

Febrile Seizures

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ABSTRACT

Febrile seizures (FSs) are the most common cause of pediatric seizures. They are defined as seizures in children age 6 months to 5 years with a temperature higher than 100.4°F, although they are more common at higher temperatures. A family history of FS is the most common risk factor. FSs are classified into three types (simple, complex, or febrile status epilepticus) based on duration and quality, with simple FSs accounting for many cases. Most FSs persist for less than 10 minutes and are self-limiting. Approximately one-third of patients will have recurrence of FSs. Safe and effective prophylaxis for FS has yet to be identified. Most patients will not have any long-term sequelae, although there is an increased risk of epilepsy, particularly for those with febrile status epilepticus. FSs are associated with caregiver anxiety, “fever phobia,” and high health care use, emphasizing the importance of education and reassurance for both the provider and family. [*Pediatr Ann.* 2023;52(10):e388–e393.]

Febrile seizures are the most common cause of seizures in children younger than age 5 years.¹⁻⁵ Similarly, prolonged febrile seizures longer than 30 minutes are the most common pediatric neurological emergency, accounting for one-third of all pediatric prolonged seizures and 1% of all pediatric emergency department (ED) encounters.⁶⁻⁸ Although most febrile seizures are self-limiting and not associated with any long-term sequelae, febrile seizures are associated with significant anxiety among caregivers and “fever phobia,” leading to frequent ED and outpatient visits.^{3,4,9-13}

To meet the definition of febrile seizures, children must be age 6 months to 5 years with a documented fever of

100.4°F or higher and without any other possible cause of seizure, including but not limited to central nervous system infection, metabolic abnormality, severe head trauma, history of afebrile seizures, or preexisting neurological abnormalities.^{1,3-6,9,10,12,14-17}

EPIDEMIOLOGY AND RISK FACTORS

Febrile seizures occur in 2% to 5% of children younger than age 5 years in the United States and Western Europe.^{1,2,4-6,9-13,15,16,18} Multiple studies have demonstrated an increased incidence of 5% to 10% in Asian countries and those of Asian descent, although this finding has not been well explained.^{4,9,12,13} Febrile seizures peak in the second year

of life, with the median age of most studies ranging from 16 to 20 months. Ninety percent of all febrile seizures occur before age 3 years.^{2,4,9,14,18-20}

There is some evidence to suggest that boys have a higher incidence of febrile seizure than their age-matched female counterparts,^{9,12,14} although this has been refuted by other authors.^{4,6} Some studies have also noted a seasonal variation in the incidence of febrile seizures, with a higher incidence in the winter months. This association is attributed to the increase in febrile illnesses typically seen in winter.^{4,18}

The most significant risk factor for febrile seizures is a family history of febrile or afebrile seizures.^{1,2,6,12} Numerous prenatal and neonatal characteristics have also been identified as risk factors for febrile seizures, including intrauterine growth restriction, neonatal intensive care unit stay longer than 28 days, being born small for gestational age, low birth weight, and prematurity.^{5,9,12,14} One large prospective Danish study with more than 2 million participants identified a stepwise increase in the risk of febrile seizure with both decreasing birth weight and decreasing gestational age independently.¹⁴

ETIOLOGY AND PATHOGENESIS

The precise pathogenesis of febrile seizures is not well understood. It is theorized that febrile seizures are an age-dependent response of the immature brain to fever, likely resulting from an enhanced susceptibility of the developing brain to neuronal excitability. Proposed cellular mecha-

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nisms, based in animal models, include excitotoxicity and inflammatory-induced blood-brain barrier dysregulation.^{3,6,9,12,14,17}

Genetics plays a significant role in the development of febrile seizures. Studies have demonstrated that up to 50% of patients with febrile seizures will have a positive family history.^{4-6,12,21} Additionally, the risk of having a febrile seizure is 20% in those with an affected sibling and 33% in those with an affected parent.^{9,17} Twin studies have confirmed these reports, indicating an incidence of 35% to 69% in monozygotic twins and 14% to 20% in dizygotic twins. This association is polygenic, with numerous potential genes identified.^{1,9,12}

