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REVIEW

Febrile seizures: an overview

Alexander KC Leung[1] MBBS, FRCPC, FRCP (UK and Irel), FRCPCH, FAAP, Kam Lun Hon[2] MD, FAAP, FCCM, Theresa NH Leung[3] MBBS, FRCPCH, FHKAM (Paed)

[1]Department of Pediatrics, The University of Calgary, Alberta Children's Hospital, Calgary, Alberta, Canada; [2]Department of Pediatrics, The Chinese University of Hong Kong, Shatin, Hong Kong; [3]Department of Pediatrics and Adolescent Medicine, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong

Abstract

Background: Febrile seizures are the most common neurologic disorder in childhood. Physicians should be familiar with the proper evaluation and management of this common condition.

Objective: To provide an update on the current understanding, evaluation, and management of febrile seizures.

Methods: A PubMed search was completed in Clinical Queries using the key terms 'febrile convulsions' and 'febrile seizures'. The search strategy included meta-analyses, randomized controlled trials, clinical trials, observational studies, and reviews.

Results: Febrile seizures, with a peak incidence between 12 and 18 months of age, likely result from a vulnerability of the developing central nervous system to the effects of fever, in combination with an underlying genetic predisposition and environmental factors. The majority of febrile seizures occur within 24 hours of the onset of the fever. Febrile seizures can be simple or complex. Clinical judgment based on variable presentations must direct the diagnostic studies which are usually not necessary in the majority of cases. A lumbar puncture should be considered in children younger than 12 months of age or with suspected meningitis. Children with complex febrile seizures are at risk of subsequent epilepsy. Approximately 30–40% of children with a febrile seizure will have a recurrence during early childhood. The prognosis is favorable as the condition is usually benign and self-limiting. Intervention to stop the seizure often is unnecessary.

Conclusion: Continuous preventative antiepileptic therapy for the prevention of recurrent febrile seizures is not recommended. The use of intermittent anticonvulsant therapy is not routinely indicated. Antipyretics have no role in the prevention of febrile seizures.

Keywords: anticonvulsants, antipyretics, epilepsy, febrile infection-related epilepsy syndrome, febrile status epilepticus, meningitis.

Citation

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Introduction

Febrile seizures are generally defined as seizures occurring in children typically 6 months to 5 years of age in association with a fever greater than 38°C (100.4°F), who do not have evidence of an intracranial cause (e.g. infection, head trauma, and epilepsy), another definable cause of seizure (e.g. electrolyte imbalance, hypoglycemia, drug use, or drug withdrawal), or a history of an afebrile seizure.[1–5] Febrile seizure is a major challenge in pediatric practice because of its high incidence in young children and its tendency to recur. In recent years, there has been more awareness about the potential complications of febrile seizures and management of this condition. Updated guidelines for the evaluation and management of febrile seizures were published by the American Academy of Pediatrics (AAP) and the Japanese Society of Child Neurology in 2011 and 2015, respectively.[6,7] This article provides an update on current knowledge about febrile seizures and outlines an approach to their evaluation and management.

A PubMed search was conducted in March 2018 using Clinical Queries with the key terms 'febrile convulsions' and 'febrile seizures'. The search strategy included meta-analyses, randomized controlled trials, clinical trials, observational studies, and reviews.

Epidemiology

Febrile seizures are the most common neurologic disorder in the pediatric age group, affecting 2–5% of children between 6 months and 5 years of age in the United States and Western

Europe with a peak incidence between 12 and 18 months.[5,7–12] Although febrile seizure is seen in all ethnic groups, it is more frequently seen in the Asian population (5–10% of Indian children and 6–9% of Japanese children).[13] The incidence is as high as 14% in Guamese.[14] The male-to-female ratio is approximately 1.6 to 1.[8,10,11,15] The condition is more common in children belonging to a lower socioeconomic status, presumably because of inadequate access to medical care.[8] Seasonal and diurnal variations in the occurrence of febrile seizures have been observed by investigators in the United States, Finland, and Japan.[16–19] Basically, the majority of febrile seizures occur in the winter months and in the afternoon.[16–19]

