

## Review Article

# Recent Advances in Febrile Seizures

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The Kuwait Medical Journal 2001, 33 (1): 7-12

### DEFINITION AND EPIDEMIOLOGY

Febrile seizures are the most common seizure disorder in young children. Though they have been described since the time of Hippocrates, it was not until the middle of the last century that these seizures were recognized as a separate syndrome distinct from epilepsy.

Febrile seizures are defined as seizures occurring in neurologically healthy children under the age of five years which are precipitated by fever arising from infection outside the central nervous system. This definition does not include children whose seizures are caused by a CNS infection, such as meningitis or encephalitis (symptomatic seizures), or those who have had a previous afebrile seizure or central nervous system abnormality (secondary febrile seizures)<sup>[1]</sup>.

Febrile seizures (FS) occur in 2-4% of all children between the ages of 6 months and 5 years, with a peak age of onset at 14-18 months. The incidence rate varies due to racial differences with higher cumulative rates of 9% in Japan and 15% in Guam<sup>[2-5]</sup>. Males and females are equally affected<sup>[4,5]</sup>.

One-third of children with an initial FS will have recurrent FS and only a small minority will develop afebrile seizures with a variety of epilepsy syndromes<sup>[6]</sup>. Febrile seizures are classified as either simple or complex. Simple FS are defined as generalized, brief in duration (<15 minutes), do not occur more than once in a 24-hour period, and are not followed by neurological deficit. Complex FS may be focal, prolonged, or recurrent within the same febrile illness, and associated with post ictal neurologic abnormality including Todd's paralysis. Most (80%) episodes are classified as simple FS. Only 20% are of the complex type<sup>[7]</sup>.

### GENETICS OF FEBRILE SEIZURES

There have been numerous articles published on the genetics of FS, which reflect the complexity of this disorder. Genetic predisposition to FS is

strongly supported by both twin and family studies, which demonstrate a higher concordance rate in monozygotic twins than in dizygotic twins<sup>[8,9]</sup>. Familial clustering studies indicated a double sibling risk when both parents had FS (55.6%) compared with a risk of 21.7% when only one parent was affected and 5.5% when both parents were unaffected<sup>[10]</sup>. Although there is evidence for genetic susceptibility, the exact mode of inheritance is not clear. A polygenic inheritance was strongly supported in families of probands who have a single FS, whereas an autosomal dominant inheritance with reduced penetrance was suggested in families of probands with multiple FS<sup>[11,12]</sup>. The most convincing evidence supporting genetic predisposition, however, is the recent report of two putative FS gene loci, FEB1 (chromosome 8q13-q21) and FEB2 (chromosome 19p)<sup>[13,14]</sup>. A further genome-wide scan and subsequent fine mapping revealed significant evidence for another febrile seizure locus (FEB3) on chromosome 2q23-24<sup>[15]</sup>.

### Risk of first febrile seizure:

The height of temperature and history of FS in a first-degree relative are significant independent risk factors for the development of a first FS<sup>[16,17]</sup>. Other suggested factors are maternal smoking during pregnancy, respiratory infections in the mother during the first trimester of pregnancy, neonatal discharge at 28 days of age or later, parental report of slow development, and daycare attendance where there is an increased exposure to infectious diseases<sup>[18,19]</sup>. Forsgren et al.,<sup>[20]</sup> reported that children with FS had infections more than the controls did and Verity et al.,<sup>[4]</sup> noted that children with a history of discharging ears or frequent sore throats were more likely to have FS. Recent studies have shown an association between primary infection with HHV-6 infection and 31% of FS in infants and young children, which often results in

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the development of a complex FS and might be a risk factor for subsequent development of epilepsy<sup>[21,22]</sup>. Another study found a correlation between low serum sodium levels and the risk for developing FS<sup>[23]</sup>.

### DIAGNOSIS AND INVESTIGATIONS

Most FS occur within the first 24 hours of an illness, often as a first sign of fever<sup>[24]</sup>. When a child is first presented, a complete medical history and physical examination should be carried out with emphasis on history of the present illness, duration of the fever and any associated symptoms. Description of the seizure by an eyewitness is very important to classify the seizure as simple or complex. History of trauma and drug ingestion should be taken to identify other possible precipitating causes of the seizure. Past medical history of any neonatal or post-natal problem, developmental delay, history of previous febrile or afebrile seizures as well as family history of febrile or afebrile seizures is also of significant importance. Physical examination should include assessment of the child's consciousness level, signs of meningitis, and any neurological abnormality, such as focal difference in muscle strength and power.

