at 12 y, diabetes insipidus at 15 to 20 y, clinical deafness >20 y. **Genetics:** Several mutations described in *WFS1* gene on 4p16.3 (also associated with dominant optic atrophy with hearing loss); deletions at this locus may predispose to multiple mitochondrial deletions. **Presentation:** Vision loss with optic atrophy; final vision usually worse than 20/200. **Evaluation:** MRI with widespread atrophy of brainstem, middle cerebellar peduncle, and cerebellum, with decreased signal intensity in posterior pituitary.

Recessive optic atrophy: Monosymptomatic, isolated, rare form of hereditary optic atrophy; present at birth or develops at an early age; severe visual defects are characteristic (acuity worse than 20/200 with achromatopsia).[25]

Behr syndrome: Form of recessive optic atrophy with other associated neurologic abnormalities including ataxia, spasticity, and mental retardation; onset usually between 1 and 8 y; may overlap with several other genetic disorders.[26]

Costeff syndrome (methylglutaconic aciduria type 3): Autosomal recessive disorder with early bilateral optic atrophy, extrapyramidal dysfunction, late-onset spasticity, and sometimes cognitive deficits; caused by homozygous mutations with complete absence of *OPA3* gene[23]; elevated urine 3-methylglutaconic and 3-methylglutaric acid.

Associated with neurodegenerative disorders: Wide variety, including congenital retinal disorders, infectious retinopathy, central retinal artery occlusion, SCA, familial dysautonomia, and PEHO (progressive encephalopathy with edema, hypsarrhythmia, and optic atrophy) syndrome. For detailed list of associated metabolic disorders, see Chapter 7.

Optic Nerve Edema

Elevation of the optic disc is caused by interruption in axonal transport in the optic nerve head from a variety of causes, including increased intracranial pressure; inflammation, ischemia, or compression of the optic nerve; metabolic effects; or intraocular inflammation.

PSEUDOPAPILLEDEMA: Anomalous elevation of the optic disc that mimics the appearance of pathologic optic nerve swelling or edema secondary to optic nerve head drusen. *Drusen* are globular concretions anterior to the lamina cribrosa, thought possibly to result from chronic, low-grade optic

neuropathy due to crowding of axons (often hereditary); *buried drusen* may be not be apparent in infants and children, but gradually become evident clinically as they enlarge and calcify; may cause visual field defects, ischemic optic neuropathy, and choroidal neovascularization. **Evaluation:** Although there are funduscopic details that may suggest pseudopapilledema, it is important to confirm the diagnosis by additional imaging techniques.

Optic nerve head drusen may be detected by ultrasound, optical coherence tomography (OCT), or on CT scan; in pediatric patients, ultrasound or OCT are the preferred techniques.

PAPILLEDEMA: Refers to bilateral optic nerve swelling secondary to elevated intracranial pressure (ICP). **Presentation:** Systemic symptoms include headaches, pulsatile tinnitus ("heart beat sound in the ears"), nausea/vomiting, neck pain. Visual symptoms include blurry vision, transient visual obscurations ("gray-outs" lasting a few seconds, often with bending over, standing, or Valsalva), visual field defects, diplopia. **Evaluation:** Complete ophthalmic evaluation, including formal visual field testing, if patient able. *MRI brain/orbits and MRV head* and when indicated lumbar puncture to confirm elevation of ICP; primary diagnostic consideration is papilledema secondary to causes of elevated ICP including intracranial mass lesion with obstructive hydrocephalus, mixed compressive optic neuropathy/obstructive hydrocephalus, developmental anomaly (aqueductal stenosis), meningitis-induced craniosynostosis vs. idiopathic intracranial hypertension (IIH); MRV to exclude venous sinus thrombosis.

Idiopathic intracranial hypertension: Signs and symptoms of increased ICP without a mass lesion or hydrocephalus. Risk factors include use of tetracycline/minocycline, accutane, all-trans retinoic acid (ATRA) in patients with acute promyelocytic leukemia. Signs on MRI and MRV associated with IIH include enlarged perioptic subarachnoid space, protrusion of optic nerves into the globe, flattening of the globe, empty sella turcica, and narrowing of the transverse sinus (see Chapter 14). Chronic papilledema may lead to optic atrophy and permanent visual loss. Treatment includes medical with ICP-lowering medication such as acetazolamide 10 to 15 mg/kg divided b.i.d. or t.i.d. vs. surgical intervention (ventricular shunt or optic nerve sheath fenestration).

DISC EDEMA IN SYSTEMIC DISORDERS: May be seen in a variety of systemic disorders; some overlap with disorders causing optic atrophy.

Optic neuritis: Commonly preceded by a febrile illness occurring days to weeks earlier; wide variety of viral and bacterial pathogens have been implicated; postimmunization optic neuritis also reported; can be a feature of ADEM. **Presentation:** Vision loss, often bilateral in pediatric patients (50%–75%); pain with eye movements more commonly reported by adults than by children. **Evaluation:** *MRI* to evaluate for intracranial lesions (demyelinating disease); *lumbar puncture* to rule out infection, elevated ICP, leukemia; consider chest X-ray (to evaluate for tuberculosis and sarcoidosis); look for signs and symptoms of systemic disorders. **Treatment:** No controlled study to determine efficacy of treatment in children, but often treated with intravenous corticosteroids based on studies in adults. **Prognosis:** Initial visual loss may be profound, but prognosis for recovery is generally excellent. **Association with pediatric multiple sclerosis:** Studies find that risk for developing MS after childhood optic neuritis is present and more likely when there are associated CNS lesions on MRI.

Neuromyelitis optica (Devic disease): Necrotizing myelopathy due to antibodies against aquaporin-4 channel; often presents with acute bilateral

optic neuritis; classically associated with severe visual loss, but some studies suggest children have a better prognosis for visual recovery.

Leber idiopathic stellate neuroretinitis: Clinical syndrome of *unilateral visual loss, optic disc swelling* with peripapillary striae, and *macular* star; thought to be due to local autoimmune vasculitis. **Etiology:** Associated with a variety of infectious agents, especially cat scratch disease; other causes include Lyme, *Toxocara*, *Toxoplasma*, mumps, influenza, varicella, EBV, West Nile virus, tuberculosis, syphilis, leptospirosis. **Presentation:** Usually follows an infectious prodrome by 2 to 4 wk; visual loss (20/50–20/200) with afferent pupillary defect; central or centrocecal scotoma; macular star develops over time. **Prognosis:** Mostly associated with excellent recovery, but recovery is more prolonged than with optic neuritis; important to distinguish from optic neuritis, as it is never associated with multiple sclerosis.

Leukemia: Leukemia may produce optic disc swelling by a variety of mechanisms, including leukemic infiltration of the optic nerve head, papilledema, and ischemic optic neuropathy.

Diabetic papillopathy: Bilateral optic disc edema may be seen in some patients with juvenile-onset diabetes, predominantly around ages 10 to 30 y; usually minimally symptomatic, may regress spontaneously.[27,28]

Optic nerve tumors: May be anterior to lamina cribrosa or retrobulbar.

- **Optic disc hemangiomas** in von Hippel–Lindau disease.
- **Astrocytic hamartomas** of the optic disc in tuberous sclerosis.
- **Optic nerve glioma** associated with neurofibromatosis type 1.
- **Optic nerve sheath meningioma** (less common in pediatric patients).

Malignant hypertension: Disc swelling due to malignant hypertension seen in the setting of glomerulonephritis, renal artery stenosis, and systemic vasculitis; blindness due to optic disc ischemia may occur if blood pressure is reduced too quickly.[29]

Sarcoidosis: Optic disc swelling may be due to local granulomatous infiltration (with characteristic "cauliflower" appearance), intraocular inflammation, or papilledema from mass effect or hydrocephalus with CNS lesions.[30]

Uveitis: Disc swelling may be secondary to intraocular inflammation; important causes include rheumatologic disorders, Kawasaki disease, and post-streptococcal uveitis (Table 21.3).

Disorders of the Optic Chiasm

ACHIASMIA: Absence of the mid-chiasmal bar, with normal optic nerves and optic tracts; visual fields and acuity are normal, but stereoacuity is absent; patients present with early onset seesaw nystagmus.[31]

CHIASMAL GLIOMA: Optic nerve glioma with involvement of the chiasm (see above); presents with unilateral or bilateral (asymmetric) optic atrophy and visual loss; may be associated with diencephalic syndrome or endocrine dysfunction from hypothalamic involvement; may be associated with obstructive hydrocephalus due to expansion into 3rd ventricle.[32]

SELLAR/SUPRASELLAR LESIONS: May cause bitemporal hemianopia by compression of the optic chiasm; include craniopharyngioma, Rathke cleft cyst, pituitary adenomas less common in pediatric patients.