Etiology and pathogenesis

The cause of febrile seizures is multifactorial. It is generally believed that febrile seizures result from a vulnerability of the developing central nervous system (CNS) to the effects of fever, in combination with an underlying genetic predisposition and environmental factors.[11,20] Febrile seizure is an age-dependent response of the immature brain to fever.[21] During the maturation process, there is an enhanced neuronal excitability that predisposes the child to febrile seizures.[21] As such, febrile seizures occur mainly in children before the age of 3 years when the seizure threshold is low.[21]

Family and twin studies suggest that genetic factors play an important role. Approximately one-third of children with febrile seizures have a positive family history.[22] The risk for febrile seizure for a child is about 20% with an affected sibling and about 33% with affected parents.[2] The concordance rate is about 35–69% and 14–20% in monozygotic twins and dizygotic twins, respectively.[2] The genes that might increase the risk for a febrile seizure have been mapped to the following loci of chromosomes: 1q31, 2q23-34, 3p24.2-23, 3q26.2-26.33, 5q14-15, 5q34, 6q22-24, 8q13-21, 18p11.2, 19p13.3, 19q, and 21q22.[23,24] Several modes of inheritance have been suggested, such as an autosomal dominant mode of inheritance with reduced penetrance and a polygenic or multifactorial mode of inheritance.[2,25–38] It has been shown that the height of the temperature rather than the rapidity of the rise in the temperature is the most significant risk factor for the development of a first febrile seizure.[8,21,30,39–43] In general, the higher the temperature, the greater the likelihood of a febrile seizure.[30,39] Children with febrile seizures have lower seizure threshold. Viral infection is the cause of fever in approximately 80% of cases of febrile seizures.[44] Roseola infantum (exanthem subitum), influenza A, and human coronavirus HKU1 pose the highest risk for febrile seizures.[4,25,41,45] Viral upper respiratory tract infection, pharyngitis, otitis media, and *Shigella* gastroenteritis are other important causes of febrile seizures.[39,45]

The risk of febrile seizures is temporarily increased for a few days after the administration of certain vaccines, notably, combined diphtheria–tetanus toxoids–whole-cell pertussis vaccine which is no longer used in North America.[46–48] Other vaccines implicated as causes of postvaccination febrile seizures include the combined diphtheria–tetanus toxoids–acellular pertussis–inactivated poliovirus–*Haemophilus influenzae type b* (DTaP–IPV–Hib) vaccine and measles–mumps–rubella–varicella vaccine, conjugated pneumococcal vaccine, and some formulation of inactivated influenza vaccines (e.g. Fluvax).[49–57] Generally, the absolute risk of postvaccination febrile seizure with these vaccines is small.[47,58]

Children born prematurely are susceptible to febrile seizures and postnatal treatment with corticosteroids further increases the risks.[59] Prenatal exposure to nicotine and/or alcohol is associated with a slightly increased risk of febrile seizure.[25,60] Prenatal or perinatal stress can have programming effects on the developing brain that enhance neuronal excitability resulting in lower seizure threshold.[61,62] Residential exposure to traffic noise and air pollution are other risk factors.[63]

Iron is essential for the functioning of certain neurotransmitters, such as monoamine oxidase and aldehyde oxidase.[64] Iron-deficiency anemia may predispose to febrile seizures.[44,64–70] Zinc deficiency is implicated as a risk factor for febrile seizures.[71–73] Several preliminary studies have shown that deficiencies in vitamin B12, folic acid, selenium, calcium, and magnesium increase the risk of febrile seizures.[71,73,74] Other risk factors include past history of febrile seizure, febrile seizure in a first-degree relative, intrauterine growth retardation, staying in a neonatal nursery >28 days, neurodevelopmental delay, and daycare attendance.[8,15,25,75]

Clinical manifestations

In most cases, febrile seizures occur within first day of the fever.[30,45] Seizures occurring ≥3 days after the onset of a fever should be suspect. At the time of a seizure, the majority of children have a temperature of ≥39°C.[10] Febrile seizures can be classified as either simple or complex based on duration, physical characteristics, and recurrence patterns.[45] Simple febrile seizures account for about 80–85% of all febrile seizures.[2,3,8] Loss of consciousness at the time of seizure is a constant feature.[76] Foaming at the mouth, difficult breathing, pallor, or cyanosis may also occur.[76]