There are several common etiologies of fevers that are associated with febrile seizures. Viral illness is responsible for up to 80% of febrile seizures. Common viruses include adenovirus, parainfluenza, and influenza A.^{2,4-6,9,12} The FEBSTAT study demonstrated that up to one-third of patients with febrile status epilepticus (FSE) have positive human herpesvirus 6/7 virology at the time of presentation, indicating that human herpes viruses may be a more common etiology than previously thought.^{19,22} Bacterial illnesses are also known to cause febrile seizures, most commonly acute otitis media, pharyngitis, pneumonia, and shigella gastroenteritis.^{4,9}

Certain vaccinations are also associated with febrile seizures, most notably whole-cell pertussis (which is no longer used in the US) and measles-mumps-rubella (MMR)-containing vaccines.^{2,4,5,9,12} The MMR and varicella vaccine is associated with an excess febrile seizure risk of 35 in 10,000 patients compared with MMR alone at age 1 year.⁵ For this reason, MMR and varicella are given as separate vaccinations at age 1 year. There are reports of febrile seizures after receiving the DTaP-Hib-Hep B-IPV combination

vaccine, although this appears to be less common. A 2019 study published in *Pediatrics* on vaccine-proximal febrile seizures found they were not significantly different from nonvaccine proximal seizures in quality, duration, risk of recurrence, or prognosis.²

MANIFESTATIONS

Febrile seizures often occur in the first 24 hours of illness, sometimes within 1 hour of fever onset, with up to 25% to 50% of caregivers reporting seizures as the first sign of illness.^{4,9,12,21} A seizure occurring more than 3 days after the onset of illness is uncommon and should increase the suspicion for alternative etiologies of seizures.⁹

Most febrile seizures are brief and self-limiting, with an average duration of 4 to 7 minutes before spontaneous termination.^{4,14}

Febrile seizures can occur at any temperature of 100.4°F or higher, although temperatures are often higher than 102°F, with a mean temperature of 103.2°F in the FEBSTAT study.^{9,12,19,21} It was previously thought that a rapid increase in temperature was associated with febrile seizures. More recent data indicate that the overall height of the fever is most predictive of febrile seizures, with the rate of febrile seizures doubling for each degree above 101°F.^{4,9,12}

The clinical features of febrile seizures include loss of consciousness, irregular breathing, foaming of the mouth, pallor or cyanosis, incontinence, repetitive involuntary motor movements, and abnormal eye movements including a fixed gaze or the patient's eyes rolling back, or some combination of these features. There may also be a postictal period of confusion, drowsiness, or irritability.^{4,9,12}

Febrile seizures can be classified into three subtypes:

1. Simple febrile seizures account for 70% to 80% of febrile seizures. They

are defined as generalized tonic-clonic seizures with a duration of less than 15 minutes that do not recur within 24 hours. They can be accompanied by a brief postictal period.^{1,4,9,12,1,9}

2. Complex febrile seizures may be focal or generalized in nature, with a duration of up to 15 to 30 minutes. They may also recur in less than 24 hours or be associated with a prolonged postictal period and other postictal neurological abnormalities, such as hemiparesis (Todd's paralysis).^{1,9,12} Complex febrile seizures account for a quarter of all febrile seizures. In the FEBSTAT study, it was found that, of the complex seizures, 63% were focal, 47% lasted between 15 and 30 minutes, and 22% recurred within 24 hours. These percentages were independent of each other.^{4,19}

3. FSE can be either focal or generalized at onset, although approximately half of focal seizures will progress to generalized seizures throughout the course of the seizure.⁶ FSE has a duration of longer than 30 minutes and does not resolve spontaneously in up to 85% of cases. Estimates vary for what percentage of febrile seizures meet the criteria for FSE, ranging from 5% to 10%.^{4,7,19-21}

