Febrile Seizures: Evaluation and Treatment
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ABSTRACT
- **Objective:** To review the current understanding and management of febrile seizures.
- **Methods:** Review of the literature.
- **Results:** Febrile seizures are a common manifestation in early childhood and very often a benign occurrence. For simple febrile seizures, minimal evaluation is necessary and treatment typically not warranted beyond reassurance and education of caregivers. For complex febrile seizures, additional evaluation in rare cases may suggest an underlying seizure tendency, though most follow a typical benign course of febrile seizures. In some cases, as-needed benzodiazepines used for prolonged or recurrent febrile seizures may be of value. There are well described epilepsy syndromes for which febrile seizures may be the initial manifestation and it is paramount that providers recognize the signs and symptoms of these syndromes in order to appropriately counsel families and initiate treatment or referral when warranted.
- **Conclusion:** Providers caring for pediatric patients should be aware of the clinical considerations in managing patients with febrile seizures.

Key words: febrile seizure; Dravet syndrome; GEFS+; PCDH19; FIRES; complex febrile seizure.

A febrile seizure is defined as a seizure in association with a febrile illness in the absence of a central nervous system infection or acute electrolyte imbalance in children older than 1 month of age without prior afebrile seizures [1]. The mechanism by which fever provokes a febrile seizure is unclear [2]. Febrile seizures are the most common type of childhood seizures, affecting 2% to 5% of children [1]. The age of onset is between 6 months and 5 years [3]; peak incidence occurs at about 18 months of age. Simple febrile seizures are the most common type of febrile seizure. By definition, they are generalized, last less than 10 minutes and only occur once in a 24-hour time-period. A complex febrile seizure is one with focal onset or one that occurs more than once during a febrile illness, or lasts more than 10 minutes. Febrile status epilepticus, a subtype of complex febrile seizures, represents about 25% of all episodes of childhood status epilepticus. They account for more than two-thirds of cases during the first 2 years of life.

The risk of reoccurrence after presenting with one febrile seizure is approximately 30%, with the risk being 60% after 2 febrile seizures and 90% after 3 [4–6]. Some families have an autosomal dominant inheritance pattern with polygenic inheritance suspected for the majority of patients presenting with febrile seizures.

Multiple chromosomes have been postulated to be associated with genetic susceptibility for febrile seizures, with siblings having a 25% increased risk and high concordance noted in monozygotic twins [7]. The pathophysiology for febrile seizures has been associated with a genetic risk associated with the rate of temperature rise with animal studies suggesting temperature regulation of c-aminobutyric acid (GABA) a receptors [2]. Other studies propose a link between genetic and environmental factors resulting in an inflammatory process which influences neuronal excitement predisposing one to a febrile seizure [8].

Debate exists between the relation of febrile seizures and childhood vaccinations. Seizures are rare following administration of childhood vaccines. Most seizures following administration of vaccines are simple febrile seizures [9]. Febrile seizures associated with vaccines are more associated with underlying epilepsy. In a study of patients with vaccine-related encephalopathy and febrile status epilepticus, the majority of patients were found to have Dravet syndrome; it was determined that the vaccine may have triggered an earlier onset of the presentation for Dravet in those predestined to develop this disease but did not adversely impact ultimate outcome [10].

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In this article, we review simple and complex febrile seizures with a focus on clinical management. Epilepsy syndromes associated with febrile seizures are also discussed. Cases are provided to highlight important clinical considerations.

**CASE 1: SIMPLE FEBRILE SEIZURE**

A 9-month-old infant and his mother present to the pediatrician. The mother notes that the infant had an event of concern. She notes the infant had stiffness in all 4 extremities followed by jerking that lasted 30 to 60 seconds. The infant was not responsive during the event. He was sleepy afterward, but returned to normal soon after the event ended. After, she noted that the infant felt warm and she checked his temperature. He had a fever of 101°F. The infant has normal development and no other medical problems.