Typically, a simple febrile seizure is generalized and associated with tonic–clonic movements of the limbs and rolling back of the eyeballs. The seizure usually lasts for a few seconds to at most 15 minutes (usually less than 5 minutes), followed by a brief postictal period of drowsiness, and does not recur within 24 hours.[2–4,10] The facial and respiratory muscles are often involved.[4] Atonic and tonic spells have also been described.[4] In contrast, a complex febrile seizure usually lasts longer than 15 minutes. The seizure is usually focal (movement limited to one side of the body or one limb). It may recur within the same day. The seizure may have a prolonged period of postictal drowsiness or be associated with postictal transient hemiparesis (Todd's palsy).[2,3,10,77] Generally, children with complex febrile seizures are younger and more likely to have

delay in development than those with simple febrile seizures.[4] The majority of children with complex febrile seizures do so with their first seizure, but children with initial simple febrile seizures may have complex febrile seizures subsequently.[4]

Febrile status epilepticus, the most severe type of complex febrile seizure, refers to continuous or intermittent febrile seizures without consciousness being regained at the interictal state for more than 30 minutes.[11,30,77] It should be noted that persistently open or deviated eyes are features of ongoing seizure activity.[4] Children with febrile status epilepticus are more likely to have hippocampal abnormalities and are also at increased risk for subsequent febrile status epilepticus.[11]

Clinical evaluation

A detailed history should be taken to find out the cause of the fever, the relationship of the onset of fever to the seizure, the characteristics of fever including the peak temperature and duration, seizure semiology, and duration of postictal drowsiness.[10] The history also should include personal history of prior seizure and whether the child was recently vaccinated, attended day care, or treated with an antimicrobial agent. Fever is common in the pediatric age group and may occur coincidentally with a more serious underlying cause of seizure. Therefore, enquiry should be made about immunization status, potential exposures to infection, toxin ingestion, CNS trauma, developmental milestones, prior seizures, and history of febrile and afebrile seizures in other family members.[10]

Vital signs should be monitored. A thorough physical examination should be done in order to find out the underlying cause of the fever. An erythematous bulging eardrum, a beefy red pharynx, enlarged and erythematous tonsils, and an exanthem may give clue to the source of the fever. The examination should search for signs of meningitis such as irritability, depressed sensorium, nuchal rigidity, bulging or tense fontanel, and Brudzinski's or Kernig's sign.[10] A formal neurological examination should be performed, including the level of consciousness, muscle tone and power, and peripheral reflexes. Any focal abnormalities should be noted. A fundus examination should be performed to look for increased intracranial pressure. Neurocutaneous stigmata that might suggest an underlying cause of the seizure should be searched for. A unilateral port-wine stain over the trigeminal area is suggestive of Sturge–Weber syndrome; facial angiofibromas, shagreen or leather patches, periungual/ungual fibromas (Koenen tumors), and hypopigmented macules ('ash-leaf spots') are suggestive of tuberous sclerosis; café au lait spots, intertriginous freckling, iris hamartomas (Lisch nodules), and cutaneous/subcutaneous nodules are suggestive of neurofibromatosis.[2,3]

Differential diagnosis

Febrile seizures should be differentiated from shaking chills (shivering), febrile delirium, breath-holding spells, CNS infection, febrile myoclonus, generalized/genetic epilepsy with febrile seizures plus (GEFS+), new-onset refractory status epilepticus (NORSE), and febrile infection-related epilepsy syndrome (FIRES).[78]

Shaking chills or shivering is defined as a perception of cold and involuntary muscle tremors that persist for several minutes. In contrast to febrile seizures, there is no loss of consciousness and no involvement of facial or respiratory muscles.

Febrile delirium refers to an acute and transient confusional state with high fever.[76] Tonic–clonic movements of the limbs and rolling back of the eyeballs are characteristically absent.

Breath-holding spells are episodes of brief, involuntary cessation of breathing that occur in children in response to stimuli such as anger, frustration, pain, or fear. Two types of breath-holding spells are recognized – the cyanotic type and the pallid type – based on the color of the child during the apneic episode. Typically, the child cries because he/she is upset, frightened, or injured. The child then holds his/her breath, usually for no more than one minute. Loss of consciousness may ensure if the apneic period is prolonged. Spontaneous recovery is the rule. The absence of fever, tonic–clonic movements of the limbs, and rolling back of the eyeballs distinguishes this condition from febrile seizure.