One-fourth of patients presenting with febrile seizures have an illness necessitating additional medical care at the time of presentation.²¹ In the FEBSTAT study, one-fifth of patients were diagnosed as having acute otitis media and 1 in 20 was diagnosed as having pneumonia. Approximately 50% of patients were clinically diagnosed as having viral illness requiring outpatient supportive care only.²¹

EVALUATION AND DIAGNOSIS

The evaluation of all febrile seizures begins with a thorough history and physical examination. Vital signs should be monitored throughout the evaluation. The clinical history should elicit the

cause of the fever, including the onset of fever and its relation to seizure onset. The history taker should also elicit a description of the event, determine the seizure duration, and establish the presence of a postictal phase. Clinicians should also inquire about any recent illnesses or antibiotic use, recent vaccinations, immunization status, and personal and family history of seizures, as well as possible ingestions, exposures, or head trauma.^{4,5,9,12}

A thorough physical examination should be performed, including a full neurological examination with fundoscopy. Clinicians should be sure to evaluate for physical examination findings indicative of meningitis, including nuchal rigidity, petechiae, and Kernig/Brudzinski maneuvers. They should also evaluate for any dermatological findings, including port wine stains, ash leaf spots, and café au lait spots, which may indicate underlying neurological abnormalities.^{5,9,12}

Recommendations on additional diagnostic tests have evolved recently. In 2011, the American Academy of Pediatrics recommended against performing lumbar punctures routinely in immunized children presenting with febrile seizures because of a decrease in the prevalence of meningitis. Subsequently, the use of lumbar punctures declined from 11.6% in 2005 to 0.6% in 2019. There is no evidence this recommendation has affected the rate of correctly diagnosed meningitis. Furthermore, in one study of 503 patients presenting with febrile seizures who ultimately had meningitis, all 503 had additional signs of meningitis on physical examination.^{5,18}

Current indications for lumbar puncture vary but generally include the following:^{4,5,9,12,16}

1. Physical examination suspicious for meningitis
2. Seizure duration longer than 30 minutes (FSE)

3. Incomplete vaccination for *Haemophilus influenzae* type b or pneumococcus

4. Recent or current antibiotic use

CSF studies of interest include opening pressures, chemistry, microbiology, and cell count. If lumbar puncture is performed, blood cultures and serum glucose should also be obtained.^{5,9,23}

Electroencephalogram (EEG) is usually not indicated at the time of presentation, with a 2017 Cochrane review concluding there was insufficient evidence to support or refute.²⁴ EEG at the time of presentation may be indicated when there is suspicion for nonconvulsive status epilepticus, such as a delay in return to baseline neurological status or subtle/focal rhythmic motor movements.²⁵ Outpatient EEG may be considered for patients with developmental delays, a family history of epilepsy, complex febrile seizures, and FSE.^{5,9,12,16}

Other imaging modalities, such as magnetic resonance imaging or computed tomography, should only be considered if there is a concern for increased intracranial pressure, focal abnormalities (focal features by history or on the neurological examination), suspected structural pathology, or significant head trauma.^{9,12,16}

Routine laboratory tests are also not indicated in most cases. If the patient is well appearing, the risk of hypoglycemia or metabolic/electrolyte abnormalities is extremely low. Evidence also demonstrates that there is no increased risk of urinary tract infection, pneumonia, or bacteremia in patients presenting with febrile seizures compared with fevers alone. As a result, the approach to the evaluation of fever is unchanged. Complete blood count, comprehensive metabolic pan-

el, and urinalysis are not indicated unless the patient appears sick or is encephalopathic, the source of the fever is obscure, or there is a concern for dehydration.^{5,9,12,16}

Possible differential diagnoses for this presentation are described in **Table 1**.⁹

MANAGEMENT AND PREVENTION

Febrile seizures often spontaneously resolve before presentation and do not require any further management.^{4,9}