**What are management considerations for simple febrile seizure?**

A simple febrile seizure is the most common type of febrile seizure. They are generalized, lasting less than 10 minutes and only occur once in a 24-hour period. There is no increased risk of developing epilepsy or developmental delay for patients after the first simple febrile seizures when compared to other children [5,6]. The diagnosis is based on history provided and a physical examination including evaluation of body temperature [11,12]. No routine laboratory tests are needed as a result of a simple febrile seizure unless obtained to assist in identifying the fever source [3,11]. Routine EEG testing is not recommended for these patients [3,11]. Routine imaging of the brain is also not needed [3,11]. Only if a patient has signs of meningitis should a lumbar puncture be performed [11]. The American Academy of Pediatrics states that a lumbar puncture is strongly considered for those younger than 12 months if they present with their first complex febrile seizure as signs of meningitis may be absent in young children. For infants 6 to 12 months of age, a lumbar puncture can be considered when immunization status is deficient or unknown [13,14]. Also, a lumbar puncture is an option for children who are pretreated with antibiotics [11]. For patients younger than 6 months, data is lacking on the percentage of patients with bacterial meningitis following a simple febrile seizure.

Daily preventative therapy with an anti-epilepsy medication is not necessary [3,11]. A review of several treatment studies shows that some anti-epileptic medications are effective in preventing recurrent simple febrile seizures. Studies have demonstrated the effectiveness of phenobarbital, primidone, and valproic acid in preventing the recurrence of simple febrile seizures; however, the side effects of each medication outweighed the benefit [3]. Carbamazepine and phenytoin have not been shown to be effective in preventing recurrent febrile seizures [3].

For anxious caregivers with children having recurrent febrile seizures, a daily medication or treating with an abortive seizure medication at the time of a febrile illness can be considered [3,5,6,15]. Treating with an abortive medication may mask signs and symptoms of meningitis making evaluation more challenging [16]. Evidence does not support that using antipyretic medications such as acetaminophen or ibuprofen will reduce the recurrence of febrile seizures. The seizure usually is the first noticed symptom due to the rise of temperature being the cause of the febrile seizure in an otherwise well child prior to the seizure [11,17]. Damage to the brain and associated structures is not found with patients presenting with simple febrile seizures [5,6]. Education on all of these principles is strongly recommended for caregiver reassurance.

**CASE 2: COMPLEX FEBRILE SEIZURES**

A 1-year-old child presents to the emergency department. Mother was with the child and she noticed stiffness followed by jerking of the left arm and leg, which quickly became noted in both arms and legs. The episode appeared to last for 15 minutes before EMS arrived to the house. A medication was given to the child by EMS that stopped the event. EMS noted the child had a temperature of 101.5°F. The child was previously healthy and has had normal development thus far.

**What is the epidemiology of complex febrile seizure?**

A complex febrile seizure is one with focal onset, or one that occurs more than once during a febrile illness or lasts more than 10 minutes. They are less common, representing only 20% to 30% of all febrile seizures [18–20]. In
The National Collaborative Perinatal Project (NCPP), 1706 children with febrile seizures were identified from 54,000 and were followed from birth until 7 years of age. The initial febrile seizure was defined as complex in about 28%. For all febrile seizures, focal features were present in 4%, prolonged duration (> 10 minutes) in 7.6%, and recurrent episodes within 24 hours in 16.2% [21]. Similar observations have been reported by Berg and Shinnar [5,6]. Of 136 children who had recurrences, 41.2% had one or more complex features and the strongest correlate of having recurrent complex febrile seizure was the number of recurrent seizures. They also found that children with complex recurrences had other recurrences that were not complex; however, complex features had a tendency to recur. Further, a strong association between focal onset and prolonged duration was found [5,6]. Previous studies established a correlation between complex attacks, particularly prolonged ones and young age (age < 1 year) [5,6]. Additionally, children with seizures with a relatively low fever (< 102°F) were slightly more likely to have a complex febrile seizure as the initial episode [5,6].