CHIASMAL NEURITIS: Presents with bilateral (often asymmetric) loss of acuity and visual field loss (bitemporal hemianopia).[33,34]

TABLE 21.3 Differential Diagnosis of Optic Disc Swelling

Isolated Visual Involvement	Visual Loss with Additional Neurologic or Systemic Signs
Optic nerve glioma	Papilledema in association with Idiopathic intracranial hypertension
Neuroretinitis	Obstructive hydrocephalus
Leber hereditary optic neuropathy	Dural sinus thrombosis
Pseudopapilledema	Craniosynostosis
	Meningitis
	Optic pathway glioma (sporadic or in NF1)
	Optic neuritis in association with
	Acute disseminated encephalomyelitis
	Multiple sclerosis
	Neuromyelitis optica
	Intrinsic optic nerve tumors in association with
	von Hippel–Lindau disease (hemangiomas)
	Tuberous sclerosis (astrocytic hamartomas)
	Uveitis
	Systemic vasculitis
	Sarcoidosis
	Leukemic infiltration of the optic nerve
	Malignant hypertension
	Diabetic papillopathy

Retrochiasmal Visual Impairment

CORTICAL VISUAL IMPAIRMENT: Partial or complete loss of vision (cortical blindness) resulting from lesions of the geniculostriate pathway.[35–37] **Etiology:** In children, often due to perinatal hypoxic-ischemic injury or stroke; can also be caused by meningoencephalitis, profound hypoglycemia, trauma, cerebral malformations, hydrocephalus, genetic or metabolic disease; may occasionally be isolated, affecting otherwise healthy children.[38] **Presentation:** Variable degrees of visual loss (minimal to complete blindness); may see objects better in a familiar environment, at close range, and against plain backgrounds; some children may display a color preference or for peripheral vision; some may have better visual acuity under low luminance conditions or for moving objects.[39] Visual loss may fluctuate with state of alertness, illness, medications, seizures, environmental changes (noise, colors, lighting conditions).[39] May have a tendency to stare at sources of bright light (light gazing); conversely, about ⅓ have mild photophobia. **Evaluation:** MRI may show diffuse cerebral atrophy, bi-occipital infarctions, parieto occipital watershed infarctions, or cerebral dysgenesis; routine VEPs may be helpful in monitoring visual recovery. **Prognosis:** Variable improvement in vision with time and early intervention for visual rehabilitation may make significant impact on recovery.

SUBCORTICAL VISUAL IMPAIRMENT (SVI): Visual loss caused by damage to the optic radiations, generally from periventricular leukomalacia in preterm infants. **Presentation:** Common findings include decreased visual acuity, optic nerve hypoplasia, inferior field constriction, esotropia with latent nystagmus[40]; even when acuity is normal, children with SVI may have difficulties interpreting visual environment, especially with visuospatial orientation and interpretation of complex patterns such as faces and words.[41]

DELAYED VISUAL MATURATION (DVM): Spontaneous, late development of visual function, without lesion on neuroimaging; function of retina, optic nerve, visual cortex, and saccadic eye movement systems is intact; thought to be due to immaturity of visual association areas. **Epidemiology:** Some children have history of prematurity or are small for gestational age; associated with cocaine exposure in utero; other children have associated systemic or ocular disease or mental retardation. **Prognosis:** In isolated DVM, visual recovery is typically within a year of age, but a substantial proportion have developmental delay or learning disabilities; when there are associated disorders, recovery is variable.

CONGENITAL HOMONYMOUS HEMIANOPIA: Pure hemianopic field defects due to congenital lesions affecting one occipital lobe; characteristic optic disc and nerve fiber layer changes (homonymous hemioptic atrophy) with band-shaped palor or atrophy of the contralateral disc and temporal pallor of the ipsilateral disc.[42] **Etiology:** Perinatal hemispheric stroke or leukomalacia,[43] porencephalic cysts, arteriovenous malformations,[44] gangliogliomas; rarely congenital optic tract lesions.[45]

TRANSIENT VISUAL LOSS

Migraine and migraine equivalents: Most common cause of episodic visual disturbances in childhood, often without characteristic throbbing headache; some describe characteristic scintillating scotoma with expansion or fortification figure (teichopsia), but children are more likely than adults to describe a variety of other visual disturbances.

- **Amaurosis fugax:** Transient monocular loss of rapid onset and resolution; in children and young adults, more commonly associated with migraine than with vascular occlusion.
- **Disturbances of higher cortical function:** Include loss of color vision (central achromatopsia); abnormal face recognition (prosopagnosia); difficulty reading (alexia); distortions of time, sense, and body image (Alice in Wonderland syndrome).
- **Persistent migraine aura (visual snow):** Some children with migraine develop persistent visual phenomena lasting months to years; involve entire visual field and consist of diffuse small particles described as TV static, snow, dots, rain, and ants; can be difficult to treat, but case reports suggest a response to furosemide[46] or valproic acid.[47]

Epilepsy: Children with seizure focus in primary visual cortex or visual association areas may have irritative visual hallucinations or cortical blindness (ictal or postictal).

- **Occipital lobe epilepsy:** More common in children than in adults; visual phenomena depend on location within the occipital lobes; seizures in primary visual cortex may consist of elementary photopsias, while seizures in secondary visual association areas may produce multicolored hallucinations with circular or spherical patterns.
- **Panayiotopoulos syndrome:** Presents in early childhood with nocturnal spells of eye deviation, nausea, vomiting, and autonomic manifestations; visual symptoms in 10% of patients, consisting of elementary or complex visual hallucinations, illusions, blurring, or blindness.[48]
- **Idiopathic childhood occipital epilepsy of Gastaut:** Presents later in childhood with brief, diurnal visual seizures with

elementary visual hallucinations, sensory illusions of eye movement, and tonic eye deviation.[49]

- **Symptomatic occipital epilepsy:** Common causes include Sturge–Weber syndrome, cortical dysplasia, neonatal hypoglycemia, celiac disease, mitochondrial disease, traumatic brain injury, porencephalic cysts, glial tumors, and angiomas.
- **Temporal lobe epilepsy:** Seizures arising from the temporal visual association areas may produce complex hallucinations of people, animals, and objects that move and interact.

Posttraumatic blindness: Occipital head trauma may cause transient blindness, sometimes minutes to hours after trauma; often accompanied by other post-concussive symptoms; lasts from several minutes to a day (usually hours), with full recovery.

Cervical dissection: Carotid artery dissection may produce transient monocular visual loss or scintillating scotoma, similar to migraine; vertebral artery dissection can also produce transient visual symptoms.

Psychogenic visual loss: Most commonly seen in girls 9 to 11 yo ("amblyopic schoolgirl syndrome"); presents as bilaterally decreased acuity, usually 20/30 to 20/100 on examination; visual field constriction with perimetry; complaints of headaches and eye strain are common. **Diagnosis:** Various maneuvers may be suggestive of nonorganic vision loss: the examination often improves with encouragement; *optokinetic nystagmus* may be normal; stereoacuity is often normal in psychogenic vision loss. Diagnosis of exclusion only after thorough ophthalmic evaluation including color vision testing and formal visual field testing if patient able to participate. **Treatment:** Identify underlying psychological triggers; tell child that this kind of visual disturbance is common in children and usually improves; most do not require psychiatric referral unless there is clear underlying psychiatric disease, significant or prolonged functional impairment, or history of trauma.

DISORDERS OF EFFERENT PATHWAY FUNCTION

Pupillary Disorders

ACCOMMODATIVE PARESIS: Preserved light response and convergence; can sometimes be benign and transient in healthy children; also caused by head and neck trauma, systemic diseases (e.g., diabetes mellitus), neuromuscular diseases, neurologic disease, ocular disease, and trisomy 21.

ADIE TONIC PUPIL: Unilaterally or bilaterally enlarged, tonic pupils with slow constriction to light or near stimulation, followed by slow, tonic redilatation; due to parasympathetic denervation; confirmed by constriction to dilute pilocarpine; rare in childhood.

Disorders of Ocular Motility

Children with ocular motility disorders may present with symptoms of diplopia and signs of ocular misalignment, head turn/head tilt, or ptosis.

THIRD NERVE PALSY: Injury to the oculomotor nerve may result in complete or partial weakness of innervated muscles (superior division: superior rectus, levator palpebrae, and inferior division: inferior rectus, medial rectus, inferior oblique, pupil constrictors).

