

PRACTITIONERS' SECTION

FEBRILE SEIZURES: A REVIEW FOR FAMILY PHYSICIANS

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ABSTRACT

Febrile seizures are the most common cause of convulsions in children. Most are simple in nature, although those with focal onset, prolonged duration (≥ 15 min) or those that recur within 24 h or within the same febrile illness are considered complex. Diagnosis of this condition is essentially clinical and based on its description provided by parents. Its pathophysiology remains unclear, but genetics plays a major role in conferring susceptibility. Although most febrile seizures are benign and associated with minor viral illnesses, it is critical that the child be evaluated immediately to reduce parental anxiety and to identify the cause of the fever. It is essential to exclude underlying pyogenic meningitis, either clinically or, if any doubt remains, by lumbar puncture. The risk of pyogenic meningitis is as low ($< 1.3\%$) as the risk in a febrile child without seizures. After an initial febrile seizure (simple or complex), 3-12% of children develop epilepsy by adolescence. However, the risk of developing epilepsy after an initial simple febrile seizure is low (1.5-2.4%). Since the vast majority of children have a normal long-term outcome, antiepileptic medication is not recommended to prevent recurrence of febrile seizures. Oral diazepam or clobazam, given only when fever is present, is an effective means of reducing the risk of recurrence. The family physician can play an important role in counseling the parents that most febrile seizures are brief, do not require any specific treatment or extensive work-up, the probability of frequent or possibly threatening recurrences is low and the long-term prognosis is excellent.

Key words: *Febrile convulsions, fever, outcome, parental counseling, primary care, prophylaxis*

INTRODUCTION AND DEFINITION

Although the relation between fever and convulsions in children had been documented by Hippocrates as early as the 5th century B.C., it was not until 1980 that febrile

seizures were recognized as a distinct clinical entity, separate from other types of convulsions in early childhood.^[1,2]

There are two operational definitions of a

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febrile seizure (FS).^[2,3] The National Institute of Health consensus statement (1980) defines an FS as 'an event in infancy or childhood usually occurring between 3 months and 5 years of age, associated with fever but without evidence of intracranial infection or defined cause for the seizure.'^[2] The International League Against Epilepsy (1993) defines an FS as 'a seizure occurring in childhood between 1 month and 5 years of age, associated with a febrile illness not caused by an infection of the central nervous system, without previous neonatal seizures or a previous unprovoked seizure and not meeting criteria for other acute symptomatic seizures.'^[3] These two definitions only differ in the lower age limit (3 versus 1 month respectively), and both do not exclude children with prior neurological impairment. Thus an FS can occur even in a child with prior neurological abnormality such as cerebral palsy or developmental delay.^[2,3]

Although the essential precursor of an FS is necessarily a fever, neither definition provides a specific temperature criterion for its diagnosis.^[2,3] Over the years, an axillary temperature of either $>38^{\circ}\text{C}$ or $>37.8^{\circ}\text{C}$ as a simple cut off level has been proposed to diagnose an FS, but there is still no consensus.^[4,5]

INCIDENCE OF FEBRILE SEIZURES

Febrile seizures are the most common cause of convulsions in children and a frequent cause of emergency hospital admissions.^[6-9] Between 2 and 5% of children (more common in boys) in Europe and the United States

experience at least one FS before the age of 5 years.^[6-9] Although earlier Indian studies suggested that up to 10% of children experience an FS, recent data indicate that the incidence rate in India is similar to western figures.^[10,11]

TYPES OF FEBRILE SEIZURES

Febrile seizures are typically divided into two types: 'simple' and 'complex.' A simple FS is a generalized seizure (without focal features) which lasts less than 15 min and occurs only once during a 24-hour period of fever in a neurologically normal child.^[12,13] Most febrile seizures are simple in nature, and children with simple febrile seizures form a relatively homogeneous group of patients.^[6,7,14,15]

A complex FS is defined as an FS with one or more of the following features: (i) a focal onset or shows focal features during the seizure or is followed by a neurological deficit or (ii) prolonged duration (≥ 15 min) or (iii) recurrent within 24 h or within the same febrile illness or (iv) the child has a previous neurological impairment, such as cerebral palsy or developmental delay. Between 9 and 35% of febrile seizures are complex.^[6,7,14,16] Since a complex FS can have one or more complex features (focal, prolonged or multiple), children with complex febrile seizures form a relatively heterogeneous group of patients.^[16]

WHAT CAUSES FEBRILE SEIZURES?