Children with febrile seizures are already at 4- to 5-fold increased risk for subsequent unprovoked seizures. A history of febrile seizures has been found in 13% to 18% of children with new-onset epilepsy. In the NCPP study, the predictors identified for the development of epilepsy following febrile seizures were an abnormal neurological and developmental status of the child before the seizure, a history of afebrile seizures in a parent or prior-born sibling, or complex features [21]. Ten percent of children with 2 or more of the previously mentioned risk factors (including complex features) developed epilepsy and 13% of them had seizures without fever [20,22]. Further, intractable epilepsy and neurological impairment have been found to be more common in children with prior prolonged febrile seizure, with no association to any specific seizure type [18,23–25]. The association between febrile seizures and mesial temporal sclerosis (MTS) is a commonly debated topic. Retrospective studies have reported an association between prolonged or atypical febrile seizures and intractable temporal lobe epilepsy. Epidemiological studies fail to show a causal relationship between febrile seizures and temporal lobe epilepsy [26]. This suggests that febrile seizures are a marker of susceptibility to seizures and future epilepsy (in some cases) rather than a direct cause. It is clear that a minority of cases of MTS or complex partial seizures are associated with prior febrile seizures [20,22].

**What is the risk of intracranial pathology in complex febrile seizure?**

Patients with complex febrile seizures usually seek medical attention [27]. However, the risk of acute pathology necessitating treatment changes based on neuroimaging was found to be very low and likely not necessary in the evaluation of complex febrile seizures during the acute presentation [27]. Imaging with a high-resolution brain MRI could be considered later on a routine basis for prolonged febrile seizures due to the possible association between prolonged febrile seizures and mesial temporal sclerosis [19,28,29].

Neuroimaging has provided evidence that hippocampal injury can occasionally occur during prolonged and focal febrile seizures in infants who otherwise appear normal. It has been speculated that a pre-existing abnormality increases the propensity to focal prolonged seizures and further hippocampal damage. Hesdorffer and colleagues [30] found definite abnormalities on MRI in 14.8% of children with complex febrile seizures and 11.4% of simple febrile seizures among 159 children with a first febrile seizure. However, MRI abnormalities were related to a specific subtype of complex seizures: focal and prolonged. The most common abnormalities observed were subcortical focal hyperintensity, an abnormal white matter signal, and focal cortical dysplasia.

**What are important aspects of the clinical evaluation?**

The evaluation and management of the child with complex febrile seizures is debated as well. The most important part in the history and examination is to look for the source of the fever and rule out the presence of a CNS infection, since complex febrile seizures are much more frequently associated with meningitis than simple febrile seizures [16]. The American Academy of Pediatrics recommended that a lumbar puncture be strongly considered in infants younger than 12 months after a first febrile
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Seizure and should be considered in children between 12 and 18 months of age, since signs of meningitis may be absent in young children [13]. If the threshold for a lumbar puncture is low in infants with febrile seizures in general, it should be even lower for children with complex febrile episodes for all the factors mentioned above. The guidelines developed in 1990 by the Royal College of Physicians and the British Paediatric Association concluded that indications for performing a lumbar puncture were complex febrile seizure, signs of meningismus, or a child who is unduly drowsy and irritable or systematically ill [21].

Obtaining an EEG within 24 hours of presentation may show generalized background slowing, which could make identifying possible epileptiform abnormalities difficult [22]. Therefore, a routine sleep deprived EEG when the child is back to baseline can be more useful in identifying if epileptiform abnormalities are present. If epileptiform abnormalities are present on a routine sleep deprived EEG, this may suggest the patient is at higher risk for developing future epilepsy and the febrile illness lowered the seizure threshold; however, it is unclear whether clinical management would change as a result [31].