Etiology: 40% to 50% congenital, often with signs of aberrant regeneration; 20% to 40% traumatic; 10% to 20% due to aneurysm or neoplasm;[50–52]

rarely due to ophthalmoplegic migraine or cyclic oculomotor palsy (see below).[53] **Presentation: (1) Complete third nerve palsy:** Marked exotropia and mild hypotropia with complete ptosis and pupillary dilatation. **(2) Aberrant regeneration (oculomotor synkinesis):** May arise from weeks to months after oculomotor nerve injury; signs include retraction of the eyelid with downgaze (pseudo–von Graefe sign), poor reaction to light stimulation but normal constriction with adduction (pseudo–Argyll Robertson pupil). **Evaluation:** *MRI/MRA* indicated to evaluate for neoplasm or aneurysm. Genetic testing of *CFEOM 3* for congenital presentation of unilateral third nerve palsy (see section on "Congenital Cranial Dysinnervation Disorders" below). **Prognosis:** Neonates with congenital third nerve palsy may recover some function over weeks to months; amblyopia is common[54] and functional outcome tends to be poor, though surgery may be useful for cosmetic purposes.

FOURTH NERVE PALSY: Most common isolated cranial nerve palsy and most common cause of isolated vertical diplopia; defect in depression and in cyclotorsion due to dysfunction of the superior oblique muscle. **Etiology:** About ⅔ congenital; less commonly due to craniofacial anomalies (10%), trauma (5%), or other causes; vascular and neoplastic causes are extremely rare; when bilateral, most often traumatic.[52,55] Congenital fourth nerve palsy generally nonfamilial, often asymptomatic; may present with torticollis; facial asymmetry may develop due to chronic head tilt. **Presentation:** Frequently presents with head tilt to the side opposite the affected eye; increases on horizontal gaze away from the affected eye and head tilt toward the affected eye. **Evaluation:** *MRI* more commonly pursued in acquired cases (e.g., for trochlear nerve schwannoma in children with NF2). **Prognosis:** Acquired palsies may resolve within 6 mo; surgical treatment may be indicated for congenital or persistent acquired 4th nerve palsy.

SIXTH NERVE PALSY: Defect in abduction of the affected eye due to dysfunction of the lateral rectus muscle. **Etiology:** In case series, neoplasm generally most common (20%–45%), but estimates may reflect referral population; other causes include trauma (20%–40%), elevated ICP (15%), infection or postinfectious inflammation (10%–20%).[52,56] **Congenital 6th nerve palsy:** Rare, usually presents in the neonatal period, may improve or resolve over the 1st month of life. **Benign recurrent 6th nerve palsy:** Unilateral 6th nerve palsy developing after a viral illness or immunization; sudden in onset and associated with a severe abduction deficit; children may have several attacks over the course of 8 to 12 wk, followed by complete resolution in most cases.[57] **Presentation:** Binocular horizontal diplopia worse at distance than at near; head turn toward the side of the lesion; incommitant esotropia increasing in gaze toward affected eye and decreasing with gaze away from affected eye. **Evaluation:** MRI indicated to evaluate for neoplastic cause and when indicated lumbar puncture to evaluate for elevated ICP. **Prognosis:** In traumatic cases, many recover spontaneously within 6 mo; associated with high rate of strabismus and amblyopia, so treatment for amblyopia often is indicated depending on the age of the patient; incomplete recovery is an indication for strabismus surgery.

OPHTHALMOPLEGIC MIGRAINE: At least 2 migraine headaches accompanied or followed within 4 days by paresis of one or more ocular motor nerves, ipsilateral to headache; tumor must be ruled out by MRI. **Epidemiology:** Onset usually before age 10 y. **Presentation:** *Usually third nerve involvement* (10:1 over 6th nerve), with involvement of all branches and pupillary involvement; opthalmoplegia occurs at height of headache

and may persist for 3 to 4 d; repeated or prolonged episodes may last for up to a month or eventually become permanent. **Evaluation:** *MRI* to evaluate for tumor.

MULTIPLE CRANIAL NERVE PALSIES: Most commonly due to trauma (including basilar skull fracture); differential diagnosis includes infiltrative neoplasms, leukemia, inflammatory disorders (Guillain–Barré, multiple sclerosis, sarcoidosis, infection).

CONJUGATE GAZE PALSIES:

Horizontal gaze palsy: Attributable to lesions in the contralateral frontal eye field, ipsilateral paramedian pontine reticular formation, or 6th nerve nucleus; seen in some congenital cranial dysinnervation disorders (see below) and Gaucher disease type 3.

Downgaze palsy: Usually due to bilateral lesions involving the midbrain reticular formation and affecting the rostral interstitial nucleus of the medial longitudinal fasciculus; characteristic of **Niemann–Pick disease type C**.

Upgaze palsy: Seen in dorsal midbrain syndrome (see below); most common causes are hydrocephalus and other compressive lesions causing dorsal midbrain syndrome; causes of isolated upgaze palsy include vitamin B_1 or B_{12} deficiency, Miller Fisher syndrome, or restriction of the inferior rectus muscles in congenital fibrosis syndrome; can also be seen in children with severe congenital visual loss.

Internuclear ophthalmoplegia: Inability to adduct one or both eyes on lateral gaze, with nystagmus in the abducting eye; attributable to lesions in the medial longitudinal fasciculus; causes include demyelinating disease, brainstem tumors, vitamin B_{12} deficiency, infection, vasculitis, trauma, and metabolic disease.

CONGENITAL CRANIAL DYSINNERVATION DISORDERS: Disorders characterized by deficient innervation to extraocular muscles and facial musculature.

Congenital fibrosis of the extraocular muscles (CFEOM): Congenital restrictive ophthalmoplegia, fixed downgaze, horizontal strabismus, ptosis; extraocular and levator muscles are replaced by fibrous tissue due to failure of normal innervation in early development.[58] **Genetics:** Three genetic loci with distinct clinical phenotypes: CFEOM1 is autosomal dominant, due to mutations of *KIF21A* gene on chromosome 12; CFEOM2 is autosomal recessive, due to mutations of *PHOX2A* on chromosome 11q13.1; CFEOM3 is autosomal dominant with variable penetrance, and maps to chromosome 16p24.2-q24.3, due to mutations of *TUBB3*. **Presentation:** CFEOM 1 and 2 generally are bilateral and CFEOM 3 may be unilateral with variable degree of ptosis of the eyelids; specific muscles may be affected differentially.

Möbius sequence: Congenital facial weakness with horizontal gaze palsy due to hypoplasia of the facial and abducens nerves (sometimes asymmetric); vertical gaze is preserved; may also affect trigeminal, vagus, and hypoglossal nerves, and frequently associated with limb and musculoskeletal malformations, general motor disability, poor coordination, and respiratory abnormalities; etiology unclear.[59]

Duane syndrome: Developmental defect characterized by anomalous innervation of the lateral rectus muscle by the third cranial nerve,[60,61] more commonly seen in females and affecting the left eye; may be unilateral or bilateral. **Genetics:** Majority of cases are sporadic; 2% to 5% autosomal dominant. **Presentation:** Three clinical phenotypes of which type I is

most common; type I with limited abduction of affected eye; type II with limited adduction of affected eye; type III with both limited abduction and adduction of affected eye. Affected patients may have narrowing of the palpebral fissure on adduction of the eye, globe retraction on adduction, and anomalous eye movements (upshoots and downshoots) in adduction. **Associations:** Additional systemic findings in about ⅓ of cases, including sensorineural deafness (10%), vertebral, kidney, and limb anomalies; seen as part of some other systemic associations (Wildervanck, Goldenhar, Okihiro, Holt-Oram, acro-renal-ocular syndrome).

CONGENITAL OCULAR MOTOR APRAXIA: Inability to make voluntary saccades with preservation of reflexive saccades; almost always affects horizontal saccades, with preservation of vertical saccades, although in rare cases vertical eye movements are affected. **Epidemiology:** Usually sporadic, although familial cases reported; may be seen in association with neurodegenerative disorders and CNS malformation syndromes. **Presentation:** Large-amplitude horizontal head thrusting to achieve visual fixation; usually appears when children acquire head and neck control around 6 mo; at early ages, blindness may be suspected due to failure to fix and follow; on testing, fast phases of vestibular nystagmus and optokinetic nystagmus are absent; children may also have verbal apraxia, truncal ataxia, hypotonia, and developmental delay. **Associations:** Include Joubert syndrome (see above), lysosomal disorders (Gaucher, type 3, Krabbe, Niemann–Pick type C), ataxia-telangiectasia, Cockayne syndrome, Pelizaeus–Merzbacher disease, recessive ataxia with ocular apraxia, spinocerebellar ataxia type 2. **Evaluation:** MRI may demonstrate associated agenesis of corpus callosum, collicular abnormalities, cerebellar vermian dysplasia.