The pathophysiology of febrile seizures remains unclear.^[17] It is generally believed

that an FS is an age-dependent response of the immature brain to fever.^[17] This postulation is supported by the fact that most (80-85%) febrile seizures occur between 6 months and 3 years of age, with the peak incidence at 18 months.^[6-8] Although the mechanism of this increased susceptibility is unclear, animal models suggest that there is enhanced neuronal excitability during the normal brain maturation.^[17]

It is well known that febrile seizures tend to occur in families, and this genetic susceptibility can be transmitted through both parents.^[18,19] A positive family history for febrile seizures can be elicited in 25-40% of children with febrile seizures, and the reported frequency in their siblings ranges from 9-22%.^[18] Familial clustering studies indicate a doubling of risk in children when both parents, rather than one parent, had febrile seizures.^[19] Studies show a higher concordance rate in monozygotic as compared to dizygotic twins.^[20] Although there is clear evidence for a genetic basis, the precise mode of inheritance is unclear.^[20,21] Most studies suggest that the mode of inheritance of susceptibility to febrile seizures is mostly polygenic and rarely autosomal dominant.^[20,21] No single human leukocyte antigen (HLA) haplotype has been found to be statistically more frequent among pooled FS subjects because of the considerable genetic heterogeneity of proneness to febrile seizures.^[20,21] In recent times, linkage studies in several large families in Japan have mapped the FS susceptibility genes to two putative loci, FEB1 (chromosome 8q13-q21) and FEB2 (chromosome 19p13.3), indicating an

autosomal dominant pattern with reduced penetrance.^[21]

Preliminary studies in children suggest that the cytokine network is activated and may have a role in the pathogenesis of febrile seizures.^[22] Children with febrile seizures have been reported to have significantly low levels of plasma ferritin, suggesting a possible role of iron insufficiency.^[23] The incidence of febrile seizures in thalassemic children is significantly lower, and iron overload may be a major factor that prevents their occurrence.^[24] Also, significantly lower levels of zinc have been reported in the serum and cerebrospinal fluid of children with febrile seizures.^[25,26] However, the precise clinical significance of these observations remains unclear.

ACUTE MANAGEMENT OF A FEBRILE SEIZURE

Control the seizure

Most often the FS has already ended spontaneously by the time a child is brought to a physician.^[27] In the rare event that the child is brought to the physician within 15 min and is still convulsing, intravenous diazepam (0.2-0.5 mg/kg of body weight) or rectal diazepam (0.5 mg/kg of body weight) should be given, and it is effective in stopping the seizure within 5 min.^[27] The child should be positioned in the left lateral position with chin up to maintain airway and allow drainage of secretions or vomitus. Nasal oxygen via a face mask should be given if the child is cyanosed.^[27] Recently a newer benzodiazepine, midazolam (0.15 mg/kg of body weight intramuscularly or 0.1 mg/kg of

body weight intravenously), has been found to be as effective as diazepam in stopping an FS, with the added advantage of quicker cessation and lesser risk of apnea.^[28]

For a child who continues to convulse, a second dose of intravenous diazepam (or midazolam) should be repeated after 15 min.^[29] In the rare event of the child still continuing to convulse, a diagnosis of febrile status epilepticus (viz., an FS or series of febrile seizures without recovery of consciousness between seizures lasting ≥ 30 min) should be made, and a standard status epilepticus treatment protocol is indicated.^[29] Optimum management of status epilepticus requires admission to a pediatric intensive care unit and is outside the purview of this review article.^[29]

Evaluate the child and locate focus of fever

The diagnosis of an FS is essentially clinical and based on the accurate description of the seizure and its clinical setting as provided by a reliable parent/caregiver.^[12] The physician should take a detailed clinical history to identify the cause of the fever and initiate its treatment. Also, family history of febrile seizures; recent antibiotic therapy, including self-medication given by parents; and recent history of immunization should be specifically asked for.^[12]