#### Factors that would favor admission after the first episode of FS include:

- a) complex seizures
- b) any child below 18 months of age
- c) inadequate home circumstances
- d) parental anxiety or parents are unable to cope

Routine laboratory investigations are not necessary in FS unless the source of the seizure is obscure<sup>[25]</sup>. A lumbar puncture (LP) should be done if there are clinical signs of meningitis, after complex FS, and if the child is below 12 months of age<sup>[26,27]</sup>. The decision to perform an LP on a child with FS should be taken by an experienced pediatrician who may decide, on clinical grounds, if the LP is necessary or not regardless of the age of the child.

Electroencephalography (EEG) has not been shown to be helpful in the evaluation of FS. Most children presenting with a first simple FS usually have normal EEGs.

In their recent published guidelines for the neuro-diagnostic evaluation of children following a first simple FS, The American Academy of Pediatrics (AAP) do not recommend performing an EEG in a healthy child with a first simple FS as it is not helpful in predicting recurrence or risk of later epilepsy. A skull X-ray, cranial CT and MRI are always normal in children following simple FS and should not be performed routinely<sup>[28]</sup>.

#### Risk of Recurrence:

The major risk to a child following a first episode of FS is the probability of having another FS. Approximately 1/3rd of children will experience recurrence, 50% of those who have one recurrence may have additional recurrences and 90% of the first recurrent episodes of FS will occur within two years of the initial attack<sup>[29]</sup>.

Several studies have reported an association between young age at onset and increased risk of recurrence. The younger the child is, the more susceptible he is to develop FS. This is due to the longer period during which a younger child is at risk, rather than greater tendency to have seizures. Recent evidence also suggests that family history of FS substantially increases the risk of recurrence<sup>[30-32]</sup>.

A prospective study by Burg et al.,<sup>[33]</sup> identified 347 children who presented with their first episode of FS. They were followed for a period of 20 months to ascertain whether they would experience recurrence. The overall recurrence rate was 27%. The duration of fever before the initial seizure was an important factor in recurrence. If the duration of fever was <1 hour, the risk of recurrence was 44%. If, however, it was >1 hour, the risk was 23%. On the other hand, if the duration of fever was >24 hours, the risk of recurrence was reduced to 13%. They also found that with each degree rise in temperature, the risk of recurrence at one year decreased by about 6%. Therefore, with a temperature of 38.3 °C, the risk is 35% and with a temperature of 40.6 °C, the risk declines to 13%. Age below 18 months and family history of FS were also associated with increased risk of recurrence. However, family history of epilepsy, complex FS, or neurodevelopmental abnormality did not increase the risk of recurrence of FS.

Another study, by Van Esch<sup>[34]</sup>, reported that a first-degree family history of FS (parents or siblings affected by FS) increases the child's 2-year recurrence risk for FS from 27 to 52%. There was no significant increase of recurrence risk for FS in children with second degree relatives (grandparents, uncles, aunts, or cousins) affected by FS.

In a prospective cohort study<sup>[35]</sup> of 98 Saudi children, the rate of recurrence of FS and the factors predicting a recurrence were evaluated. During a follow-up period of 3-6 years, 26% of the 98 untreated children had at least one recurrence and only 8% had more than three recurrences. A total of 30% of the first recurrence took place within three months.

Four major risk factors for recurrent FS were identified:

- a) early age at onset (below 12 months)
- b) first degree consanguinity of parents

- c) epilepsy in a first degree relative
- d) complex initial FS

Gender, family history of FS, and the degree of fever were not found to influence recurrence.

In conclusion, a young age of onset and a family history of FS are the strongest and most consistent predictors of recurrence. Other risk factors include shorter duration of fever before the initial FS and the lower degree of temperature<sup>[36]</sup>. Complex FS is not associated with increased recurrence and family history of FS is a controversial factor.