TRANSIENT OCULAR MOTOR DISTURBANCES OF INFANCY: Neonates may have a variety of benign, transient supranuclear eye movement disturbances.

Transient neonatal strabismus: Healthy term neonates may have exotropia or esotropia initially; for esotropia, most become orthotropic between 2 and 3 mo of age; for exotropia, most become orthotropic as late as 4 to 6 mo of age.

Tonic downgaze: Intermittent downward deviation of the eyes when infant is awake (absent during sleep); may be overcome with oculocephalic rotation or "Doll's head" maneuver; usually resolves by 6 mo of age; must be distinguished from "setting sun sign" (downward gaze in primary position sometimes with eyelid retraction) that may be seen in the setting of hydrocephalus.

Tonic upgaze: Less common than tonic downgaze; may be a variant of hereditary downbeat nystagmus.

OCULAR MYOPATHIES AND MYASTHENIA GRAVIS: Extraocular muscles are thought to have higher energy demands than skeletal muscles due to smaller motor unit sizes, higher motor neuron discharge rates, higher blood flow, and higher mitochondrial volume fractions; they are therefore thought to be especially sensitive to mitochondrial and neuromuscular disorders[62,63] (see Chapter 6 for further discussion).

Chronic progressive external ophthalmoplegia: Insidious onset of slowly progressive, symmetric, external ophthalmoplegia, and blepharoptosis, seen in a variety of mitochondrial diseases; **Kearns–Sayre** syndrome includes a triad of CPEO, pigmentary degeneration of the retina, and heart block; when suspected, a cardiac workup should be pursued.

Myasthenia gravis: Characterized by selective fatigability of skeletal muscles because of impairment at the level of the neuromuscular junction that may be isolated to ocular muscles (ocular myasthenia) or may include ocular muscles as part of a more diffuse systemic process.

Congenital myasthenia syndromes: Patients present shortly after birth or in early childhood; distinct from myasthenia gravis insofar as underlying etiology is *not* secondary to an autoimmune process and therefore patients do not respond to immunosuppressive therapy; patients present shortly after birth or in early childhood; by definition must not have serum antibodies to acetylcholine receptor (AChR) or muscle-specific kinase protein (MuSK). Treatment includes acetylcholinesterase inhibitors.

Juvenile myasthenia gravis: Classic autoimmune process involving antibodies against the neuromuscular junction. Ptosis and diffuse opthalmoplegia may be presenting symptoms. Evaluation includes serum antibody testing: AChR blocking, binding, and modulating as well as MuSK-antibody testing, although many patients with myasthenia gravis may be seronegative; lab testing for associated conditions, including thyroid disease. EMG is useful to establish the diagnosis; imaging of chest to exclude thymoma. Treatment includes immunosuppressive agents, acetylcholinesterase inhibitors.

Nystagmus and Ocular Oscillations

Nystagmus may be congenital, latent (present on occlusion of one eye), or acquired; in cortical vision loss, usually nystagmus is not present, but may be present in children with SVI due to periventricular leukomalacia; should be distinguished from roving eye movements (slow, aimless drifting of the eyes back and forth) in children with very poor visual function. By definition, nystagmus is distinguished by other oscillations as the initial phase of eye movement is a slow phase.

INFANTILE NYSTAGMUS: Conjugate, rhythmic, oscillation of the eyes, usually horizontal; pendular or jerk nystagmus; sometimes called congenital nystagmus, but rarely appears at birth except in familial cases. **Genetics:** Isolated infantile nystagmus may be sporadic or follow X-linked, autosomal dominant, or autosomal recessive pattern. **Presentation:** Usually onset is between 8 and 12 wk of age; patients may manifest head turn to keep eyes in "null zone," in which nystagmus is least marked and visual acuity is best (Table 21.4).

TABLE 21.4 Characteristics of Infantile Nystagmus

Binocular and conjugate
Uniplanar (plane of nystagmus unchanged in all positions of gaze)
Similar amplitude in both eyes
Dampened by convergence
Increased by attempted fixation, intense visual effort, or anxiety
No oscillopsia
Inversion of optokinetic reflex (induced nystagmus in opposite direction to that expected)
Can frequently identify "null zone"
Associated head nodding or oscillation (10%)

Adapted from Dell'Osso LF, Daroff RB. Nystagmus and saccadic intrusions and oscillations. In: Glaser JS, ed. *Neuro-ophthalmology.* Philadelphia, PA: Lippincott Williams & Wilkins; 1999:369–401, with permission.

Evaluation: Must evaluate for primary sensory visual deficit (found in ~50% of cases) or features that may suggest an underlying neurologic etiology (acquired nystagmus, vertical/torsional component to nystagmus, unilateral); clinical features of nystagmus alone cannot reliably predict presence or absence of sensory deficit. **Neuroimaging:** May be indicated to exclude an underlying neurologic basis for eye movements. **Treatment:** Optimize visual acuity with appropriate refractive correction if indicated, low vision evaluation, strabismus surgery can help to ameliorate a significant torticollis related to the null zone for the nystagmus.

LATENT NYSTAGMUS (FUSION MALDEVELOPMENT NYSTAGMUS SYNDROME): Jerk nystagmus that occurs with monocular occlusion; the jerk or fast phase is toward the uncovered eye when the other eye is occluded; seen in association with processes that disrupt the development of binocular fusion (e.g., in children with infantile esotropia). **Manifest latent nystagmus:** May be present with both eyes open when there is amblyopia or strabismus; one eye is functionally occluded by cortical suppression, and both eyes develop horizontal jerk nystagmus increasing with abduction of fixating eye; can be difficult to distinguish from infantile nystagmus.

SPASMUS NUTANS: Constellation of nystagmus, head nodding, and torticollis; nystagmus may be asymmetric and sometimes monocular (most common cause of unilateral nystagmus); begins in 1st 18 mo (usually 6–12 mo of age), resolves usually within 1 to 2 y of onset but may persist for up to 8 y. **Evaluation:** *MRI* to exclude optic pathway glioma, which may present similarly and cannot easily be distinguished from spasmus nutans on the basis of the clinical presentation alone.

PERIODIC ALTERNATING NYSTAGMUS (PAN): Reversal in direction of nystagmus at ~2-min intervals; transition period may include upbeating or downbeating nystagmus or square-wave jerks. May be congenital or associated with neurologic disease. **Congenital PAN:** Up to 17% of children with infantile nystagmus have periodic alternations; associated with albinism. **Acquired PAN:** Usually seen in older children and adults; causes include multiple sclerosis, posterior fossa lesions, cerebellar degeneration, hydrocephalus, Arnold–Chiari malformation.

NYSTAGMUS ASSOCIATED WITH NEUROLOGIC DISEASE:

Seesaw nystagmus: Pendular nystagmus with elevation and intorsion of one eye, accompanied by depression and extorsion of the other eye; usually seen in patients with tumors involving the suprasellar/parasellar region (in children consider craniopharyngioma); also characteristic of achiasmia; rarely congenital.

Dorsal midbrain syndrome (Parinaud syndrome): Convergence-retraction nystagmus with upward gaze paresis, light-near dissociation, and upper lid retraction (Collier sign), due to compression of the dorsal midbrain. **Etiology:** Suggestive of congenital aqueductal stenosis in infants; pineal region tumors including pinealoma, germinoma, or tectal glioma in school-age children; shunt failure in older children with hydrocephalus.

Upbeat nystagmus: Fast phase up in primary position of gaze; associated with brainstem lesions.

Downbeat nystagmus: Fast phase down in primary position of gaze; associated with lesions at the cervicomedullary junction (e.g., Chiari malformation), cerebellar lesions, including spinocerebellar degeneration, lithium toxicity.

OCULAR OSCILLATIONS

Opsoclonus: Rapid, involuntary, multivectorial, chaotic, conjugate fast eye movements, without intersaccadic interval; called ocular flutter when movements are in the horizontal plane only. **Etiology:** Major diagnostic consideration in children is neuroblastoma; may also occur as part of benign autoimmune encephalitis with polymyoclonia and shock-like torsions of the head and neck ("dancing eyes and dancing feet"); a variety of other causes reported including toxic exposures and infections; in neonates, may be a benign, transient phenomenon. **Evaluation:** *Abdominal imaging and urinary catecholamines* to evaluate for neuroblastoma; pareneoplastic panel to identify antineuronal antibodies (may be present even if neuroblastoma is occult). **Treatment:** ACTH associated with best early response in paraneoplastic opsoclonus; steroids, intravenous immunoglobulin and plasma exchange also used; autoimmune cases responsive to corticosteroids or intravenous immunoglobulin.

