Febrile seizures

Update and controversies

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ABSTRACT

Febrile seizures are the most common seizure disorder in children younger than 5 years of age. Most febrile seizures are brief, do not require any specific treatment or workup, and have benign prognoses. Generalists and pediatricians are frequently faced with anxious parents and are required to make rational decisions regarding the need to investigate and treat such a child. They subsequently need to provide further prognostic information and counseling to the families. The aim of this article is to provide an updated overview of febrile seizures and review the most recent diagnostic and therapeutic recommendations. Despite the progress in the understanding of this benign syndrome, a wide variation in physician evaluation and management persists. However, there is recent evidence that pediatricians are becoming more selective in admitting and investigating children with febrile seizures. Admitted children frequently had complex seizures, status epilepticus, or were ill looking. Considering the full scope of febrile seizures, the yield of investigations that might alter management remains low and does not justify extensive work-up or prolonged hospitalization.

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Febrile seizures are the most common seizure disorder in children <5 years of age.[1] They occur in 2-5% of children, but the incidence has been reported as high as 14% in certain populations.[2] This has been attributed to higher rates of consanguinity. However, racial and geographic variations may also be important. Most febrile seizures are brief, do not require any specific treatment or workup, and have benign prognoses.[3] Generalists and pediatricians are frequently faced with anxious parents and are required to make rational decisions regarding the workup and management of these children. Physicians are subsequently required to provide counseling and information regarding the prognoses to the involved families. The aim of this article is to provide an updated overview of febrile seizures and review the most recent diagnostic and therapeutic recommendations.

Definitions. A febrile seizure is defined as a seizure accompanied by fever without central nervous system infection, occurring in infants and children 6 months to 5 years of age.[4] The majority occurs in children between 12-22 months. It is generally accepted that a febrile seizure is associated with a temperature of at least 38.5ºC, no acute systemic metabolic abnormalities that may predispose to seizures, and no history of afebrile seizures.[5] Febrile seizures can be simple (typical) or complex (atypical), based on their clinical characteristics. Simple febrile seizures are the most common (85%) and are characterized by a brief generalized seizure, specifically without any

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lateralizing features. Complex febrile seizures are focal, prolonged (>15 minutes), or multiple within 24 hours of the same febrile illness,[6] or both. Complex febrile seizures are less common accounting for <15% of febrile seizures. An initial simple febrile seizure may be followed by complex seizures, but the majority of children who develop complex febrile seizures do so from the onset. When an initial seizure is prolonged, subsequent recurrences are more likely to be prolonged.[7] Febrile status epilepticus accounts for 5% of febrile seizures and for up to 25% of all status epilepticus in children.[8]

Febrile illness. The majority of children have their febrile seizures on the first day of illness. In some cases the seizure is the first manifestation that the child is ill, that is before the parents detect the fever.[9] The degree of fever is variable, and approximately 75% have temperatures of 39ºC or higher at the time of the seizure. Recurrent febrile seizures do not necessarily occur with the same degree of fever as the first episode and do not occur every time the child has a fever. Although it is often contended that a febrile seizure is more likely to occur when temperature increases rapidly, there is no scientific data to support this belief.[5] Febrile seizures occur more commonly during viral than bacterial infections. Some viral infections, such as roseola (herpes virus 6), appear to be particularly prone to be associated with seizure activity in infants according to Hall et al,[10] who observed seizures in up to 13% of such children. In another study, roseola accounted for up to 33% of first febrile seizures and frequently was of the complex type.[11] Interestingly, when gastroenteritis is the cause of the fever, seizures are extremely uncommon, which has an inverse relationship.[12]

Genetics. Genetic factors appear to be important in the expression of febrile seizures and in the relationship to future epilepsy.[13] Males generally have a higher incidence with a male to female ratio of 1.5-2:1.[14,15] Among first-degree relatives of children with febrile seizures, 7-31% had history of febrile seizures. Other siblings of an affected family have a 20-30% risk of having febrile seizures. In addition, monozygotic twins have a much higher concordance rate than dizygotic twins, in whom the rate is similar to that of other siblings. Susceptibility to febrile seizures has been recently linked to several genetic loci in different families, including the long arm of chromosome 8q13-21, chromosome 19p, chromosome 2q23-24, and chromosome 5q14-15.[16-20] The suggested mode of inheritance is autosomal dominant.