### What treatment options are available?

Complications with prolonged and/or recurrent seizures can occur. Treatments options can be stratified into 3 possible categories: emergency rescue treatment for prolonged or a cluster of febrile seizures, intermittent treatment at the time of illness, and chronic use of medication. Treatment options for complex febrile seizures may include the use of a rescue seizure medication when the febrile seizure is prolonged. Rectal preparations of diazepam gel can be effective in stopping an ongoing seizure and can be provided for home use in patients with known recurrence of febrile status epilepticus [3]. For children and adolescents where a rectal administration is not ideal, intranasal valproic acid can be utilized instead of rectal diazepam. In addition, the use of an intermittent benzodiazepine at the onset of febrile illness can also be considered a treatment option. Using oral diazepam at the time of a febrile illness has been demonstrated in reducing the recurrence of febrile seizures [3]. Other studies have shown similar results when using buccal midazolam [32]. No adequate studies have been performed using second- or third-generation anti-epilepsy medications in the treatment of recurrent of complex febrile seizures [3].

It is unclear whether benefit is present to using intermittent benzodiazepine doses prior or during a febrile illness for those prone for recurrent febrile seizures [33]. Physicians may consider this option in patients with frequent recurrent seizures, when caregivers can identify the fever before the seizure occurs.

Overall, parental education of efficacy and side effect profiles should be discussed in detail when considering any treatment options for complex febrile seizures [34]. It is important to remember that the long-term prognosis in terms of developing epilepsy or neurological and cognitive problems is not influenced by the use of antiepileptic medications for recurrent febrile seizures [17]. Even in the case of prolonged febrile seizures in otherwise neurodevelopmentally normal children, antiepileptics have not been shown to cause damage to the brain [19].

### Febrile Status Epilepticus

Febrile status epilepticus is a subtype of complex febrile seizures and is defined as a febrile seizure lasting greater than 30 minutes. Overall, febrile status epilepticus accounts for approximately 5% of all presentations of febrile seizures [35]. It represents about 25% of all episodes of childhood status epilepticus and more than two-thirds of cases during the first 2 years of life. Literature suggests that an increased risk for focal epilepsy exists [36]. Children presenting with febrile status epilepticus are more likely to have a family history of epilepsy and a history of a previous neurological abnormality [22]. It is likely to reoccur if the first presentation was febrile status epilepticus. However, increased risk for death or developmental disability as a result of the seizure is not seen [37].

The prospective multicenter study of the consequences of prolonged febrile seizures in childhood (FEBSTAT) has been conducted. The study reported that febrile status epilepticus is usually focal (67% of episodes), occurs in very young children (median age 1.3 years), and is frequently the first febrile seizure [22]. In this study, the median duration of the seizure was about 68 minutes and 24% of children had an episode lasting more than 2 hours. In 87% of the events, seizures did not stop spontaneously and benzodiazepines were needed. Focal features observed were eye and head deviation, staring, and impaired consciousness prior to the seizure and an asymmetric convolution or Todd’s paresis.
A 1-year-old female presents for evaluation of seizures that began at age 8 months. Seizures are described as occurring in the setting of fever with bilateral symmetric tonic clonic activity lasting durations of less than 10 minutes on average, but at least 2 instances of seizure lasting 20 minutes or more. The family notes that seizures have occurred almost every time the child has had a febrile illness and often cluster over several days. They report at least 1 seizure that occurred in the absence of fever. Development has been normal to date and an EEG done by their primary provider was also normal.

Case 3: Epilepsy Syndromes Associated with Febrile Seizures

While febrile seizures represent a benign and infrequent type of seizure in the majority of patients, rare circumstances exists for which febrile seizures represent the first symptom of an epilepsy syndrome. The severity of these syndromes can vary from milder phenotypes of Genetic Epilepsy with Febrile Seizures Plus syndrome (GEFS+) to the more devastating epileptic encephalopathy of Dravet syndrome. Recognizing the early signs and symptoms of these disorders, particularly the more severe phenotypes, is essential to avoid misdiagnosis and misleading reassurance. Likewise, early recognition of many of these syndromes may alter the treatment paradigm which in turn may impact outcome. The sections below provide an overview of the most common epilepsy syndromes for which febrile seizures are a central and often initial symptom of the disorder (Table).