However, the longer a seizure persists the less likely it is to terminate spontaneously; for example, fewer than 15% of FSE cases resolves without intervention.^{4,7-9} Antiepileptic drugs (AEDs) are indicated for any seizure with a duration longer than 5 minutes. First-line AEDs are benzodiazepines, specifically lorazepam or diazepam.^{4,5,7,8,12} A 2018 Cochrane review comparing 0.1 to 0.2 mg/kg of intravenous diazepam to 0.05 to 0.1 mg/kg of intravenous lorazepam concluded neither was superior, with similar cessation rates (72.9% vs 72.1% respectively) and low rates of adverse events.^{26,27} Alternative benzodiazepines may also be used, including rectal (0.5 mg/kg), buccal (0.5 mg/kg), and intranasal (0.2 mg/kg) diazepam or midazolam (0.2 mg/kg).^{4,7,8} Non-benzodiazepine AEDs may be used as second-line medications, particularly for prolonged febrile seizures, as more than 75% of all patients in FSE will require more than 1 AED to achieve seizure cessation.^{4,7,9,16,26} The most commonly used second-line medications include fosphenytoin/phenytoin (20 mg/kg loading), phenobarbital (20 mg/kg), levetiracetam (60 mg/kg), and valproic acid (20 to 40 mg/kg). In cases where multiple AEDs are needed, a second dose of benzodiazepines may

be given after 5 minutes. If seizure activity is ongoing after an additional 5 to 10 minutes, nonbenzodiazepine AEDs should be considered.^{4,7-9,16,28}

Although most patients will not require additional management, the use of AEDs increases the risk of requiring respiratory support, with up to 48% of those in FSE receiving positive pressure ventilation or intubation in the ED. This risk is highest with the use of multiple AEDs.^{7,8,27}

Additional recommended management includes any indicated treatment of the underlying cause of fever and antipyretics for comfort.^{9,12,13}

Most cases of febrile seizures will not require admission and patients may be discharged to home after a brief observation period at their baseline neurological status. Indications for admission include serious infection, prolonged or focal neurological abnormalities, delayed recovery, and the need for ongoing respiratory support.^{4,9}

Caregiver guidance is also an important part of febrile seizure management, including reassurance and education regarding the benign and self-limiting nature of simple febrile seizures as well as proper seizure safety and first aid measures.^{5,9,12}

Prevention of febrile seizure recurrence has been studied extensively in past decades. One area of focus has been the use of prophylactic AEDs, including diazepam, valproic acid, and phenobarbital. Multiple randomized controlled trials (RCTs) and a 2017 Cochrane review found that both continuous and intermittent AEDs are effective in reducing recurrence. However, the rates of adverse events in these studies were high, with 30% to 40% of patients reporting adverse side effects.^{4,9,11,29} There is also some concern that the prophylactic use of AEDs in subsequent fever episodes may mask symptoms of meningitis and

TABLE 1 Differential Diagnosis for Presentations Consistent with Febrile Seizures	
Differential diagnoses	Differentiating factors from febrile seizures
Shivers/chills	No loss of consciousness, no abnormal facial motor movements, no change in respiratory status
Febrile delirium	Acute confusion, no abnormal motor movements or eye rolling
Breath holding spell	No fever, no eye rolling, no tonic-clonic movements
Febrile myoclonus	Myoclonic jerk for minutes to hours
Generalized epilepsy with febrile seizures plus	Older than age 6 years, presence of afebrile seizure

unnecessarily complicate evaluation. As a result, it is generally accepted that the risks of prophylactic AEDs outweigh the potential benefits, and their use is not recommended. Additionally, prophylactic AEDs have not been shown to decrease the risk of developing epilepsy later in life, decreasing their potential therapeutic benefits.^{5,9,11,12,15}

It is, however, reasonable to prescribe abortive medications, most commonly rectal diazepam, to use as a “rescue medication” for the recurrence of seizures longer than 5 minutes while awaiting emergency medical services arrival.