The recently described syndrome of generalized epilepsy with febrile seizures plus, has been mapped to chromosome 2q.[21] Involved children have febrile seizures that continue beyond 6 years of age or associated with afebrile generalized seizures or other seizure types such as absence, myoclonic, or atonic seizures.[21] The epilepsy typically remits by mid-adolescence. A subsequent report described other unrelated families with the same clinical syndrome.[22] Genetic analyses suggested autosomal dominant inheritance with a penetrance of approximately 60%. In one of the families, the syndrome was linked to chromosome 19q and a mutation was identified in the beta-subunit of sodium channels.[23] A similar autosomal dominant syndrome was studied in 2 French families.[24] The gene was mapped to chromosome 2q21-q33 and 2 mutations of the gene encoding the alpha-subunit of sodium channels were found.[25]

In summary, the evidence in febrile seizures suggests autosomal dominant inheritance, low penetrance, variable expression, and locus heterogeneity.

Recurrence of febrile seizures. Children with febrile seizures are at risk for developing recurrent febrile seizures. A major factor influencing the recurrence rate is the age of the infant at the time of the first seizure. The overall recurrence rate is approximately 30-35% and increases to 50% after the second febrile seizure.[26,27] However, the values vary with age from as high as 50-65% in infants <1 year of age to as low as 20% in older children.[28] A prospective cohort study of 428 children with a first febrile seizure identified 4 important factors influencing seizure recurrence; 1. age <1 year, 2. family history of febrile seizures, 3. low grade fever, and 4. seizures following brief fevers.[26] Children who had all 4 factors were much more likely to have a recurrent febrile seizure than were those with none. Complex features were not associated with a higher recurrence risk. Overall, 30% had at least one recurrence, 17% had 2 recurrences, 9% had 3 recurrences, and 6% had more than 3 recurrences.[26] Other factors identified in other studies included; abnormal developmental history, history of epilepsy in first-degree relatives, and attendance of day care.[27,29,30] Most recurrences occurred within one year of the initial seizure.[29] Among children who had one recurrence, younger age at the time of the first recurrence was the most important predictor of subsequent recurrences.[26]

Hospital admission and diagnostic evaluation. It is generally accepted that hospital admission should be reserved for those with recurrent or prolonged complex seizures, with an underlying serious infection, or where parental anxiety and other social circumstances indicate.[31] A brief period of observation may be indicated in a young febrile child with no clear focus of infection. However, routine hospital admission increases the tendency to perform unnecessary investigations and therefore should be discouraged. In the following section, we will discuss the indications, yield, and current recommendations regarding obtaining

various investigations including blood studies, lumbar puncture, electroencephalogram (EEG), and neuroimaging in children with febrile seizures. The latest American Academy of Pediatrics (AAP) practice recommendations, which were based on reviewing 203 articles addressing the diagnostic evaluation of children with simple febrile seizures, will be highlighted.[4]

Laboratory studies. It is not uncommon for children with simple febrile seizures to be subjected to various laboratory tests such as a complete blood count (CBC), serum electrolytes, calcium, phosphorous, magnesium, glucose, and urine or blood cultures. An underlying metabolic disorder presenting as a seizure in a febrile child is extremely uncommon as compared to those with afebrile seizures.[32] The history and physical examination can direct the physician towards the underlying etiology. Infants with a history of vomiting, diarrhea, and altered fluid intake should have serum electrolyte profiles to exclude hypernatremia or hyponatremia, both of which may lead to seizures. Clinical evidence of dehydration and prolonged drowsiness or postictal obtundation are indications for measurement of serum electrolytes, blood sugar, calcium, and urea nitrogen. The yield of these tests, if carried out routinely, is very low. Despite these recommendations, a wide variation in physician evaluation and management persists.[4] Sweeney et al,[33] found marked variation in the number of investigations performed in each hospital of a regional population. Blood cultures and CBC were performed on 6-56% and 8-70% of children and 23-78% were prescribed antibiotics.[33] In another study, the risk of occult bacteremia was 2.1%, which is similar to those with fever alone.[34] Other investigators who performed routine blood and urine cultures on all admitted children with febrile seizures found positive results in only 4.3% and 2.6% of the children.[35] Overall, the rates of bacteremia or serious bacterial illness were low and consistent with those published for febrile children without seizures.[14]