### Genetic Epilepsy with Febrile Seizures Plus
GEFS+ was first described in 1997 following recognition of a pattern of febrile seizures followed later by the development of various epilepsy syndromes within the same family [38]. As such, the syndrome is defined based on the familial occurrence of febrile and afebrile seizures in at least 2 family members and can have a wide range of phenotypes. The most common presentation is of typical febrile seizures which can persist beyond the typical upper age limit of 6 years. Unprovoked generalized seizures of multiple types (ie, myoclonic, absence, atonic) occur at a later age, though focal seizures may also be present. The presence of focal onset seizures led to the naming change from “generalized” epilepsy with febrile seizures plus as it was previously referred. Seizure frequency and severity may vary between family members, as can response to treatment, making prognosis difficult to predict.

#### Table. Epilepsy Syndromes Frequently Associated with Seizures in the Setting of Fever

<table>
<thead>
<tr>
<th>GEFS+</th>
<th>Dravet Syndrome</th>
<th>PCDH19-Associated Epilepsy</th>
<th>HHE</th>
<th>FIRES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at onset</td>
<td>&lt; 1 y</td>
<td>&lt; 1 y</td>
<td>&lt; 1 y</td>
<td>&lt; 4 y</td>
</tr>
<tr>
<td>Common seizure types</td>
<td>Tonic-clonic, myoclonic, absence, atonic, focal</td>
<td>Hemiclonic, tonic-clonic, absence, myoclonic, tonic, clonic</td>
<td>Focal seizures presenting in clusters, tonic, tonic-clonic</td>
<td>Hemiclonic presenting as status epilepticus</td>
</tr>
<tr>
<td>Status epilepticus</td>
<td>Rare</td>
<td>Common</td>
<td>Rare</td>
<td>Common</td>
</tr>
<tr>
<td>Family history</td>
<td>Strong</td>
<td>Rare</td>
<td>Rare</td>
<td>Rare</td>
</tr>
<tr>
<td>Common treatments</td>
<td>None specific. Depends on frequency of seizures. PRN benzodiazepines common.</td>
<td>Clobazam, valproate, stiripentol. Avoid sodium-channel antiepileptic drugs.</td>
<td>No specific antiepileptic drugs known to be more effective</td>
<td>Benzodiazepines 1st line. Multiple other antiepileptic drugs can be used.</td>
</tr>
<tr>
<td>Prognosis</td>
<td>Varies—most normal to mild delays. Remission in many patients.</td>
<td>Moderate-severe developmental delays, autism, ADHD. Unlikely to remit.</td>
<td>Mild-moderate developmental delays. Remission in 1/3 of patients.</td>
<td>Permanent hemiplegia in 80%</td>
</tr>
</tbody>
</table>

- What epilepsy syndromes are associated with febrile seizures?
As even in typical febrile seizures a family history of febrile seizure may be common, it may be difficult to diagnose the syndrome after the initial febrile seizure. However, if the family history is strong for a family member with a GEFS+ phenotype, one can appropriately counsel the family on the possibility that a similar course may evolve. While the majority of GEFS+ patients have milder phenotypes, some more severe phenotypes can have cognitive delays. Dravet syndrome falls within the spectrum of GEFS+ and is a prime example of the phenotypic continuum to more severe presentations in some patients.