Disorders of Eyelid Function

CONGENITAL PTOSIS: Previously thought to be a congenital myopathy, but now recognized as a congenital cranial dysinnervation syndrome, with misdirection of levator innervation to the ipsilateral superior rectus; characterized by excessive elevation of the ipsilateral eye beneath the ptotic eyelid in upgaze, but no vertical deviation in primary gaze; several genetic loci identified.[64,65]

MARCUS GUNN JAW WINKING (TRIGEMINO-OCULOMOTOR SYNKINESIS): Usually presents as variable unilateral ptosis in the neonatal period; when infant nurses, lid jerks upward with each sucking movement; thought to be due to aberrant activation and co-contraction of third cranial nerve innervating the levator palpebrae superioris and a branch of the motor division of the trigeminal nerve innervating the pterygoid muscles of the jaw.[66]

EXCESSIVE BLINKING: Spontaneous blink rate varies with age (under 18 mo: 2–5/min; older children: 10/min; >20 y: 20/min); may occur in tic disorders or in seizures; when accompanied by absence seizures, suggestive of Jeavons syndrome (eyelid myoclonia with absences), where jerking of the eyelids and upward deviation of the eyes is associated with irregular spike-wave discharges occurring after eye closure and evoked by photic stimulation.[67]

HORNER SYNDROME: Results from lesions affecting sympathetic innervation of the eye; clinical features include miosis with greater anisocoria in darkness, mild upper lid ptosis (1–2 mm) and elevation of lower eyelid (reverse ptosis), iris heterochromia with the lighter pupil on the affected side; if lesion is proximal to the carotid bifurcation, anhidrosis may be present. **Etiology:** Most important consideration is neuroblastoma, found in 3.5% of children with Horner syndrome; may be congenital or due to perinatal trauma (e.g., brachial plexus injury)[68,69]; ipsilateral agenesis of the internal carotid artery[70,71]; carotid dissection[72]; mass lesions other than neuroblastoma (e.g., ganglioneuroma, neurofibroma in patients with NF1).[73] **Evaluation:** Confirmation of diagnosis may be done with pharmacologic testing. *MRI/MRA of brain/neck/upper chest* indicated to evaluate for congenital masses and vascular anomalies with *urine catecholamine metabolite testing* (homovanillic acid and vanillylmandelic acid) for neuroblastoma.[69]

OPHTHALMOLOGIC MANIFESTATIONS OF NEUROCUTANEOUS DISORDERS

Specific neuro-ophthalmologic findings in Table 21.5. Please see Chapter 12 for complete details of these disorders.

TABLE 21.5 Ophthalmologic Manifestations of Neurocutaneous Disorders

NF1	Lisch nodules, optic nerve and optic pathway glioma, corneal nerve enlargement, retinal hamartomas; plexiform neurofibromas of the eyelid
NF2	Posterior subcapsular cataract, retinal hamartoma
Tuberous sclerosis	Retinal or peripapillary astrocytic hamartoma (75%), RPE depigmentation
von Hippel–Lindau	Retinal hemangioblastoma, optic disc hemangioma
Sturge–Weber	Glaucoma; choroidal hemangioma
Klippel–Trénaunay–Weber	V1 port-wine stain, orbital varix, heterochromia irides, retinal varicosities, choroidal angioma
Ataxia-telangiectasia	Conjunctival telangiectasia, oculomotor apraxia, ophthalmoplegia

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22 Central Nervous System Infections in Children

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OVERVIEW OF CNS INFECTIONS IN CHILDREN

Important to interpret general features of CSF. Normal values vary by age of the patient (Table 22.1).

Meningitis

Acute Meningitis[1,2,3]

Definition: Inflammation of the meninges (dura, pia, and arachnoid) or leptomeninges (pia and arachnoid). **Pathogenesis:** (1) Hematogenous dissemination of microorganisms from distant site of infection. (2) Spread of organism through emissary veins from infected sinuses, middle ear, or mastoid. **Clinical Presentation**[1,4]**:** Classic signs include fever, headache, vomiting, and nuchal rigidity. However, depending on age of patient, these signs may be absent. Signs of increased intracranial pressure may also be apparent such as Cushing triad and cranial neuropathies (specifically a 6th nerve or 4th nerve palsy). Seizure occurs in up to 40% of affected children.[5]

Acute Bacterial Meningitis

Presents in one of two ways: (1) sudden fulminant onset, with rapid progression, seen through shock, purpura, DIC, coma, and/or death within 24 h, or (2) signs of meningitis preceded by several days of fever, URI, or GI illness leading to increasing lethargy and irritability.

Viral/Aseptic Meningitis

Defined as presence of clinical and lab signs of meningitis but with negative cultures. While it is often thought that a more fulminant course of meningitis or encephalitis is suggestive of a bacterial etiology, this is not always the case. Systemic features such as rash, anorexia, arthralgias, and malaise represent viremia and can suggest a viral etiology. **Clinical presentation by age:** Neonate: In the newborn period, fever may be absent. Common

TABLE 22.1 Normal CSF Features by Age

	Preterm	Term (0–30 d)	Child
WBC (count/μL)	0–25	7.3 ± 13.9	0–7
Gluc (mg/dL)	24–63	51.2 ± 12.9	40–80
Prot (mg/dL)	65–150	64.2 ± 24.2	5–40

Custer JW. Blood chemistries and body fluid. In: Custer JW, Rau RE, eds. *The Harriet Lane Handbook*. 18th ed. Philadelphia, PA: Elsevier; 2009:686.

presentations include apnea, tachypnea, seizure, focal neurologic deficit, depressed state of consciousness, irritability, failure to thrive, emesis, jaundice, sepsis, hypothermia, hyperthermia, opisthotonic posturing. **Child and adolescent:** Headache (difficult to elicit in child <3 y), fever, nuchal rigidity, photophobia, phonophobia, vomiting, pain with eye movement, petechial rash. **Physical exam:** Nuchal rigidity: Evidenced by Kernig sign (flexion of the hip 90° with subsequent pain upon extension of the leg) and/or Brudzinski sign (involuntary flexion of the knees and hips after passive neck flexion while supine). Also try chin to chest (more sensitive in early stages) or ask child to kiss his/her knee.[5] Both considered positive if pain elicited. **Note**: Lateral neck movement should not produce pain.[5] Full/bulging anterior fontanelle in neonatal period—only present in ~⅓ of patients.[1] This is a late sign. Papilledema rare in acute meningitis and suggests more chronic etiology, such as venous sinus thrombosis, idiopathic intracranial hypertension, chronic forms of meningitis. **Cranial Neuropathies** suggestive of increased ICP include abducens/6th nerve palsy most commonly. Others include trochlear/4th nerve, oculomotor/3rd nerve palsy, or trigeminal/5th nerve palsy less commonly. These are often considered false localizing signs. An oculomotor/3rd nerve palsy indicates uncal herniation. Other physical exam findings such as lymphadenopathy, hepatosplenomegaly, rash, and oral lesions may accompany meningeal signs and when present, speak toward a viral etiology. **Etiology:** Common bacteria by Age[1,4,6]: Neonates: *Streptococcus agalactiae*, *Escherchia coli*, *Listeria monocytogenes*, *S. pneumoniae*. Children & adolescents: *Neisseria meningitidis, S. pneumoniae, Haemophilus influenzae*. Common etiologies of viral meningitis: See Tables 22.2 and 22.3. **Diagnostic workup:** Blood culture: Important—reveals responsible bacteria in 8% to 90% of cases.[1] LP: Timing of LP guided by clinical suspicion for increased ICP. Signs of increased ICP: empiric antibiotics > neuroimaging > consider LP upon results (short course of antibiotics not thought to significantly alter CSF findings). No signs of increased ICP: LP with empiric antibiotics. Contraindications for immediate LP: (1) evidence of increased ICP (Cushing triad, cranial neuropathies [specifically a 6th nerve or 4th nerve palsy] in setting of altered consciousness), (2) severe cardiopulmonary compromise, (3) infection of the overlying skin, (4) underlying bleeding disorder. (thrombocytopenia is a relative contraindication)[1,6] (see Table 22.4) **Differential diagnosis:** Peritonsillar abscess, brain abscess, retropharyngeal abscess.

Treatment: Do not wait for CSF results before starting treatment!

TABLE 22.2 DNA Viruses

Family	Type	Spread	Season
Herpesviridae	HSV-1,[1] HSV-2,[2] CMV, VZV, HHV-6[3]	Human contact	All seasons
Adenoviridae	Adenovirus	Human contact	Winter/late fall

[1]HSV-1 most common cause of sporadic encephalitis.
[2]HSV-2 most common cause of herpes infection in the neonate due to maternal transmission.
[3]HHV-6 more common in immunocompromised patients.