Lumbar puncture (LP). Meningitis and meningo-encephalitis are the main concerns in a child presenting with fever and seizures. Seizures can be the presenting, but not the only feature, of up to 15% of children with meningitis. Although most of the infants (<18 months) who have seizures as an initial manifestation of meningitis, do not have meningeal signs, they have other symptoms and findings that strongly suggest the correct diagnosis (for example altered state of consciousness, persistent vomiting, bulging fontanel, and abnormal neurological signs). A thorough evaluation by an experienced clinician almost always will detect the child with meningitis. It is exceedingly rare for bacterial meningitis to be unsuspected clinically, only to be detected on the basis of routine evaluation of the cerebrospinal fluid (CSF) after a febrile seizure. The AAP recommends that LP be strongly considered in infants less than 12 months, considered in infants 12-18 months, and if clinically indicated in those greater than 18 months of age.[4] It should also be strongly considered if the child had received prior oral antibiotics that may mask the clinical manifestations or results in transient improvement. Routine LP in all children with febrile convulsions is clearly not warranted. Others also concluded that excluding meningitis and encephalitis through careful history, examination, observation, and occasionally lumbar puncture in children less than 2 years of age, is all that is needed.[3,36]

Electroencephalography (EEG). The yield of routine EEG is low in neurologically normal children with febrile seizures even if the seizure is complex.[37,38] We recently reported our prospective experience in 438 consecutive pediatric EEGs over a one-year period.[38] Overall, 6.5% had febrile seizures (including complex) and none had epileptiform discharges. Abnormal posterior slowing may occur shortly after the seizure and may be detected for as long as 10 days afterwards. This finding can serve to confirm the clinical impression that a seizure has occurred.[5] However, EEG abnormalities are not predictive of recurrence or development of future epilepsy. This led to the conclusion that the routine practice of obtaining EEG in neurologically normal children with febrile seizures is not justified.

Neuroimaging (CT, MRI). Neuroimaging with CT or MRI should not be performed routinely. They should be considered in children with abnormal developmental history, abnormal head size, or focal neurological abnormalities.[4] However, clinically important intracranial structural lesions are extremely uncommon in children with febrile seizures. Skull x-rays are not useful in investigating these children.[4]

Therapeutic interventions. Febrile seizures longer than 5-10 minutes should be treated actively. Airway, respiratory status, and circulatory status must be assessed. Blood should be obtained for electrolytes and glucose determination, if indicated. Anti-epileptic drugs should be administered rectally or intravenously starting with lorazepam (0.1 mg/kg) or diazepam (0.3-0.5 mg/kg). If the seizure persists, an additional dose may be given. The child's respiratory status needs to be monitored carefully and intubation undertaken if the ventilatory status becomes compromised. Persistence of the seizure is rare. Rectal diazepam can also be used at home to treat febrile seizure recurrences of longer than 5 minutes.[39] It is particularly useful in children at high risk for recurrent febrile status epilepticus or frequent repetitive febrile seizures. Parents can be taught to

give the medication safely after providing an initial test dose under supervision. Antipyretics, such as acetaminophen and sponging with tepid water can help in reducing the body temperature. The role of prophylactic antipyretic and antiepileptic drugs in the management can be controversial. In the following section, we will discuss the indications, effectiveness, and current recommendations regarding various treatment modalities. The latest AAP practice recommendations, which were based on reviewing 300 articles addressing various therapeutic interventions of children with simple febrile seizures, will be highlighted.[40]

Intermittent antipyretics. Treatment with antipyretics at the time of a febrile illness is helpful in providing comfort. The use of prophylactic antipyretics during a febrile illness is not effective in preventing recurrence of febrile seizures.[41] Camfield et al,[41] in a randomized controlled trial compared recurrences in children who were given either phenobarbitone and antipyretics or antipyretics and placebo. The febrile seizure recurrence rate was 5% for the first group and 25% for the second group. In another study, neither moderate (10 mg/kg) nor high (20 mg/kg) doses of acetaminophen alone reduced the incidence of recurrent febrile seizures.[42]