The syndrome is believed to be inherited in an autosomal dominant fashion with incomplete penetrance. Multiple genes have been implicated as a cause, though only 11.5% of families with clinical GEFS+ may have mutations. SCN1A, encoding the α-subunit of the voltage-gated sodium channel is most frequently reported in GEFS+ families, yet is only found in 10% of patients. When associated with GEFS+, SCN1A mutations are more often missense type, whereas truncating and nonsense mutations are more commonly encountered in Dravet syndrome. Mutations in SCN1B encoding the β1 subunit of the voltage-gated sodium channel has also been reported. Finally, the GABA(A) receptor gamma 2 subunit GABRG2 has been found in <1% of GEFS+ families. The variability in causative genes underscores the reasons for phenotype variability and it is likely that other modifier genes are responsible for the heterogeneity within GEFS+ families.

**Dravet Syndrome**

Dravet syndrome, often referred to as severe myoclonic epilepsy of infancy, was first described in 1978 and has since become one of the most recognized genetic epilepsy syndromes. The clinical presentation often begins with seizures in the first year of life, frequently in the setting of febrile illness. The initial seizures are generalized or hemiclonic in the majority and are often prolonged evolving to status epilepticus. Unlike typical febrile seizures, one should suspect Dravet syndrome in children that present with repetitive bouts of complex febrile seizures or febrile status epilepticus, especially if the associated seizure semiology is of hemiclonic type. In addition, seizures in the setting of modest hyperthermia (ie, hot baths) should raise suspicion for this condition. Commonly EEG and MRI are normal in the first year of life and psychomotor development remains normal until typically the second year of life.

By the second year, other seizure types including myoclonic, atypical absence, clonic, and tonic seizures arise. The EEG frequently begins to show generalized spike wave and polyspike wave discharges. Seizures continue occurring frequently during early childhood, often resulting in status epilepticus. Cognitive development begins to stagnate between the ages of 1 and 4 years with emergence of autistic traits and hyperactivity. Development may stabilize between the ages of 5 and 16 years, but fails to demonstrate much improvement. Higher frequency of seizures may correlate with increase in cognitive impairment and behavior problems, supporting the need for rapid diagnosis and appropriate therapy.

Over the years, several cases of atypical or borderline Dravet syndrome have been described, most highlighting the absence of myoclonic seizures. Others may present with primarily clonic or tonic-clonic type seizures only. Despite these differences, all cases share a similar drug resistance and cognitive delay and are categorized as Dravet syndrome.

In 2001, Claus et al discovered the genetic alteration in SCN1A responsible for 70% of Dravet syndrome cases. The disorder is inherited in an autosomal dominant fashion, though 40% to 80% of mutations resulting in Dravet syndrome are de novo. Mutations can be present in other family members, as this syndrome is part of the spectrum of GEFS+, though parental phenotypes are often much less severe. Approximately 50% of mutations resulting in Dravet syndrome are truncating, while the other 50% are missense mutations involving splice site or pore forming regions leading to loss of function. Finally, small and large chromosome rearrangements make up 2% to 3% of cases. Other genes reported to result in Dravet syndrome include SCN1B and GABRG2 mutations. In addition, PCDH19 can produce a phenotype similar to Dravet syndrome in females and is discussed in more detail below.

With the emergence of more rapid and cheaper forms of genetic testing, molecular diagnosis can now be made earlier in life before all the typical clinical features of Dravet syndrome arise. As a result, one might hope to alter treatment strategy and gear therapy towards the most effective medications. While drug resistance is the norm for the condition, certain drugs such as benzodiazepines, valproate, and stiripentol may be most effective. Topiramate and levetiracetam have been reported as efficacious in small series, as has the ketogenic diet.
Varieties of medications which target sodium channels are known to exacerbate seizures in Dravet syndrome and should be avoided, including lamotrigine, carbamazepine, oxcarbazepine, and phenytoin [56]. In addition to maintenance therapy, it is important to provide patients with a rescue plan for acute seizures in an effort to avoid status epilepticus. In addition, measures to avoid overheating may provide additional benefit.

**CASE 3 CONTINUED**

After a careful history, the physician discovers that the child also has frequent myoclonic seizures described as brief jerks of the extremities or sudden forward falls. The family notes they have seen these seizures more frequently since antiepileptic therapy was started. The physician recognize that this child may have Dravet syndrome and suspect her medication may be resulting in aggravation of seizures.