#### **Risk of epilepsy:**

Estimates of the risk of developing epilepsy after FS vary depending on the population sampled, methods of data collection, and the duration of follow-up. The National Collaborative Perinatal Project (NCP)<sup>[37]</sup> assessed 431 pairs of siblings discordant for febrile seizures at the age of seven years. The risk of epilepsy was found to be 0.5% in children without FS, 1.5% after simple FS, and 4% after complex FS.

In this study, three predictive factors for later epilepsy were identified:

- 1) epilepsy in a first degree family member
- 2) abnormal neurological or developmental status before the onset of FS
- 3) complex FS

Similar results were reported by the British CHES cohort study<sup>[38]</sup> where the risk of epilepsy by the age of 10 years was 0.4% in children with no history of FS, 4% in those who had multiple seizures within 24 hours, 6% after prolonged FS, and 29% after focal seizures.

In the Rochester study<sup>[39]</sup>, Annegers et al., found that the risk of epilepsy ranged between 2.4% among those who had simple FS, 6-8% in the presence of one complex feature, 17-22% if two complex features and 49% if all three complex features exist. In spite of these results, they did not suggest an association between complex FS and the later development of epilepsy. Instead, they gave an alternative explanation that the tendency to have complex FS reflects a pre-existing brain disease that is also responsible for the subsequent development of complex partial epilepsy.

In conclusion, there is only a slight risk of developing epilepsy in the majority of children with simple FS. Risk factors include pre-existing neurodevelopmental abnormalities, complex FS, and family history of epilepsy. The most common type of epilepsy is the idiopathic generalized tonic clonic type as evidenced by the Nova Scotia study<sup>[40]</sup>. Only a very small

proportion of children with prolonged FS developed complex partial seizures because of a pre-existing brain anomaly.

#### **Febrile convulsions and mesial temporal sclerosis:**

Diagnostic advances in imaging of the brain, made possible by magnetic resonance imaging (MRI), have shown that prolonged FS may produce hippocampal injury, which plays a role in mesial temporal sclerosis and the later development of intractable temporal lobe epilepsy<sup>[41]</sup>. Kuks et al.,<sup>[42]</sup> pointed out that, although this finding was strongly associated with a history of complex FS, it did not indicate a causal relationship as 64% of those with hippocampal volume loss gave no history of complex FS. It, therefore, can not be the only mechanism. The presence of pre-existing congenital cerebral abnormality, such as focal cortical dysplasia, predisposes these patients to complex FS and later epilepsy.

#### **Neurological impairment and intellectual outcome:**

Most hospital-based studies have shown relatively high rates of mental retardation (8-22%), behavioral disturbances (30%), and academic difficulties at follow-up among children with FS<sup>[43]</sup>. In contrast, population-based studies have documented comparable intelligence and academic performances in children with FS and the control group. No child in the NCP developed persistent neurological deficit during or immediately after FS. In addition, at the age of seven years, children who were normal before FS did not differ in the intelligence quotient (IQ) from the normal seizure-free sibling<sup>[44]</sup>. Neither recurrent seizures nor those lasting longer than 30 minutes were associated with IQ deficit.

In a population-based study, Verity et al.,<sup>[45]</sup> found that children who had febrile convulsions performed as well as other children in terms of their academic progress, intellect, and behavior at 10 years of age. A recent population-based study done by Chang et al.,<sup>[46]</sup> found that FS in early childhood does not have any adverse effects on behavior, scholastic performance, or neurocognitive attention. On the contrary, the FS group demonstrated significant better control of distractibility and attention at school age.

This contrast between hospital-based and population-based studies is attributed to selection bias in the former studies as they included children who had suffered from seizures as a complication of meningitis or encephalitis. Other studies included children who were known to be

developmentally or neurologically abnormal before they had their first FS.

### TREATMENT OF THE ACUTE EPISODE OF FEBRILE SEIZURES

The acute occurrence of FS requires prompt medical attention and appropriate oxygenation until the seizure either stops spontaneously or is controlled by drugs. Diazepam is the most widely used drug for the acute management of all types of seizures in both adults and children<sup>[47]</sup>. Diazepam, given either intravenously (IV) or rectally, is usually effective in aborting seizures. It is given either immediately or after five minutes as most FS are aborted spontaneously after two minutes.