Intermittent diazepam. Intermittent rectal or oral diazepam given 3 times per day during a febrile illness has been proven effective in preventing febrile seizure recurrence. In a randomized controlled trial, oral diazepam (0.33 mg/kg Q8hr for 2-3 days of a febrile illness) was as effective as continuous phenobarbitone in preventing recurrent febrile seizures with a 44% risk reduction per patient per year.[43] This practice has not been widely used by pediatricians and neurologists for several reasons. First, the seizures may occur before the fever is noticed. Adverse effects such as lethargy, drowsiness, and ataxia are troublesome. Finally diazepam may mask evolving clinical signs of meningitis. The AAP advised that this treatment is not generally recommended.[40]

Continuous antiepileptic drugs. Carbamazepine and phenytoin have not been shown to be effective in preventing febrile seizure recurrences.[40] In randomized controlled trials, both phenobarbitone and valproic acid were found effective in preventing febrile seizure recurrences.[44,45] Daily phenobarbitone reduced the rate of subsequent febrile seizures from 25-8% per year.[44] Only 4% of children on valproic acid as compared to 35% of controls had recurrent febrile seizures.[45] However, the risks and potential side effects of phenobarbitone (sleepiness, hyperactivity, cognitive effects) and valproic acid (hepatotoxicity, pancreatitis, thrombocytopenia) outweigh their benefits. Also, there is no available data suggesting that the prevention of recurrent febrile seizures reduces the risk of developing epilepsy.

Experience at King Abdul-Aziz University Hospital in Jeddah. This paragraph summarizes our experience with febrile seizure patients admitted consecutively to King Abdul-Aziz University Hospital in Jeddah over a 5-year period ending the first of January 2002. Sixty-nine children aged 7-70 months (mean 20) were reviewed (60% males). They were admitted for 1-14 days (mean 4.7). Fifteen (22%) had a previous febrile seizure and 33% had positive family histories of febrile seizures. Most admitted children (60 out of 69) had complex seizures (55%), were ill looking (24.5%), had febrile status epilepticus (17.5%), or had positive meningeal irritation signs (4%). These figures are higher than those reported earlier by Deng et al,[15] who found 33% of their admitted febrile seizure children to have complex features. Thus, the difference presumably reflects our higher admission selectivity. The source of the febrile illness was evident in 65%, mostly due to upper respiratory tract infection.

Regarding the investigations, CBC and serum electrolytes were performed on all children. Electrolyte abnormalities were uncommon and minor in 10%. However, CBC showed abnormalities suggestive of an infection in 45%, increasing their likelihood of receiving IV antibiotics. In most cases antibiotics were not necessary, as only 2 children had positive blood cultures. The abnormal CBC was therefore most likely seizure (stress) related. Lumbar puncture was performed on 75%, particularly on those who presented with a first seizure compared to recurrent seizures (81% versus 53%, p=0.04) or <2 years of age (OR 3.4, 95% CI 0.7-17). A 1977 study documented that 96% of admitted children with febrile seizures had a lumbar puncture.[46] Again, this reflects the trend of being more judicious in the use of LP. Only one child had a positive CSF culture confirming meningitis. He presented with febrile status, looked ill, and had positive meningeal irritation signs. Ten (19%) had mild nonspecific CSF abnormalities. Partially treated meningitis was suspected in 2 children but was not confirmed. Electroencephalogram was performed selectively on 33%. Obtaining an EEG was less likely if the seizure was simple (13% versus 50% in cases with complex seizures, p=0.002). Electroencephalogram were normal in 12 and showed minor nonspecific changes in 6. Epileptiform discharges were noted on 4 EEGs. However, no correlation with seizure type was found. Brain CT scans were performed on 13%. No focal lesions were identified. However, 2 scans showed mild brain edema. One of these patients had a prior LP confirming meningitis and the other was suspected to have partially treated meningitis.