Children with CNS infection such as meningitis and encephalitis typically present with fever and seizure. Impaired consciousness, petechial rash, neck rigidity, Kernig's sign, and Brudzinski' sign, if present, give clue to the diagnosis. The differentiation can be difficult in a child younger than 12 months of age because meningeal signs can be subtle or absent.

Febrile myoclonus is a benign disorder affecting children mainly 6 months to 6 years of age.[79] Affected children present with myoclonic jerks, mostly involving the upper limbs during fever.[25] The myoclonic jerks may occur infrequently or several times per minute and may last from 15 minutes to several hours.[79,80]

GEFS+ is a syndromic autosomal dominant disorder with at least six phenotypes, delineated by their causative genes (e.g. *SCN1A*, *SCN2A*, *SCN1B*, and *GABRG2*). In contrast to febrile seizure, in GEFS+, the seizures with fever continue beyond 6 years of age, and afebrile seizures which could be myoclonic, atonic, or absence seizures also occur.[81–84]

NORSE is a clinical presentation, but not a specific diagnosis, in a patient without active epilepsy or other existing relevant neurological disorder, with new onset of refractory status epilepticus in the absence of a clear acute or active structural, metabolic, or toxic cause.

FIRES is regarded as a subset of NORSE that requires a febrile infection between 24 hours and 2 weeks prior to the onset of refractory status epilepticus, with or without fever at the onset of status epilepticus, and with no restriction to the age of the patient.[85]

It is difficult to distinguish the first episode of febrile seizure from a seizure resulting from epilepsy, GEFS+, and FIRES in a child with fever. The diagnosis of epilepsy, GEFS+, and FIRES could only be made with evolution of the clinical symptomatology and laboratory investigations.

Diagnostic evaluation

Blood tests usually are unnecessary if the history and physical examination are typical that of a febrile seizure.[6,7,30,39,77,86] A complete blood cell count and blood tests for glucose, electrolytes, urea nitrogen, creatinine, calcium, phosphorous, and magnesium are usually not helpful in evaluating a child with febrile seizure.[30,77] The basic laboratory workup should be individualized, guided by the history and physical examination results.[3,6,87] A complete blood cell count should be considered in children who appear ill. Children with bacteremia have a higher rate of febrile seizures.[88] Determination of serum glucose, electrolytes, creatinine, and urea nitrogen should be considered if there is a history of insufficient fluid intake, vomiting, or diarrhea or if there are physical signs of dehydration or edema. Urinalysis should be considered if the cause of the fever is obscure. Urine culture would be in order if the urinalysis is abnormal.

Lumbar puncture is not necessary in the majority of well-appearing children who have returned rapidly to a normal baseline after the seizure.[4] The AAP strongly urges clinicians to consider a lumbar puncture in children <12 months of age who present with a febrile seizure, especially if the immunization status for Hib and *Streptococcus pneumoniae* is unknown or deficient.[5] Other investigators suggest that a lumbar puncture should be considered in children <12 months of age who present with a febrile seizure regardless of their immunization status owing to lack of abnormal neurologic sign in a child of this age.[89] Lumbar puncture should be performed in children with any symptoms or signs of meningitis or febrile status epilepticus. The procedure should also be considered in children who have the seizure after the second day of fever, who have had prior antimicrobial therapy, or who do not 'look right'.[2,3,23] If lumbar puncture is performed, it is advisable to obtain blood culture and serum glucose determination concurrently.[4] Pleocytosis, low glucose level, and high protein level in the cerebrospinal fluid are indicative of bacterial meningitis, necessitating the need for culture of the cerebrospinal fluid.

There are no febrile seizure–specific electroencephalogram (EEG) findings, and EEGs are of limited value to predict recurrence of a febrile seizure.[5,8,30,77] A routine EEG is not helpful and is not recommended in the evaluation of a neurologically healthy child with a simple febrile seizure.[6,7,30,77] An EEG should be considered in children who have prolonged or complex febrile seizures, have a recurrence not associated with fever, or in children with recurrent febrile seizures who have developmental delays or neurologic deficits.[4,45,90] A 2017 Cochrane systematic review found no randomized controlled trials to refute or support the use of EEG and its timing after complex febrile seizures.[91]

Skull radiographs are useless in the evaluation of a child with febrile seizure. Neuroimaging studies such as magnetic resonance imaging (MRI) or cranial computed tomography (CT) are not routinely indicated in children with febrile seizures.[7,8,30] MRI or CT should be considered in patients with signs of increased intracranial pressure, focal neurologic abnormality, suspected structural defect in the brain, abnormally large heads, and severe head injury.[4,9,30]

Complications

Febrile seizures can be extremely frightening and emotionally traumatic for parents.[92–94] The condition can cause undue anxiety and panic to parents who may be under the impression that their child might die during the seizure and brain damage is inevitable if their child is going to survive.