The physician decides to discontinue the medication suspected to aggravate the seizures and chooses to start the child on clobazam. The physician also begins evaluation for Dravet syndrome by sending directed SCN1A genetic testing. The testing comes back negative for mutations in the SCN1A gene.

**What other investigations would be warranted now?**

**PCDH19**

PCDH19 was first recognized as a cause of epilepsy and mental retardation limited to females (EFMR), a syndrome characterized by onset of seizures in infancy or early childhood with predominantly generalized type seizures including tonic-clonic, absence, myoclonic, tonic, and atonic [57]. Since that initial description, the phenotype associated with PCDH19 mutations has expanded to include female patients with primarily focal epilepsy, variable cognitive impairment, and commonly onset with seizures in the setting of fever [58,59]. Typically seizures begin around age 10 months presenting as a cluster of focal seizures in the setting of fever, often followed by a second cluster 6 months later [59]. Generalized seizures occur in a small proportion of patients (9%) and this feature, along with relatively fewer bouts of status epilepticus and less frequent seizures (most monthly to yearly frequency) can differentiate PCDH19 associated epilepsy from Dravet syndrome [59]. Seizures tend to improve with age and no particular antiepileptic drug has been found especially efficacious in the syndrome. Unlike Dravet syndrome, up to a third of patients with this syndrome may ultimately become seizure-free [59].

Cognitive development is normal prior to seizure onset in the majority of patients and most but not all patients will develop some cognitive impairment ranging from mild to severe [59]. It is the more severe patients that most often have overlapping characteristics of Dravet syndrome, thus PCDH19 mutations should be investigated in female patients with Dravet phenotype yet negative SCN1A testing.

PCDH19 is a calcium-dependent adhesion protein involved in neuronal circuit formation during development and in the maintenance of normal synaptic circuits in adulthood [60,61]. Disease causing mutations in PCDH19 are primarily missense (48.5%) or frameshift, nonsense, and splice-site mutations resulting in premature termination codon [59]. Ninety percent of mutations are de novo. When inherited, the disorder is X-linked and may come from an unaffected father or a mother that is similarly affected or not, suggesting variable clinical severity in females and gender-related protections in males [59].

**CASE 3 CONTINUED**

Given the negative SCN1A testing, the physician chooses to pursue other genetic testing that may explain the patient’s phenotype. A more extensive “epilepsy gene panel” that includes 70 different genes associated with epilepsy syndromes is ordered.

**Hemiconvulsion-Hemiplegia Epilepsy Syndrome**

Hemiconvulsion-hemiplegia epilepsy syndrome (HHE) is characterized by the occurrence of unilateral convulsive status epilepticus followed by transient or permanent ipsilateral hemiplegia. The syndrome occurs in otherwise healthy children often in the setting of nonspecific febrile illness before the age of 4 years, with peak occurrence in the first 2 years of life [62]. Seizures are characterized by unilateral clonic activity with EEG demonstrating rhythmic 2–3 Hz slow wave activity and spikes in the hemisphere contralateral to the body involvement. MRI frequently demonstrates diffusion changes congruent with EEG findings, often in the perisylvian region. The hemiplegia that remains following status epilepticus is permanent in up to 80% of cases [63]. As hemiplegia...
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Febrile seizures can occur following complex febrile seizures, it is recommended a minimum duration of hemiplegia of 1 week be used to differentiate HHE [64]. Status epilepticus is persistent in this syndrome and can last for hours if untreated. Focal onset seizures will often continue to occur in the patient even after the status has been aborted.

The etiology of HHE is variable with many cases idiopathic. Some cases are reported as symptomatic, as the syndrome can present in the setting of other underlying brain disorders such as Sturge-Weber and tuberous sclerosis complex. While some viruses have been proposed as a cause, they are not found in the cerebral spinal fluid of patients [65]. Treatment consists of rapid treatment of status epilepticus with benzodiazepines as first-line therapy, often followed by other intravenous antiepileptic drugs as necessary.