Regarding the management, 36% received intravenous fluids (IVF) in the emergency room (ER) and 68% during the hospitalization. Giving IVF was not routine and was reserved for ill-looking children who were 10.8 times more likely to receive IVF in the ER (95% CI 2.6-52, p=0.0002), or during hospitalization (p=0.01). Only 7% received IV antibiotics in the ER, however, 90% received them during hospitalization. This practice appeared more or less routine, which should be discouraged given the low risk of bacteremia and meningitis. Twenty-five (36%) children received an anti-epileptic drug (AED**)** in the ER, mostly for ongoing seizures or status epilepticus (p=0.02). However, only 13% continued to receive an AED during hospitalization, after the presenting seizures were abolished. These children were more likely to have atypical seizures (p=0.03) or status epilepticus at presentation (p=0.04).

We conclude from this review that pediatricians are becoming more selective in admitting and investigating children with febrile seizures. There was usually a valid reason for admission. However, the yield of investigations remains low and does not justify extensive work-up or prolonged hospitalization.

Relationship to epilepsy syndromes. Febrile seizures are classified as a special (situation related) epilepsy syndrome, according to the International League Against Epilepsy (ILAE) classification system. Rarely, febrile seizures can evolve to, or become associated with, other epilepsy syndromes including; 1. generalized epilepsy with febrile seizures plus syndrome, 2. temporal lobe epilepsy (TLE) due to mesial temporal sclerosis (MTS), 3. hemiconvulsion hemiplegia syndrome, 4. hemiconvulsion hemiplegia epilepsy syndrome, or 5. severe myoclonic epilepsy of infancy. The recently described syndrome of generalized epilepsy with febrile seizures plus has been previously discussed in the genetics section. The development of TLE secondary to MTS will be discussed in detail in the next section. We will discuss the other 3 syndromes briefly. Prolonged status epilepticus with a marked unilateral predominance can be followed by a long lasting hemiplegia characterizing the hemiconvulsion hemiplegia syndrome (HH syndrome) described by Gastaut et al.[47] After several years, partial epilepsy originating from the affected hemisphere gives rise to the hemiconvulsion hemiplegia epilepsy syndrome (HHE syndrome). Brain MRI is characteristic, with initial edematous swelling of one hemisphere followed by global atrophy, independent of any vascular territory. Affected children frequently have cognitive impairments and intractable epilepsy.[47] With the development of effective medications and aggressive management of status epilepticus, these 2 syndromes are becoming very uncommon. Finally, febrile seizures can be the initial manifestation of severe myoclonic epilepsy of infancy (SMEI). Recurrent mixed seizures occur in the first year of life with developmental and cognitive deterioration.[48] The EEG shows fast spike wave and multifocal epileptiform discharges. The seizures are intractable, although myoclonic seizures tend to disappear. The syndrome is rare with recent evidence suggesting a genetic etiology. De novo mutations of the neuronal sodium channel alpha-subunit gene (SCN1A) were described recently in 7 isolated SMEI patients.[49] This is similar to the mutations described in patients with generalized epilepsy with febrile seizures plus syndrome, suggesting a link between the 2 syndromes.[50]

Future epilepsy and mesial temporal sclerosis. Epilepsy occurs more frequently in children with a history of febrile seizures than in the general population. In a normal child with a simple febrile seizure, the risk is 1-2.5%, which is slightly higher than the 0.5% risk in the general population.[51] Factors that increase this risk include abnormal neurological development, complex febrile seizures (particularly focal), and family history of epilepsy.[51] Neurological abnormalities and complex seizures were associated with 9.2% incidence of afebrile seizures by 7 years of age. In another population based study, in which children with febrile seizures were observed into adulthood, risk factors for developing epilepsy were identified including; focal seizures, prolonged seizures, and repeated episodes within 24 hours during the same illness.[52] The risk of developing recurrent partial epilepsy was 6-8%, 17-22%, and 49% in children with one, 2, or 3 of these risk factors.

One of the most controversial issues in epilepsy of temporal lobe origin is whether prolonged febrile seizures cause MTS and therefore predisposing to TLE.[53] Retrospective studies from tertiary epilepsy centers report that patients with refractory TLE considered for surgery often have a history of prolonged febrile seizures.[54] However, population based studies have failed to confirm this association, as have prospective studies of febrile seizures.[55] Studies assessing hippocampal volume have found an association between a smaller hippocampus and a history of febrile seizures.[56,57] Data are conflicting as to whether a correlation exists between the duration of epilepsy and the reduction in hippocampal volume. The possibility of hippocampal injury was assessed using MRI in infants with complex febrile seizures.[58] Abnormalities were found in the children with prolonged focal seizures but not in those with generalized seizures. Several infants developed hippocampal atrophy on follow-up imaging. Although these observations suggest seizure related hippocampal injury, the possibility of preexisting lesions leading to susceptibility to injury could not be excluded.