It is the seizure type that defines risk of future epilepsy. Children with simple febrile seizures have a slightly higher risk of subsequent epilepsy of around 1% compared with the incidence in the general population of approximately 0.5%.[39,77] The risk of future epilepsy in children with complex febrile seizures is around 4–6%, depending on the number of complex features.[8,25,45,51,75,95] Other risk factors for the development of epilepsy include shorter duration of fever (<1 hour) before the seizure, an onset of febrile seizures before the age of 1 year or after the age of 3 years, multiple episodes of febrile seizures, an underlying neurodevelopmental abnormality, a positive family history of epilepsy, and epileptiform discharges on EEG.[8,51,95–98] Generally, the number of febrile seizures does not alter the risk of subsequent epilepsy.

Encephalopathy is rarely a complication with febrile seizures.[99] Recent evidence shows that missense mutations in sodium channel *SCN1A* and *SCN2A* genes may predispose children to severe febrile seizures.[100] Febrile seizure, especially if recurrent, severe, and prolonged, may induce persistent alternations of hippocampal neuronal circuits in balance between excitatory and inhibitory responses as well as mesial temporal sclerosis, leading to epileptogenesis following febrile seizures.[1,99,101,102] Prolonged febrile seizures may also cause disruption in white matter maturation, with subsequent neuroplasticity and microstructural reorganization.[103]

It is generally believed that children with simple febrile seizures are not at increased risk for the later development of a neurologic deficit, and their intelligence and cognitive function are not affected.[5,104] A population-based cohort study in Rotterdam showed that there was no association of febrile seizures with the risk of behavioral problems or executive functioning.[105] In contrast to single febrile seizures, recurrent febrile seizures were significantly associated with an increased risk of delayed vocabulary development (odds ratio: 3.22; 95%

CI: 1.3–7.94). In the Child and Adolescent Study in Sweden targeting twins born since July 1, 1992, parents of 27,092 twins were interviewed using a validated Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV-based interview for early symptomatic syndromes eliciting neurodevelopmental clinical examinations (ESSENCE), in connection with the twins' ninth or twelfth birthday.[106] ESSENCE refers to autism spectrum disorder, learning difficulty, developmental coordination disorder, and attention-deficit/hyperactivity disorder. The authors, however, found that the rate of ESSENCE in febrile seizures and epilepsy was significantly higher than in the total population without febrile seizures (all $p<0.001$). After adjusting for epilepsy, a significant association between febrile seizures and developmental coordination disorder, autism spectrum disorder, and intellectual disability remained.

Studies on the relationship between febrile seizures and subsequent development of attention-deficit/hyperactivity disorder have yielded contradictory results.[3,10,30] Recent studies showed that children, especially boys, with febrile seizures are at increased risk for attention-deficit/hyperactivity disorder.[107,108] Bertelsen et al. followed up a population-based cohort of all children born in Denmark from 1990 through 2007.[107] Of a total of 906,379 individuals followed, 21,079 individuals developed attention-deficit/hyperactivity disorder. In children with febrile seizures, the fully adjusted incidence rate ratio of attention-deficit/hyperactivity disorder was 1.28 (95% CI: 1.2–1.35). In individuals with both febrile seizures and epilepsy, the fully adjusted incidence rate ratio of attention-deficit/hyperactivity disorder was 3.22 (95% CI: 2.72–3.83). It is hoped that future well-designed, large-scale studies will provide us with more information on febrile seizures and subsequent development of attention-deficit/hyperactivity disorder.