The risk of serious bacterial illness such as pyogenic meningitis or bacteremia in a child with a simple FS is as low (<1.3%) as the risk in a febrile child without seizures.^[30] It is generally believed that the risk of serious bacterial illness with a complex FS is higher

(~9%), but the exact figure is not known.^[4] The common causes of fever in USA in up to 60-65% children with a simple FS include viral infections, viz., otitis media, upper respiratory tract infection and tonsillitis.^[30] Urinary tract infection as the cause of fever occurs in 3% children.^[30] In up to one-third of children with simple febrile seizures, the fever focus cannot be identified.^[30] In recent years, human herpes virus-6 and influenza virus type A have been implicated as etiologic agents.^[31-34] Receipt of diphtheria, whole-cell pertussis and tetanus toxoid (DPT) vaccine; and measles, mumps and rubella (MMR) vaccine has been reported to be associated with a transiently increased risk of an FS on the day of vaccination and 8-14 days after vaccination respectively.^[35] DPT and MMR vaccines cause between '6 and 9' and '25 and 34' additional extra-febrile seizures per 100,000 immunized children respectively.^[35,36] However, these risks do not outweigh their benefits and do not appear to be associated with any long-term adverse consequences.^[35,36] In our country since malaria is endemic, it should always be suspected as a cause of fever.

Most children with a simple FS regain full consciousness within 30 min of the convulsion.^[12,15] A thorough clinical examination should be done (including otoscopic examination) to identify the cause of fever. Neurological examination for evidence of meningitis or encephalitis or any underlying neurological deficit is essential.^[12,15] Consequently, one of the most important clinical decisions to make is whether a lumbar puncture (LP) is necessary to rule out pyogenic meningitis or encephalitis.^[12,15]

Earlier it was recommended that an LP should be (i) 'almost certainly' performed in every child less than 1 year of age who presents with a first simple FS and (ii) 'considered' in every child less than 18 months of age who presents with a first simple FS; because the signs of meningitis may be subtle.^[4,12] In recent years, it is being increasingly recognized that doing an LP in infants following a first simple FS who do not have symptoms or signs of meningitis is unnecessary.^[27,30]

However, since the consequences of missing even one case of meningitis will be disastrous, all children with a simple FS who are below 18 months of age, all children with a simple FS who have had prior antibiotic treatment and all children with a complex FS should be admitted to a hospital for close observation.^[37-39] Regular clinical review by the physician in the first few (at least four) hours after the convulsion, with an emphasis on examination for signs of meningitis, will help detect meningitis.^[37-39] If no deterioration occurs and the child appears well, LP need not be done.^[37-39] Of course, a physician should not hesitate to perform LP if his or her clinical judgment considers the procedure necessary.^[27]

The two clear-cut indications for doing an LP in a child with an FS include (i) a complex FS (focal, prolonged or multiple), (ii) clinical history and examination being highly suggestive of occult meningitis (child unwell for 3 days or more before convulsion, decreased feeding or vomiting or drowsy at home, presence of bulging fontanel, dubious

nuchal rigidity, presence of petechiae or prolonged (>30 min) drowsiness/altered consciousness/delirious behavior after the convulsion).^[38-41]

Investigations to be done

No significant association has been found between complete blood counts and the characteristics of febrile seizures.^[42,43] In the developed countries, routine blood tests are not recommended unless where clinically indicated.^[12,27,39] However, a complete blood count may be useful in evaluating the cause of fever in children younger than 2 years.^[12] In our country, it would be prudent to do a peripheral blood smear examination for malarial parasites in every child with an FS. When no source of infection is found clinically, a urine sample should be taken for microscopy and culture.^[12,27,39]

Electroencephalography (EEG) is not indicated, irrespective of whether the FS is simple or complex, as it is of no use in predicting recurrence or development of epilepsy.^[12,44] Recurrent simple or complex febrile seizures also do not justify an EEG, as it is of no use in identifying an underlying structural abnormality or predicting development of epilepsy.^[44,45] Neuroimaging (CT scan or MRI) is not indicated in a child with a simple FS.^[4,12] Even for well-appearing children with a first complex FS (focal, multiple or prolonged), routine emergency neuroimaging is unnecessary as there is no risk of intracranial pathologic conditions such as a mass lesion, hemorrhage, hydrocephalus or abscess that requires emergency neurosurgical or medical intervention.^[46]