Patients presenting to an epilepsy clinic were prospectively questioned regarding febrile seizures.[59] Febrile seizures were reported by 13% of the patients. Temporal lobe epilepsy (25%) was more likely to be preceded by febrile seizures than by extra-temporal epilepsy (6%) or generalized epilepsy (11%). Long duration was the most common feature associated with TLE. In another study, 524 children with epilepsy starting after the first year of life were evaluated.[54] Febrile seizures were present in 14% and complex features were associated with a younger age at onset. No evidence that focal or prolonged febrile seizures were associated with TLE was found. Children had hippocampal atrophy on their initial MRI, but none had a history of febrile seizures. The authors concluded that febrile seizures do not appear to cause TLE and the association may represent an inherent susceptibility in some children who are predisposed to prolonged febrile seizures and epilepsy simultaneously. Another study linking febrile seizures and TLE described 2 families with familial febrile seizures.[60] Magnetic resonance imaging was performed on family members free of seizures, with febrile seizures only, and febrile seizures with subsequent TLE. All subjects with febrile seizures only and 6 normal relatives showed asymmetry in hippocampal size with changes in the internal architecture of the hippocampal bodies suggesting that the subtle preexisting hippocampal abnormalities facilitated the febrile seizures and contributed to the development of subsequent hippocampal sclerosis. The hippocampal abnormalities did not appear to be a consequence of the febrile seizures. Finally, a controlled animal study examined the effects of prolonged febrile seizures on immature rats.[61] Prolonged hyperthermia-induced seizures did not result in subsequent spontaneous seizures in adult rats. However, the experimental animals developed hippocampal seizures after administering systemic kainate indicating a lowered seizure threshold. An analogous situation may exist in humans. Individuals predisposed to developing epilepsy, by a variety of factors, may become symptomatic in later years after having their thresholds modified by febrile seizures in infancy.

To conclude, researchers still need to address the longstanding controversy regarding the relationship between prolonged febrile seizures and MTS. Large, longitudinal, prospective, multicentered trials of children with prolonged febrile seizures may provide answers to this key clinical question.

Cognitive & behavioral effects. Long-term neurological sequelae including cognitive and behavioral disorders are extremely uncommon following febrile seizures. Reports of such associations have been anecdotal and derived from biased populations consisting of children assessed in tertiary care settings. This may reflect preexisting abnormalities. Most reports of new deficits have occurred after complex or prolonged febrile seizures. However, population based studies do not corroborate these reports.[30,62] In the National Collaborative Perinatal Project, approximately 5% of children had febrile seizures lasting >30 minutes. None of these children sustained permanent motor deficits or impaired mental development unless they developed epilepsy.[30] Similar findings were noted in a long-term, controlled, population-based study from the United Kingdom.[62] Children with preexisting neurological or developmental abnormalities were excluded. At 10 years of age, no differences were noted in measurements of academic and behavioral functions in children with simple, complex, or recurrent febrile seizures compared to controls.[62]

In conclusion, febrile seizures are common events, affecting up to 5% of children between the ages of 6 months and 5 years. Most febrile seizures are brief, do not require any specific treatment or workup, and have benign prognoses. Excluding meningitis and encephalitis, through careful history, examination, observation, and occasionally LP, is the most important task of management. However, identifying the cause of fever is also a priority. Routine hospital admission increases the tendency to perform unnecessary investigations and should be discouraged. Admission should be reserved for recurrent or long complex seizures, underlying serious infection, or where parental anxiety and other social circumstances necessitate such admission. Lumbar puncture should be strongly considered in infants <12 months of age, considered at 12-18 months, and if clinically indicated in infants >18 months. Electroencephalogram, blood studies, and neuroimaging should not be performed routinely. Neither intermittent nor continuous antiepileptic drug treatments are recommended. However, parental education and emotional support are of paramount importance in all cases to alleviate associated anxieties.

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