Febrile seizures may increase risk of subsequent Tourette syndrome.[109] Using the Taiwan National Health Insurance Research Database, Tu et al. conducted a retrospective analysis on 1,586 patients with febrile seizures.[109] The authors found that the overall incidence of Tourette syndrome was higher in the cohort with febrile seizures than in the cohort with no febrile seizures (28.5 versus 13.9 per 10,000 person-years; adjusted hazard ratio: 1.91; 95% CI: 1.32–2.75). Risk factors for patients with febrile seizures to develop Tourette syndrome were male sex, children living in rural areas, and children whose parents held blue-collar positions. The risk of Tourette syndrome in patients with febrile seizures rose from 0.89 to 16.0 (trend test $p<0.0001$) when the frequency of febrile seizure-related medical visits increased from one to two times to more than four times. The adjusted hazard ratio for Tourette syndrome in relation to febrile seizure-related medical visits was 1.02 (95% CI: 1.02–1.03) per one frequency increment.

In contrast to the former belief that no association exists between febrile seizures and sudden unexplained death in childhood,[1,5,39] recent studies show otherwise.[110–113] Children with febrile seizures, mainly those with complex febrile seizures and febrile status epilepticus, can die suddenly and unexpectedly in a manner reminiscent of adult sudden unexpected death in epilepsy.[112] In a recent study, Stampe et al., through the usage of nationwide registries in Denmark, identified 245 cases of sudden cardiac death, 14 (5.7%) of them were admitted with febrile seizures.[113] The study showed a significantly two-fold increase in the frequency of febrile seizures prior to death in young sudden cardiac death cases compared with the controls. The authors suggest that febrile seizures could potentially contribute in a risk-stratification model for sudden cardiac death.

Children with febrile seizures have higher risk for atopic diseases such as allergic rhinitis and asthma.[4,114,115] A high prevalence of stress hyperglycemia has been reported in children with febrile seizures.[116] Rarely, febrile seizures may be complicated by neurogenic pulmonary edema.[117]

Prognosis

The prognosis is favorable as the condition is usually benign and self-limiting.[11] Typically, children outgrow the condition by 6 years of age. Approximately, one-third of children who have had a febrile seizure will have a recurrence during early childhood, but less than 10% will have ≥ three recurrences.[9–12,30] If recurrence is going to occur, approximately 75% of recurrences will occur within 1 year and 90% will occur within 2 years.[12,45] Risk factors for recurrences of febrile seizures include age of onset <15 months, relatively lower temperature at the time of the first febrile seizure, shorter interval (less than 1 hour) between the onset of fever and the initial seizure, febrile seizure and epilepsy in a first-degree relative, day-care attendee, frequent febrile illnesses, multiple febrile seizures during the same febrile illness, a first febrile seizure that is complex, and neurodevelopmental delay.[9–15,25,39] Generally, the greater the number of risk factors, the higher the recurrence rate.[8,39,45] Children without any of these risk factors have a 4% chance of recurrence, whereas those with all the risk factors have up to 80% chance of recurrence.[12] The majority of children with simple febrile seizures have normal growth and development.[75]

Management

Intervention to stop the seizure usually is unnecessary as the seizure has typically resolved by the time the child is evaluated by a physician. On the other hand, treatment should be initiated if the seizure is still ongoing by the time the child arrives at a medical facility. If that is the case, the child can be treated with intravenous lorazepam (0.05–0.1 mg/kg) or diazepam (0.1–0.2 mg/kg) which is very efficient in terminating the seizure.[2,11,23,39,96] A 2018 Cochrane systematic review showed that intravenous lorazepam was as effective as intravenous diazepam in stopping acute tonic–clonic convulsions in children (3 trials; n=414; risk ratio: 1.04; 95% CI: 0.94–1.16) and both medications had similar rates of respiratory depression.[118] In a double-blind, randomized clinical

trial of 273 children (aged 3 months to 17 years) with status epilepticus, patients were randomized to receive either 0.2 mg/kg of diazepam (n=140) or 0.1 mg/kg of lorazepam (n=133).[119] Cessation of status epilepticus for 10 minutes without recurrence within 30 minutes occurred in 101 of 140 (72.1%) in the diazepam group and 97 of 133 (72.9%) in the lorazepam group, with an absolute efficacy of 0.8% (95% CI: –11.4 to 9.8). When the intravenous route is unavailable or inaccessible, diazepam administered rectally (0.5 mg/kg), buccally (0.5 mg/kg), or intranasally (0.2 mg/kg) and midazolam administered buccally (0.2 mg/kg) or intranasally (0.2 mg/kg) are safe and effective alternatives.[3,11,30,39,96]