Adapted from Swaima SF, Ashwal S, Ferriero DM, et al. *Pediatric Neurology: Principles and Practice.* 4th ed. St. Louis, MO: Mosby; 2006:1569–1684 and Roos KL, Greenlee JE. Meningitis and encephalitis. *Continuum (Minneap Minn).* 2011;17(5):1010–1023, with permission.

TABLE 22.3 RNA Viruses

Family	Type	Spread	Season
Picornaviridae	Non-polio enteroviruses Coxsackievirus Echovirus Numbered enteroviruses[1] Poliovirus 1–3	Fecal–oral	Summer & early fall
Togaviridae	EEE, West Nile	Mosquito	Summer and fall
Paramyxoviridae	RSV, measles and mumps, parainfluenza	Human contact	Winter
Orthomyxoviridae	Influenza	Human contact	Winter

[1]Enterovirus: Most common cause of aseptic meningitis.

Adapted from Swaima SF, Ashwal S, Ferriero DM, et al. *Pediatric Neurology: Principles and Practice.* 4th ed. St. Louis, MO: Mosby; 2006:1569–1684 and Roos KL, Greenlee JE. Meningitis and encephalitis. *Continuum (Minneap Minn).* 2011;17(5):1010–1023, with permission.

Antibiotics for suspected bacteria[1,5]:

- Neonate/infant <3 mo: Ampicillin + Cefotaxime or Gentamycin
- Neonate/preterm: Vancomycin + Ceftazidime
- >3 mo to <50 y: Ceftriaxone or Cefotaxime
- Drug-resistant *S. pneumoniae*: Ceftriaxone + Vancomycin or Rifampin
- Neurosurgery, shunt, or head trauma: Ceftazidime + Nafcillin or Flucloxacillin (or Vancomycin + aminoglycoside)
- Prophylaxis for contacts of patients with *Neisseria*: Rifampin (2 d), I.M. Ceftriaxone (1 dose), Azithromycin (1 dose)

Steroids: Recommended early in course of suspected pediatric bacterial meningitis. Thought to decrease CNS inflammation and ICP, while decreasing overall mortality, acute complications, and long term sequelae (specifically auditory function). There is likely no benefit if given 1 h after antimicrobials. Dexamethasone 0.6 mg/kg/d in four divided doses for 2 to 4 d should be given before or with the first dose of antibiotics. Use in the neonatal period has not been established.[1,5] **Complications of meningitis:** Hydrocephalus, subdural effusions, epidural abscess, venous sinus thrombosis, increased ICP, hyponatremia (SIADH), seizures, cerebral

TABLE 22.4 CSF Analysis

	Pressure	Appearance	WBC	Cell Type	Protein	Glucose
Bacterial	↑↑	Cloudy	50–100/>1,000	PMN	↑/↑↑↑	Low
Viral	Nml/↑	Clear	N/10–1,000	Lymph	Nml/↑	Nml
TB	↑	Clear	10–1,000	Lymph	Nml/↑↑	Nml/Low
Fungal	↑	Clear	N/100–1,000	Mixed	Nml/↑↑	Nml/Low

Note: Pleocytosis with lymph predominance may be present in early stages of acute bacterial meningitis (e.g., Listeria)[6]. PMN pleocytosis may be present in acute viral meningitis.[3]

Adapted from Swaima SF, Ashwal S, Ferriero DM, et al. *Pediatric Neurology: Principles and Practice.* 4th ed. St. Louis, MO: Mosby; 2006:1569–1684 and Behrman R. *Nelsons Textbook of Pediatrics.* 18th ed. Philadelphia, PA: Saunders; 2007:2513–2524.

vasculitis. **Neurologic sequelae:** Deafness is the most frequent neurologic sequelae of bacterial meningitis; frequency up to 15% to 30% (highest risk with *S. pneumoniae*).[1] Epilepsy in <5%.[1] Intellectual disability, motor impairment, hemiparesis, blindness, learning disability.

Chronic Meningitis

Definition: Clinical symptoms of meningitis occurring for >4 wk. **Differential diagnosis:** *Mycobacterium*, viral meningitis, parasitic, neoplastic.

TB MENINGITIS[1]: Secondary to infection with *M. tuberculosis*.

Clinical presentation: Thought to be subacute to chronic, but may present acutely. **History:** May be significant for family member with TB or from an endemic country. **Pathogenesis:** CNS infection from spread of primary lesion from another source in the body. **Signs and symptoms:** Vague presentation surrounded by overall poor health. Children tend to be irritable with low-grade fever, nausea, vomiting, and headache. GI symptoms are often prominent. Depressed level of consciousness may develop in later stages. **Physical exam:** Nuchal rigidity is typically absent, papilledema may be present. Tuberculous lesions may be present on exam of choroid of the eye. Unilateral or bilateral CN deficits may be present (specifically CN7), secondary to basilar meningitis. **Diagnostic workup:** Neg. CXR and neg. PPD does not exclude TB meningitis. PPD positive in up to 60%, CXR positive from 50% to 90%. Brain MRI and head CT may show parenchymal lesions, evidence of infarction, or tuberculomas. Hydrocephalus may also be present. Consider spine imaging if exam shows spinal involvement. **Treatment:** Isoniazid, rifampin, ethambutol, streptomycin, pyrazinamide. Course: 2 mo of isoniazid, rifampin, pyrazinamide, and an aminoglycoside (given with initial therapy until drug susceptibility is known) or ethionamide daily, followed by 7 to 10 mo of isoniazid and rifampin once a day or twice a week (9 to 12 mo total) for drug-susceptible *M. tuberculosis*. If the patient is from an area with known resistance to streptomycin, then kanamycin, amikacin, or capreomycin may be used instead.[7] Steroids: Indicated for children with TB meningitis, although evidence is incomplete. Prednisone 2 mg/kg/d (max of 60 mg/d) for 4 to 6 wk is thought to be appropriate with a taper afterward.[1,4,7] **Sequelae:** Neuro: visual and auditory impairment, hemiparesis, intellectual disability, seizures. Other: Endocrinopathies such as DI, precocious puberty, obesity, and growth retardation may develop with lesions involving hypothalamus and basal cisterns.

Fungal Meningitis

Epidemiology: CNS fungal infections are quite rare in healthy children. Risk factors include VLBW infants, HIV infection, oncologic disease (e.g., leukemia or lymphoma), s/p transplant (bone marrow or solid organ), recent neurosurgery, indwelling catheters.[8] Children at risk tend to be immunocompromised and may be unable to mount an inflammatory response. Index of suspicion must be high as *fever and meningeal signs can be absent*. **Pathogenesis:** CNS infection usually secondary to a primary infection (e.g., pulmonary infiltration).

Common Etiologies[9,10]: *Candida:* Yeast. Common organisms: *Candida albicans* and non-albicans species. **Pathogenesis**: *Candida* reaches the brain and other organs secondary to vascular dissemination. **Clinical presentation**: Meningitis or abscess formation. Symptoms include lethargy, fever,

vomiting, and other signs meningitis. **Diagnosis:** Blood cultures. CSF with PMNs, protein 100 mg/dL, glucose nml or slightly ↓. **Treatment**: Amphotericin B or fluconazole is alternative.

Cryptococcus neoformans: Encapsulated yeast found in soil. **Pathogenesis:** Organisms harbored in feces of pigeons and other birds. Transmission secondary to inhalation and/or ingestion. **Clinical presentation:** Meningitis/encephalitis as well as abscess and granuloma. *Insidious chronic headache is main feature*, also N/V, fever, photophobia, and change in mental status. **Diagnosis:** Latex agglutination for detection of cryptococcal Ag (most sensitive and specific), India Ink preparation of organism (50% positive), or CSF culture. (75% positive).[9] CSF may be normal but usually shows increased opening pressure, WBC <100 cells/mm^3 (lymphocytic predominance), glucose <40. **Treatment:** IV amphotericin B and flucytosine by mouth.

Histoplasma capsulatum: Dimorphic fungus. Grows as a yeast at body temp and mycelia form at room temp. Endemic to central United States (Ohio and Mississippi River Valley). **Pathogenesis:** Spores present in damp environments (caves, coops, open fields) and become airborne in dry climate. **Clinical presentation:** Intracranial hypertension, confusion, seizures, urinary incontinence. **Diagnosis:** CSF histoplasmal Ab (positive in 70%–90%), Ag (positive in 40%–70%), and culture (positive in 20%–60%).[10] **Treatment:** Amphotericin B recommended for disseminated disease and other serious infections. Itraconazole may also be effective.