Antipyretics have also been investigated as a potential preventive therapy, but clinical studies have largely failed to demonstrate any benefit. Multiple RCTs and a 2017 Cochrane review determined that both acetaminophen (15 mg/kg) and ibuprofen (10 mg/kg) were ineffective in preventing seizure recurrence.^{4,5,9,11,12,15,29} However, a 2018 Japanese RCT found that rectal acetaminophen every 6 hours for 24 hours after the febrile seizure was effective in preventing seizure recurrence until the resolution of the same illness.^{1,5} It is important to note that, although there is no clear evidence regarding seizure prevention, antipyretics are still rec-

ommended as a comfort measure as would be indicated in any febrile illness.^{9,12,13}

Routine childhood vaccinations are also an important part of febrile seizure prevention as they decrease the rate of febrile episodes in general, leading to lower rates of febrile seizures.⁹

PROGNOSIS

Recurrence of Febrile Seizures

Up to one-third of patients with an initial febrile seizure will go on to have additional febrile seizures. Roughly 15% of patients will have a recurrence in the same febrile illness and 75% of recurrences occur within 1 year of the initial febrile seizure. The risk of recurrence is the same for both simple and complex febrile seizures.^{1-5,9-12,15,16} Risk factors for recurrence include seizure onset within 1 hour of fever onset, age younger than 18 months at the time of initial febrile seizure, a family history of seizures, and below-average fever at seizure onset. Studies have found that there is a stepwise increase in recurrence risk with the presence of each additional risk factor with the risk of recurrence as low as 5% to 15% in those with no risk factors and up to 75% to 80% in those with four or more

risk factors.^{1-5,9,12,15} FSE recurrence after initial FSE occurred in 11.6% of patients in the FEBSTAT study, higher than the rate of FSE in those who initially presented with simple febrile seizures.¹⁹

Subsequent Development of Epilepsy

Most patients with febrile seizures will not have epilepsy. Approximately 1% of those with simple seizures and 4% to 8% of those with complex seizures will have epilepsy, compared with 0.5% of the general population.^{1,2,4,9,12,16} Risk factors for afebrile seizures include complex febrile seizures, seizure onset within 1 hour of fever onset, age younger than 1 year or older than 3 years at the time of first febrile seizure, neurodevelopmental abnormalities, and a family history of epilepsy. The number of simple febrile seizure episodes is not predictive of epilepsy development.^{4,5,9,12,15} Data indicate that 5% to 10% of patients with FSE will have afebrile seizures or epilepsy within 5 years, although 1 cohort within the FEBSTAT study reported 30% of participants were diagnosed as having epilepsy during a 15-year follow-up period.^{3,19}

WHEN TO REFER

Generally, normally developing children with simple febrile seizures do not need to be evaluated by a pediatric neurologist. Specific clinical criteria that indicate a referral to pediatric neurology include complex febrile seizures or FSE, afebrile seizures, febrile seizures in children younger than 6 months or older than 5 years, and children with comorbid neurodevelopmental abnormalities. Referral to pediatric neurology may also be appropriate in other instances, such as a family history of epilepsy or severe

caregiver anxiety related to febrile seizures, at the primary care physician's clinical discretion.

FUTURE DIRECTIONS AND CONCLUSION

Possible future studies regarding febrile seizures are vast but include safe and effective recurrence prophylaxis, as well as the relationship between acute hippocampal injury and subsequent hippocampal sclerosis/mesial temporal lobe epilepsy. Given the spectrum of febrile seizures, there also exists a need to further differentiate the various phenotypes and their association with long-term outcomes.^{4,10,20}

In conclusion, febrile seizures are the most common cause of pediatric seizures and are a source of significant anxiety for caregivers. Febrile seizures are classified by duration and quality, with simple febrile seizures accounting for many cases. Although simple febrile seizures are generally benign and self-limiting, incidents of complex febrile seizures and FSE are associated with increased rates of future epilepsy and more commonly require additional management.

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