Febrile status epilepticus rarely stops spontaneously and often requires more than one antiepileptic medication to control.[11,120] The initial treatment consists of intravenous administration of lorazepam (0.1 mg/kg) or diazepam (0.2 mg/kg).[121] If the seizures continue after 5 minutes, the dose of lorazepam (0.1 mg/kg) or diazepam (0.2 mg/kg) can be repeated intravenously.[121] If the seizures continue for 10–15 minutes, fosphenytoin at a dose of 20 mg phenytoin equivalents/kg or phenobarbital at a dose of 20 mg/kg can be given intravenously.[121] If the seizures persist, an additional dose (5–10 mg phenytoin equivalents/kg) of fosphenytoin can be given intravenously 10 minutes after the loading dose. The other option is to give intravenous phenobarbital at a dose of 20 mg/kg, valproic acid at a dose of 20–40 mg/kg, or levetiracetam 20–60 mg/kg.[121]

Vital signs such as temperature, heart rate, respiratory rate, and blood pressure should be monitored during a seizure.[77] Children admitted to hospital should be monitored with continuous pulse oximetry. Hypoxic children should be given supplemental oxygen through nasal cannulae, head box, face mask, or high-flow delivery device to maintain SaO_2 >92%. Removal of excessive clothing and blankets may help to bring down the fever. An antipyretic may be given if the fever is high enough to cause discomfort in the child. Suffice to say, normalization of the body temperature might not prevent further febrile seizures; the use of an antipyretic may make the child more comfortable.[2,3,30,77] Of course, the cause of the fever should be treated whenever possible.

Febrile seizures can be anxiety-provoking for parents as a result of poor parental knowledge. It has been shown that parental anxiety can be minimized with an educational intervention program.[3,39] Parents should be reassured of its benign nature and favorable outcome and rare association of simple febrile seizures with epilepsy.[12,39] They also should be reassured of the benign nature of the condition and that treatment often is unnecessary. In this regard, organizing effective educational intervention programs for parents on what they should do if further febrile seizures occur at home can be helpful.[3,12,92,93] It is recommended that every parent take a community cardiopulmonary resuscitation course. Parents should be taught to place the child with a febrile seizure in a semiprone position so as to decrease the risk of aspiration.[2]

The majority of children with febrile seizures do not require hospitalization. They can be discharged home once they have returned to their normal selves and judged to be well after parental education has been given (vide supra).[11] Hospital admission should be considered to those suspicious to have a serious infection and those with prolonged and/or focal seizures, especially if there is delayed recovery to baseline or residual neurological findings.[11,76]

Prevention

Children with febrile seizures are at risk for recurrence and subsequent development of epilepsy.[8,12,25,51,95] A 2017 Cochrane systematic review showed that daily administration of valproic acid (10–15 mg/kg/day in divided doses) or phenobarbital (5–8 mg/kg/day for children <2 years of age and 3–5 mg/kg/day for children >2 years of age in divided doses) is effective in the prevention of febrile seizures.[2,9,122] Adverse events occur in 30–40% of children on chronic antiepileptic therapy.[11,122] Adverse side effects of valproic acid include flu symptoms, headache, nervousness, insomnia, alopecia, renal toxicity, pancreatitis, gastrointestinal disturbances, thrombocytopenia, and fatal hepatotoxicity.[5,9,81] Adverse side effects of phenobarbital include dizziness, loss of appetite, nausea, vomiting, transient sleep disturbances, daytime drowsiness, decreased memory, loss of balance, irritability, impaired cognitive function, aggression, attention deficit, and hyperactivity.[5] The potential adverse effects of valproic acid and phenobarbital outweigh their benefits.[5] Other anticonvulsants such as phenytoin and carbamazepine are ineffective in the prevention of recurrent febrile seizures.[5,96] Given the relatively benign nature of most febrile seizures, the majority of children do not have recurrences, and the significant adverse side effects associated with anticonvulsants, the current consensus is that ongoing prophylaxis with anticonvulsants is not necessary for children with either simple or complex febrile seizures.[5,8,11,39] The AAP does not recommend continuous antiepileptic therapy with phenobarbital or valproic acid for the prevention of recurrent febrile seizures.[5] Also, use of chronic antiepileptic therapy does not reduce the risk of epilepsy.[5,11]

Salehiomran et al. conducted a single-blind, randomized clinical trial on children with febrile seizures to compare effectiveness of continuous oral phenobarbital versus intermittent oral diazepam in the prevention of recurrence.[123] Of the 145 children, 74 children (mean age 20.59±7.93 months) received oral phenobarbital 3–5 mg/kg/day in two divided doses for at least one year. The remaining 71 children (mean age 22.61±9.11 months) received oral diazepam 0.33 mg/kg three times a day during febrile illness for 2 days. The recurrence rate was 17/74 (23%) in the phenobarbital group and 11/71 (15.5%) in the diazepam group. The difference was not statistically significant (p=0.296). The adverse effects were less with intermittent therapy compared with continuous therapy.