However, rare events such as (i) post-ictal neurological deficit persisting for more than a few hours following a complex FS, (ii) febrile status epilepticus, (iii) recurrent complex febrile seizures are indications for doing an MRI brain study, which would help detect any underlying inflammatory focal encephalitis (Rasmussen's encephalitis) or any structural defect such as cortical dysgenesis.^[27]

Reassure and counsel parents

Witnessing an FS is emotionally traumatic for parents, and many think that their child is dying or their child's brain is getting damaged.^[47,48] After an initial FS, parents can develop persistent fear of fever, of their recurrence and of future epilepsy - all which negatively affect their family life and routines.^[47,48] Therefore, reassuring and counseling parents is one of the most important aspects of management of febrile seizures.

After the acute episode resolves, the physician should reassure the parents that there is no risk of death or brain damage.^[4,27,38,39] Since viral infections are the commonest cause of fever which triggers an FS, the only medication required is an antipyretic.^[4,27,38,39] Either syrup paracetamol or ibuprofen (both 10 mg/kg of body weight per dose every 6 h) should be started and continued until the child is afebrile for 24 h.^[4,27,38,39] Parents should also be instructed to strip the child naked and to tepid sponge the whole body using tap water (not cold water) to control the fever.^[4,27,38,39,49] Rarely, oral antibiotics are indicated if follicular tonsillitis or urinary tract infection is the cause of fever.^[27,38,39]

NATURAL HISTORY AND OUTCOME OF FEBRILE SEIZURES

Risk of recurrence

After an initial FS, about a third of children will experience a recurrence.^[6,50-52] Half the recurrences occur within 6 months of the first FS, three-quarters within a year and 90% within 2 years.^[50-53] Risk factors identified for recurrence include (i) young age (<18 months), (ii) family history of febrile seizures in a first- or second-degree relative, (iii) a low temperature (<40°C) at the initial FS and (iv) multiple febrile seizures occurring during the first episode.^[50-53] Even febrile status epilepticus in a neurologically normal child does not increase the risk for recurrence.^[54] It should be remembered that an episode of fever is, in fact, the only time that the child is at risk of recurrence.^[2]

Risk of epilepsy

After an initial FS (simple or complex), about 3-12% of children will subsequently develop epilepsy by adolescence.^[10,14,55,56] However, the risk of developing epilepsy after a simple FS is low (1.5-2.4%).^[10,14,55,56] Risk factors for developing epilepsy include (i) preexisting neurodevelopmental abnormalities, (ii) complex FS and (iii) family history of epilepsy in a first- or second-degree relative.^[55-57] It should be noted that these risk factors are different from the risk factors associated with recurrence of febrile seizures.

Children with history of a simple FS who later develop epilepsy usually develop generalized epilepsy.^[55-57] It had earlier been suggested that a prolonged (complex) FS in infancy can

lead to hippocampal injury and mesial temporal sclerosis resulting in temporal lobe epilepsy in later childhood.^[58,59] Subsequent research has indicated that a hippocampus that has already been damaged either by a prenatal or perinatal insult or by genetic predisposition causes prolonged FS in infancy and that there is no causal association between a prolonged FS and mesial temporal sclerosis.^[60,61]

Risk of cognitive impairment

Population-based studies have found that previously normal children who had febrile seizures (simple or complex, including febrile status epilepticus) perform as well as other children in terms of their academic progress, intellect and behavior at 5 and 10 years of age.^[62,63]

Also, recent studies have reported that cerebrospinal fluid levels of neuron-specific enolase and lactic dehydrogenase, markers for neuronal injury, are not elevated in children following a simple or complex FS, including febrile status epilepticus, which confirms that febrile seizures are not associated with neuronal damage.^[64,65]

Risk of death

There is no increased risk or incidence of death in children with febrile seizures, including febrile status epilepticus.^[14,54]