A recent study by Lahat et al.,<sup>[48]</sup> compared the safety and efficacy of intranasal (IN) midazolam with IV diazepam in the treatment of children with prolonged febrile seizures. They found that while the seizures were controlled more rapidly with IV diazepam than with IN midazolam, the overall time to cessation of seizures after arrival at hospital was faster with intranasal midazolam than with IV diazepam due to the easy access and application and that both drugs had the same efficacy and safety margin.

After controlling the seizure, all attempts should be made to bring the temperature down in order to promote the comfort of the child and to prevent dehydration. Paracetamol is the most commonly used antipyretic through either oral or rectal application. It is safe if the recommended total daily dose is not exceeded. Physical methods such as fanning, cold bathing and tepid sponging are likely to cause discomfort and are not recommended<sup>[49]</sup>.

The source of fever should be sought in every child with FS and therapy should be directed towards treatment of the infectious process; e.g. tonsillitis, otitis media, urinary tract infection, etc.

### LONG-TERM MANAGEMENT OF FEBRILE SEIZURES

Whether prophylaxis with medication is effective in preventing recurrence of FS is controversial. Several studies had shown that both phenobarbitone and sodium valproate are both effective in preventing recurrence of simple FS than placebo<sup>[50]</sup> whereas carbamazepine and phenytoin are ineffective<sup>[51,52]</sup>. Several clinical trials have confirmed that intermittent diazepam prophylaxis solely at times of high fever when the child is at greatest risk of developing FS is another treatment option which is feasible and cheap, well-tolerated by the child and well-accepted by the parents<sup>[53]</sup>.

Although effective therapies that prevent recurrence exist, their potential adverse effects do not equal their benefits. The long-term detrimental

effects on cognition, behavior, and learning were seen in children receiving phenobarbitone<sup>[54]</sup>. Sodium valproate has been shown to cause severe liver damage in children, especially those below two years of age when FS are most common<sup>[55]</sup>. It also causes thrombocytopenia, weight gain, and gastrointestinal disturbances. Diazepam has been shown to cause drowsiness, lethargy and ataxia.

As there is no convincing evidence that treating children who have FS will decrease their incidence of epilepsy or that FS will cause structural brain damage and affect cognition, a consensus has emerged that long-term prophylaxis with anti-epileptic drugs is rarely justified in FS. This is especially true when considering the side effects and the favorable prognosis. The AAP advised that neither continuous nor intermittent anticonvulsant therapy are recommended for children with one or more simple FS<sup>[56]</sup>.

No treatment at all, however, does not appear quite satisfactory either, as FS have a high recurrence rate, disrupt family life and may have emotional consequences for the family. Long-term management of FS, therefore, should focus on decreasing parental anxiety. The general level of knowledge of FS among parents of young children is low and the reaction of the parents to the first fit is often severe and emotionally traumatic. Therefore, it is important to provide parents with general information about FS as well as of the prognosis. Such information must be both verbal and written. Perhaps we should acknowledge that the best treatment for the child after the first FS is not necessarily to prescribe medication but rather to sit with the family and talk<sup>[57,58]</sup>.

In conclusion, febrile seizures are the most common seizure disorder in young children between the ages of 6 months and 5 years who exhibit genetic susceptibility to seize with the acute onset of fever. Risks for the initial episode of FS include history of FS in a first-degree family member, the frequent exposure to viruses, especially HHV-6, and low serum sodium levels. The overall recurrence risk of FS is 27% and risk factors for recurrence are young age at onset and family history of FS. The risk for developing later epilepsy is slightly increased especially after complex FS and the most common type of epilepsy is generalized grand mal. Only a very small proportion of children will develop complex partial seizures as a result of a pre-existing brain anomaly, which predisposes them to FS also.

In view of the benign nature of FS and the good neurological and intellectual outcome, the routine use of prophylactic antiepileptic medications is not recommended as the child will be subjected to various unwanted side effects and there is no

convincing evidence that these drugs would affect the risk of later epilepsy. Therefore, the best approach is to share this information with the parents and teach them what to do when the child develops another seizure.

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