Diazepam, when administered intermittently either orally or rectally in sufficient doses (0.3–0.5 mg/kg, maximum 10 mg) at the onset of fever, has been shown to be effective in the prevention of the recurrence of febrile seizures.[5,124] However, some seizures occur before a fever is noticed, rendering intermittent diazepam treatment impractical.[5,23] Adverse side effects of diazepam therapy include lethargy, drowsiness, nausea, constipation, dry mouth, slurred speech, ataxia, dizziness, headache, irritability, hypotension, bradycardia, and respiratory depression.[5] The adverse effects might mask evolving signs of meningitis. Generally, the adverse events associated with intermittent use of diazepam in the prevention of febrile seizures outweigh the potential benefits.[5] Other antiepileptic medications that have been used for intermittent prophylaxis of recurrent febrile seizures include oral clobazam and levetiracetam.[81,125,126] The present consensus is that the use of intermittent anticonvulsant in preventing febrile seizures is not routinely indicated.[5] In situations where parental anxiety is high, particularly in patients with a history of multiple and/or prolonged febrile seizures (especially febrile status epilepticus) and those at high risk for recurrence, intermittent therapy with oral or rectal diazepam or nasal/buccal midazolam at the onset of a febrile illness may be considered.[2,3,5,6,11]

Both acetaminophen (15 mg/kg/dose every 6 hourly p.r.n.) and ibuprofen (5 mg/kg/dose every 8 hourly p.r.n.) are effective antipyretic agents in children with fever and may be used to relieve the discomfort of a febrile child.[2,13,81] Controlled studies of antipyretic medications given during a febrile illness, however, have failed to show a preventive effect on the recurrence of febrile seizure.[5,12–14,39] Rosenbloom et al. performed a systematic review on three randomized controlled trials comparing the efficacy of antipyretic drugs in reducing the rate of recurrence in children aged 6–72 months with previous febrile seizures during a 1- to 2-year follow-up period.[127] The antipyretics used were acetaminophen (15 mg/kg), ibuprofen (5–10 mg/kg), and diclofenac (1.5 mg/kg). The authors found that 79 out of 328 children (22.7%) in the treatment group and 43 out of 192 children (24.4%) in the placebo group had recurrence of febrile seizures during the follow-up, showing no statistical significant difference (odds ratio: 0.9; 95% CI: 0.57–1.43).

Likewise, there is no evidence to suggest physical methods of temperature reduction (e.g. tepid sponging, direct fanning of the child, cooling room, and removing clothing) are useful to prevent recurrence of febrile seizure in children with previous febrile seizures.[6,7,14]

Effective childhood vaccinations help to reduce the morbidity and mortality attributable to many infectious diseases.[52,128] Some of these diseases may cause fever and febrile seizures. Therefore, universal childhood vaccinations are essential and should be strongly encouraged to reduce the risk of febrile seizures in the years to come. Use of prophylactic antipyretic before vaccinations is not indicated as no statistically significant reduction in the rate of febrile seizures has been documented.[129] In addition, prophylactic antipyretic use may decrease the immune response to certain vaccines.[129]

Conclusion

Febrile seizures are the most common type of seizure in the pediatric age group, affecting 2–5% of children between 6 months and 5 years of age. The majority of febrile seizures are simple, and the only 15–20% are complex febrile seizures. Simple febrile seizures are usually benign, but children with complex febrile seizures are at risk for future epilepsy. Approximately one-third of children who have a febrile seizure will have a recurrence during early childhood. Typically, children outgrow the condition by 6 years of age.

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Correspondence: Alexander KC Leung, The University of Calgary, Alberta Children's Hospital, #200, 233 – 16th Avenue NW, Calgary, Alberta, Canada T2M 0H5. aleung@ucalgary.ca

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