Aspergillus:[1,9,10] **Clinical Presentation:** (1) Intracranial space-occupying lesion. (2) Involvement of sinuses, skull base, cranial nerves, and brain. (3) Stroke-like symptoms. May also present with altered mental status, seizures, and focal deficits. **Diagnosis:** Biopsy from lung, sinus, brain, and skin is gold standard. Serum galactomannan testing available but high false-positive. **Treatment:** Voriconazole (not studied in HIV-infected children), amphotericin B.

Encephalitis

Definition: Infection of brain parenchyma causing change in mental status or behavior. **Clinical presentation:** Fever (suggests infectious), headache, confusion, behavioral abnormalities, decreased level of consciousness. **General workup:** History and physical exam are key. MRI with gadolinium and LP.

HSV Encephalitis[1,11,12]

HSV-1: Acquired by oral transmission during childhood. Children may have vesicular pharyngitis, gingivostomatitis, lesions of the face and mouth. More common in childhood and early adulthood. HSV-1 is the most common form of sporadic encephalitis.

HSV-2: Typically acquired by sexual contact causing genital lesions in young adults (although may be asymptomatic). Acquired by neonates through maternal transmission. Most common cause of HSV in the neonatal period. HSV-2 manifests as: (1) disseminated disease involving multiple organs, (2) localized CNS disease, (3) disease localized to the skin, eyes, and mouth. Initial signs will present from birth to 4 wk of life. CNS disease typically manifests between the 2nd and 3rd week of life.[7] HSV-2 is the most common form of herpes meningitis. **Pathogenesis:** (1) direct invasion via trigeminal nerve after episode of primary HSV-1 infection of oropharynx. (2) CNS

invasion after viral reactivation. (3) reactivation of latent HSV already in CNS. **Clinical presentation:** Children/young adults: fever, altered mental status, seizure (partial or generalized), behavioral change, aphasia, mutism, focal neurologic signs. High index of suspicion is key as children can progress rapidly and may simply present with vague olfactory hallucination. Neonates: apnea, FTT, seizure, hypo/hyperthermia, focal neurologic signs. **Diagnostic workup:** CSF: Lymphocytic pleocytosis with normal glucose. RBC/xanthochromia may be present. CSF PCR is gold standard (highly sensitive and specific),[12] may be falsely negative in 1st 72 h. Viral culture rarely helpful. Neuroimaging: MRI findings—T2 prolongation in temporal lobe or insula. CT findings—focal hemorrhagic lesions localized to medial temporal lobes, insula, and orbital regions of frontal lobes. Extratemporal regions often involved in children.[11] EEG: focal or diffuse slowing, PLEDS. **Treatment:** Acyclovir 14 to 21 d. Dose: <35 wk postconceptual age: 40 mg/kg/d divided q12h; >35 wk post-conceptual age: 60 mg/kg/d divided q8h. **Neurologic sequelae and prognosis:** Developmental delay, epilepsy, personality change/behavioral dysregulation, attention deficit. 70% of patients die without treatment.[1,11]

EBV Encephalitis[1,13]

Pathogenesis: Neurologic sequelae likely secondary to immunologic phenomena as opposed to viral replication. **Clinical presentation:** Prodromal symptoms common prior to neuro symptoms and range from several days to weeks. Behavioral changes, altered mental status, fever, headache, sore throat, lymphadenopathy, vomiting, seizures, focal neurologic deficits. **Diagnostic workup:** Coinfection with other pathogens is common. Peripheral blood: elevated serum transaminase, thrombocytopenia, leukopenia, atypical lymphocytes. CSF: EBV PCR. MRI: Increased T2-weighted signal in gray matter structures as well as subcortical white matter. **Treatment:** Consider steroids and ganciclovir on case-to-case basis. **Neurologic sequelae:** Ranges from encephalitis, aseptic meningitis, ADEM, transverse myelitis, acute cerebellar ataxia, Bell palsy, Alice in Wonderland syndrome, Guillain–Barré syndrome.[1,13]

VZV[1,9]

Pathogenesis: After infection, VZV lies dormant in sensory ganglion cells. **Clinical presentation:** Prodrome usually present, consisting of malaise, cough, rhinorrhea, and fever followed by maculopapular rash. Children contagious 2 d before and 5 d after the rash. **Diagnostic workup:** CSF VZV DNA PCR to assess for neurologic sequelae. **Treatment:** Acyclovir. Corticosteroids are indicated in cases of vasculitis, ADEM, and myelopathy. **Neurologic sequelae:** Found in <0.1% of healthy children with chicken pox and include aseptic meningitis, encephalitis, acute cerebellar ataxia, ADEM, Bell palsy, Ramsay Hunt syndrome (facial palsy, pain, unilateral hearing loss), CNS vasculitis with potential for stroke, Reye syndrome (vomiting, coma, increased ICP in setting of aspirin therapy). Zoster may develop weeks to years after primary infection.

CMV Encephalitis[1]

Clinical presentation: Occurs mostly in immunocompromised children. Symptoms are nonspecific and may include malaise, low-grade fever, and headache. **Pathogenesis:** Acquired by children with contact of humans that shed CMV in saliva or urine. Blood and organ transplant may also aid in transmission to children. **Diagnostic workup:** Detection of CMV DNA in

urine, serum, CSF. **Imaging:** MRI may show demyelinating lesions, or evidence of cortical or periventricular inflammation. **Treatment:** ganciclovir. **Neurologic sequelae:** Meningitis, encephalitis, Guillain–Barré syndrome, retinitis, myelitis.

Eastern Equine Encephalitis[1,5]

Highest mortality among arthropod-borne encephalitis. **Epidemiology:** Endemic to the states bordering the Atlantic Ocean and Gulf of Mexico, most prevalent during summer months. **Clinical presentation:** Two distinct presentations have been observed: (1) Abrupt onset with fevers, vomiting, lethargy, and seizures. (2) Prior prodrome consisting of malaise, arthralgias, headache, fever. **Diagnostic workup:** EEE-specific IgM in serum and CSF as well as viral culture. EEG with nonspecific diffuse slowing. Imaging studies may be normal or may show edema, may involve thalamus and/or basal ganglia. **Treatment:** Supportive care.

Subacute Sclerosing Panencephalitis (SSPE)

A progressive neurodegenerative disease. **Clinical presentation**: Children present years after measles infection with myoclonus, behavioral and intellectual decline, extrapyramidal dysfunction, seizures, and abnormal vision.[14] **Pathogenesis**: Unknown. **Diagnostic workup:** Based on clinical presentation as well as MRI and EEG findings. History commonly suggestive of measles infection. CSF and serum measles antibody is key. MRI may be normal in the early stages of disease. Most common findings include high T2-signal intensity in the periventricular and subcortical white matter as well as brain atrophy. Involvement of the corpus callosum, brainstem, Cb, and basal ganglia have been documented but are rare. **Prognosis:** Complete or partial remission may occur; however, death is a frequent result.

CNS Manifestations of Lyme[7,15,16]

Epidemiology: Peak seasons are summer and early fall. Endemic to the northeastern and mid-Atlantic United States. **Pathogenesis:** Transmission of the spirochete *Borrelia Burgdorferi* from animal reservoirs to human hosts via tick vector. **Stages of Disease:** Stage 1: Early localized disease/localized erythema migrans. Stage 2: Early disseminated/blood-borne dissemination/spirochetemia and antibody response. 15% of patients manifest multiple erythema migrans.[7] Neurologic manifestations are most common during this stage and can be seen within weeks to months. Stage 3: Late disease/chronic arthritis is most common feature; however, late syndromes of CNS and peripheral nervous system occur. Late disease is uncommon in children who are treated in the early stage. **Clinical manifestations:** Symptoms may be vague and consist of fatigue, malaise, headache, arthritis, low-grade fever. Patients may develop symptoms of lymphocytic meningitis, unilateral or bilateral facial palsy, peripheral neuritis. 2% to 12% of children with Lyme disease present with meningitis.[15] Ddx: Aseptic meningitis (enterovirus). **Diagnostic workup:** In the early stages this is a clinical diagnosis. Lyme titer may be negative in the early stages as antibodies are not detected within the first few weeks of initial infection. Some patients who are treated in the early stage with appropriate antimicrobials may never develop antibodies. **Serologic diagnosis:** Two-step approach: (1) Perform a screening test for serum antibodies with either enzyme immunoassay or immunoflourescent assay (both may yield false-positives due to cross-reactivity of spirochetes in normal oral flora or coexistent spirochetal infection). (2) Positive or equivocal screening tests need confirmation with

a Western blot. Negative screening does not require confirmation. To confirm early disease, IgG and IgM immunoblots are needed. To confirm late disease, only IgG immunoblot is necessary. Lyme PCR is not reliable due to its low sensitivity. **Treatment:** See Table 22.5.