LONG-TERM MANAGEMENT OF FEBRILE SEIZURES

Although antipyretics (paracetamol or ibuprofen) prescribed during a subsequent febrile illness provide comfort and

symptomatic relief to a child, they do not prevent FS recurrence.^[66,67] Daily anticonvulsant therapy with phenytoin or carbamazepine is also not effective in preventing FS recurrence.^[68,69] Although daily anticonvulsant therapy with phenobarbitone or valproic acid has been shown to reduce the risk of FS recurrence, its potential significant side effects (impairment of short-term memory, reduced concentration, paradoxical hyperactivity - with phenobarbitone; and hematopoietic disturbances, renal toxicity, pancreatitis, fatal hepatotoxicity - with valproic acid) outweigh the relatively minor risks associated with FS recurrences.^[68,69] Since the vast majority of children with either simple or complex febrile seizures have a normal long-term outcome, continuous daily use of antiepileptic medication is no longer *routinely* recommended to prevent recurrence.^[4,69,70] Also, no antiepileptic medication has been shown to prevent future epilepsy.^[68,70]

Parents assign tremendous value to the prevention of FS recurrence.^[71] Parents should be made aware that the risk of FS recurrence declines rapidly after 6 months from the previous seizure.^[50-53] Parents should be educated about the natural history of febrile seizures to reduce their anxieties.^[72] They should be taught how to measure temperature using a thermometer and how to do tepid sponging when the child has fever. They should be explained the correct dose of an antipyretic agent (paracetamol or ibuprofen) which needs to be given at home when fever is detected in order to comfort the child. They should soon consult a family physician as any febrile illness, per se, requires medical

attention. They should also be taught by actual demonstration how to place their child in the left lateral position with chin up for optimal airway patency in case of recurrence.^[72] Parents should be told not to indulge in incorrect, but culturally prevalent, practices such as putting devices in the child's mouth or applying an onion over the nostrils. Also, a prescription for rectal diazepam should be given and the parents instructed how to administer it at home (a single dose of 0.5 mg/kg body weight) in the rare event of the recurrence being lengthy (>15 min).^[73,74] Imparting such educational information to parents has been shown to reduce their anxieties and improve their skills in managing subsequent febrile episodes.^[72,75]

Parents may still demand a specific medication to prevent FS recurrence. In such situations where parental anxieties remain high or when the child is at risk for recurrence, prescribing use of an oral rapidly acting benzodiazepine (diazepam or clobazam) at the onset of febrile illness is an effective measure in reducing the risk of recurrence.^[50-53,76-79] Oral diazepam (0.33 mg/kg of body weight/dose, 8 hourly) is given till the child is afebrile for 24 h.^[76] Oral clobazam (0.3-1.0 mg/kg of body weight/day) is given in two divided doses, viz., 12 hourly, and continued for 48 h and stopped after 48 h irrespective of whether the fever persists or not.^[78] Both are equally effective and safe but can have side effects such as drowsiness, muscular weakness and pseudoataxia.^[76-79] However, ataxia is less marked with clobazam use.^[79] Since oral clobazam therapy has fewer side effects and since its 12 hourly dosage schedule ensures better compliance, it is now

preferred to diazepam in the intermittent treatment of FS recurrence.^[78,79] However, clobazam is available only in tablet form, and the parent needs to be explained to crush the prescribed tablet and prepare a palatable syrup dose.^[79] The recommended dosage schedule for clobazam according to the child's weight is as follows: 6-10 kg, 5 mg twice daily; 11-15 kg, 7.5 mg twice daily; >15 kg, 10 mg twice daily.^[79]

IMPORTANT ROLE OF FAMILY PHYSICIAN

Since febrile seizures are a common occurrence in children, the family physician plays an important role in acute seizure management, initial assessment and long-term management. Children with an initial simple FS can be managed by the family physician. The family physician can also play an important role in counseling the parents that most febrile seizures are brief, do not require any specific treatment or extensive work-up, the probability of frequent or possibly threatening recurrences is low and the long-term prognosis is excellent.^[4,13,14,19] However, children with recurrent simple febrile seizures, with a complex FS which is associated with neurological impairment (such as cerebral palsy or developmental delay), multiple complex febrile seizures or febrile status epilepticus should be referred to a pediatric neurologist for detailed assessment and further management.

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