Febrile Infection–Related Epilepsy Syndrome

Febrile infection–related epilepsy syndrome (FIRES) is presented under several names in the literature including idiopathic catastrophic epileptic encephalopathy [66], devastating encephalopathy in school-age children [67], new-onset refractory status epilepticus [68], as well as fever-induced refractory epileptic encephalopathy syndrome [69] and fever-induced refractory epileptic encephalopathy in school-age children [70]. All describe rare catastrophic epilepsy presenting in otherwise healthy children during or days following a febrile illness. While febrile illness precedes the epilepsy in 96% of cases, up to 50% of patients may not have fever at the time they present [41,65]. While age of onset is typically in early childhood, presentation in adulthood also occurs. Initial seizures are often focal, presenting as forced lateral head or eye deviation, oral or manual automatisms, and clonic movements of the face and extremities. Seizures will inevitably progress to status epilepticus with ictal onset often multifocal predominating in the perisylvian regions [41]. MRI is often normal at onset or shows only subtle swelling of the mesial temporal structures. Over months, MRI often shows T2-hyperintensity and atrophy of the mesial temporal structures, though as many as 50% of MRIs may remain normal [71].

The evaluation for cause in FIRES is often unrewarding. Inflammatory markers are typically absent from both serum and CSF. CSF may show minimal pleocytosis with negative oligoclonal bands and absence of common receptor antibodies. Treatment is equally unrewarding with patients typically failing conventional antiepileptic drugs and continuous infusions titrated to burst suppression. Immunomodulatory therapies are mostly ineffective as well. The most useful therapy reported has been the keto-genic diet with efficacy in up to 50% of patients [72]. Recently, therapeutic hypothermia has also been reported to be effective in 2 cases [73]. For the majority of patients, therapy will remain ineffective and seizures will continue for weeks to months with gradual resolution, though seizures often continue intermittently following the end of status epilepticus. Prognosis is poor for seizure control and neurocognitive recovery with mortality of 30% reported [41].

Case 3 Conclusion

The epilepsy gene panel ordered returns with the result of a disease-causing mutation in the PCDH19 gene. The child is diagnosed with PCDH19-associated epilepsy and is treated with phenobarbital. For the first years of life, she presents on average once per year with a cluster of seizures in the setting of febrile illness which is often managed with short durations of scheduled benzodiazepines. Seizures slow by age 6. She has mild delays in speech and receives some accommodations through her school system. By age 10, she has been seizure-free for several years. She is able to be weaned off medications without recurrence of seizures.

Summary

Febrile seizures are a common manifestation in early childhood and very often a benign occurrence. For simple febrile seizures, minimal evaluation is necessary and treatment typically not warranted beyond reassurance and education of caregivers. For complex febrile seizures, additional evaluation in rare cases may suggest an underlying seizure tendency, though most follow a typical benign course of febrile seizures. In some cases, as needed benzodiazepines used for prolonged or recurrent febrile seizures may be of value. There are well described epilepsy syndromes for which febrile seizures may be the initial manifestation and it is paramount that providers recognize the signs and symptoms of these syndromes in order to appropriately counsel families and initiate treatment or referral when warranted. Providers should have a high index of suspicion for these syndromes when they encounter children that repeatedly present with prolonged febrile seizures, clusters of febrile seizures, or febrile seizures in addition to afebrile seizure events. Early referral, diagnosis, and treatment has the potential
to alter outcome in some of these syndromes, thus the importance of becoming familiar with these diagnoses.

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Financial disclosures: Dr. Patel disclosed that he has consulted for GW Pharmaceuticals and Supernus and is on the Scientific Advisory Board for UCB Pharma.

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Vol. 24, No. 7 July 2017 JCOM 333