Brain Abscess[1,17]

Pathogenesis: Hematogenous spread or direct spread of the organism. Initially, the lesion is consistent with cerebritis. This may persist for several weeks followed by edema that may create mass effect. The tissue then becomes necrotic and is surrounded by granulation tissue. Brain abscesses may be polymicrobial involving aerobic and anaerobic organisms. **Common organisms:** Mostly anaerobic in nature, streptococcal, staphylococcal, *Bacteroides fragilis*. *Proteus* is common in the neonate. **Predisposing factors:** Brain abscesses tend to occur in children with cyanotic congenital heart disease, sepsis, endocarditis, after neurosurgical procedures, pulmonary infections, infection or trauma of paranasal sinus or otomastoid regions. Immunodeficient/immunodepressed children are also at risk. **Clinical characteristics:** Subacute onset of headache and fever. Focal neurologic signs may be present. Vomiting, confusion, nuchal rigidity, and seizures may also be apparent. **Diagnostic workup:** Blood culture may play a role in isolating the organism. Neuroimaging is key and contrast is needed for definitive diagnosis. **Imaging characteristics:** (1) CT: Low attenuation and a thin wall of slightly increased attenuation. Contrast enhancement of the wall. (2) MRI: Abscess wall is isointense on T1 and hypointense on T2. The center is isointense to hypointense on T1 and hyperintense on T2. Ring enhancement present with contrast. Diffusion studies are key to deciphering abscess from cystic or necrotic tumors. Abscess will have restricted diffusion (hyperintense on DWI, hypointense on ADC). Diffusion abnormalities will normalize 1 to 2 wk after treatment. **Treatment**: Do not delay antibiotics. First control increased ICP. Drainage and surgical incision may play a role followed by antibiotics depending on the stage of the abscess. In the early stage or if multiple abscesses are present, medical therapy is usually the first option. Serial imaging studies will help gage response to medical therapy. **Neurologic sequelae**: Chronic seizures/epilepsy.

TABLE 22.5 Treatment of Lyme Disease

Early Localized Disease	
8 y and older	Doxycycline 100 mg PO b.i.d., for 14–21 d
All ages	Amoxicillin, 50 mg/kg/d, PO divided t.i.d. (max 1.5 g/d) for 14–21 d or Cefuroxime, 30 mg/kg/d in 2 divided doses or 1 g/d for 14–21 d
Early Disseminated and Late Disease	
Facial palsy	Same as early localized disease but for 21–28 d
Meningitis/encephalitis	Ceftriaxone or penicillin: Ceftriaxone 75–100 mg/kg IV or IM daily for 14–28 d. *Or* penicillin 300,000 units/kg IV given in divided doses every 4 h for 14–28 d

Modified from American Academy of Pediatrics. In: Pickering LK, Baker CJ, Kimberlin DW, et al., eds. *Red Book: 2009 Report of the Committee on Infectious Diseases*. 28th ed. Elk Grove Village, IL: American Academy of Pediatrics; 2009:201–732.

Neurocysticercosis[18]

Epidemiology: Most common parasitic disease of the CNS worldwide, endemic to Latin America, Mexico, India, China, and sub-Saharan Africa. **Etiology**: Encysted larvae of *Taenia solium*. **Pathogenesis:** Humans acquire an intestinal infection due to ingestion of undercooked pork. Eggs are transmitted in feces and contaminate produce that indirectly affect humans. There is also direct fecal–oral spread to humans. **Clinical presentation**: Headache, vomiting, focal neurologic deficits, and encephalitis. Infection may be parenchymal or extraparenchymal (uncommon in children). Seizures are the initial presentation in 80% of cases. **Diagnostic workup:** Pathology is the gold standard. Neuroimaging is key. Identification of the scolex is pathognomonic. Cysts found at gray–white junction and mostly prefer parietal lobe. (1) CT: calcified, hyperdense lesion. May have surrounding edema. Multiple cysts have the appearance of a "starry sky." (2) MRI: Isointense or hyperintense relative to white matter on T1. Isointense or hyperintense relative to CSF on T2. Ring enhancement with gadolinium. Calcified lesions are hypointense on all MRI sequences. Serology: Immunologic tests have not proven to be sensitive or specific. CSF: Normal in most parenchymal infections but analysis may be helpful if extraparenchymal. Eosinophilia is present ~⅓ of the time. Radiographs to look for calcified cysts and stool examination for tapeworms are rarely helpful. **Treatment**: Seizures should be treated symptomatically. Corticosteroids have a role in the acute phase. Enhancing lesions represent degenerating cysts; treatment efficacy is unclear in this case. Albendazole is the drug of choice. Praziquantel is second-line.

HIV[6,7,9,19]

Definition: Human retrovirus, HIV-1, and less commonly HIV-2. **Pathogenesis**: Humans are the only known host reservoir. Most children acquire HIV through mother-to-child transmission in utero, at time of birth, or through breastfeeding. Other forms of transmission include sexual contact, percutaneous via contaminated instruments/needles, and mucous membrane exposure to contaminated blood or other body fluids. **Clinical presentation:** Children may be asymptomatic for >5 y. Children present with failure to thrive, generalized lymphadenopathy, thrush, hepatosplenomegaly, opportunistic infections, recurrent diarrhea, and neurologic symptoms, including developmental delay, microcephaly in neonates, and encephalopathy. **Diagnostic workup:** Antibody assays are not reliable within the 1st 3 mo of life due to maternal transfer of antibodies. In children <18 mo of age, the gold standard of diagnosis is HIV PCR assay (95% sensitive, 97% specific).[7] Infant considered positive if 2 separate samples are positive. Infants should be tested in the first 14 d of life, at 1 to 2 mo of age, and at 2 to 4 mo of age. In adolescents and children, enzyme immunoassays are the initial test for diagnosis and are confirmed with Western blot. **Treatment**: Zidovudine after birth for the first 6 wk of life. Adolescents and children, not exposed in utero, should start antiretroviral therapy based on viral load, CD4 count, and clinical grounds. **Neurologic sequelae:** Primary sequelae: HIV encephalopathy, aseptic meningitis, meningoencephalitis, myopathy, peripheral neuropathy. Secondary sequelae: CNS infections with PML/JC virus, toxoplasmosis, CMV, VZV, HHV-6, mycoplasma, fungal infections, primary CNS lymphoma, stroke.

HIV Encephalopathy[6,9]

Clinical presentation: Onset may be 2 mo to 5 y after exposure to the virus. Prominent features are loss of developmental milestones, dementia,

spasticity, and acquired microcephaly. Children may also present with ataxia, movement disorders, myoclonus, and seizure.[9] **Imaging characteristics**: *CT:* cortical atrophy, enlarged ventricles, basal ganglia calcifications. *MRI:* T2 hyperintensities in the periventricular white matter and centrum semiovale. Patchy in the early stages, progresses to diffuse involvement.

Progressive Multifocal Leukencephalopathy (PML)[6,20]

Definition: Progressive demyelinating disease secondary to dormant JC virus infection. **Pathogenesis**: Destruction of oligodendrocytes. **Clinical presentation:** Children may present with slowly evolving deficits such as blindness, sensory loss, hemiparesis, language problems. **Diagnosis:** CSF JC virus DNA PCR. MRI: Increased signal intensity on T2. CT: hypodense non-enhancing white matter lesions. **Prognosis**: Rapid neurologic decline. Death ensues in ~ 6 mo.

VP Shunt Infections[1]

Clinical presentation: Shunt infections tend to be most prevalent ~1 to 2 mo after insertion. They are known to occur in ~5% to 10% of patients. Onset is usually subacute; however, may be acute in the setting of coexistent shunt malfunction. Patients may present with low-grade fever, irritability, vomiting, and other signs of increased ICP. Patients with underlying epilepsy may have increased seizure frequency. Shunt infection must be considered in any child with an indwelling CNS catheter in the setting of fever. Peritonitis may be the presenting feature of a child with a VP shunt infection. **Etiology**: Coagulase-negative staphylococcus or *Staphylococcus aureus*. Gram-negatives and skin flora may also be the cause. **Diagnostic studies:** NCHCT and radiographic shunt series to assess for worsening hydrocephalus, CSF analysis to assess for infection. **Treatment:** Ceftazidime + nafcillin or flucloxacillin (or vancomycin + aminoglycoside).

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