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Febrile seizures and genetic epilepsy with febrile seizures *plus* (GEFS+)

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ABSTRACT – *Aim*. To review the literature about febrile seizures and GEFS *plus* with special emphasis on management and outcome. *Methods*. Selected literature review. *Results*. Febrile seizures are the most common convulsive event in humans, occurring in 2-6% of the population. The aetiology is complex with strong evidence for a heterogeneous genetic predisposition interacting with fever of any cause, with certain viral infections having a greater effect. A large amount of literature has established that febrile seizures have no long-term consequences on cognition or behaviour. Unfortunately, about 40% of children with a first febrile seizure will have a recurrence. The strongest predictor of recurrence is age <14-16 months at the time of the first febrile seizure. Epilepsy follows febrile seizures in ~3% cases, with the concepts of simple and complex febrile seizures providing relatively weak prediction. Very prolonged febrile seizures may lead to mesial temporal sclerosis and temporal lobe epilepsy although the degree of risk remains uncertain. Investigations beyond establishing the cause of the provoking fever are nearly always unnecessary. Treatment is mainly reassurance and there is some evidence that parents eventually "come to grips" with the fear that their children are dying during a febrile seizure. Antipyretic medications are remarkably ineffective to prevent recurrences. Daily and intermittent prophylactic medications are ineffective or have unacceptable side effects or risks. "Rescue" benzodiazepines may prevent prolonged recurrences for selected patients with a first prolonged febrile seizure although this has not been proven. Genetic epilepsy with febrile seizures *plus* (GEFS+) is a complex autosomal dominant disorder usually caused by mutations in *SCN1A* (a voltage-gated sodium channel). One third of patients have febrile seizures only; two thirds have a variety of epilepsy syndromes, both focal and generalized. *Conclusions*. Febrile seizures may distress parents but rarely have any long-term consequences. Reassurance is the only treatment for the vast majority. Identifying patients with GEFS *plus* may lead to further investigations and counselling.

Key words: febrile seizure, convulsion, infant, outcome

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Definition

Febrile seizures are the result of a particular sensitivity to fever in the developing brain, have a major genetic predisposition, and nearly always have a benign outcome. They have been defined as any seizure associated with fever of >38ºC (rectal or tympanic), but without CNS infection, in a child aged 6 months to 5 years (American Academy of Pediatrics, 2008). The age range is somewhat arbitrary with some authorities suggesting two months as a lower cut off (Capovilla *et al*., 2009). Febrile seizures occur in older children, but very infrequently.

Basic epidemiology

The life-time prevalence of one or more febrile seizures is 3-4% of all children in North America and Western Europe, but has been reported to be somewhat higher in Finland, Japan and Guam (Nelson and Ellenberg, 1976; Verity *et al*., 1985; Annegers *et al*., 1987). This means that febrile seizures are the most common convulsive events in humans and account for about 50% of the 8% lifetime risk of a seizure. The peak age is 18 months with about 80% of incident febrile seizures occurring between 1 and 3 years of age (Nelson and Ellenberg, 1976; Verity *et al*., 1985; Annegers *et al*., 1987). As far as we are aware, mortality from a febrile seizure has not been reported.

Risk factors for a first febrile seizure

Several studies have explored the profile of children with a first febrile seizure. Bethune *et al*. compared 75 children presenting to an emergency room with a first febrile seizure with 150 age-matched children in the same emergency room (Bethune *et al*., 1993). Factors statistically associated with a febrile seizure were family history of febrile seizures, any suggestion of neurological dysfunction or developmental disability, delayed neonatal discharge, and attendance at day care. Huang *et al*. summarized the statistically significant independent risk factors for febrile seizures reported in articles that employed multivariate analysis (Huang *et al*., 1999). These included: day care attendance, parental education, prenatal maternal smoking and/or alcohol intake, late-neonatal discharge, slow development, degree of fever, gastroenteritis, and family history of febrile seizures. Every study has identified family history of febrile seizures as an important risk factor, while other factors vary between studies.

Based on these many studies, it becomes clear that febrile seizures have a major genetic predisposition. If a child has a febrile seizure, the risk that his/her sibling will have a febrile seizure is 10-45% (Van Esch *et al*., 1998). Monozygotic twins are more often concordant for febrile seizures than dizygotic twins (53% versus 18%) (Berkovic and Scheffer, 1998). Dizygotic twins have a similar rate to that of their other siblings. The febrile seizure tendency has been linked to at least nine chromosome linkage sites, indicating locus heterogeneity (Nakayama and Arinami, 2006). In the past eight years, several more linkage sites have been identified but the specific genes involved have rarely been identified. Clearly, there are multiple genes that influence the febrile seizure tendency. The mode of inheritance is likely polygenic or autosomal dominant with variable penetrance (Annegers *et al*., 1982; Tsuboi and Endo, 1991). The specific disorder of GEFS+ is discussed below.

A single twin study has examined the concordance of three febrile seizure types: "true" febrile seizures, febrile seizures plus (seizures with fever which occurred beyond 6 years of age or were associated with afebrile generalized tonic-clonic seizures) and febrile seizures with later epilepsy (Eckhaus *et al*., 2013). Monozygotic twin pairs showed much greater concordance for these febrile seizure types than dizygotic twins, suggesting that there may be different genetic factors that determine different febrile seizure types.

A genetic tendency is clearly insufficient in itself to cause febrile seizures. Fever is required and several studies suggest that the higher the temperature, the higher the risk. Attendance at day care may increase the risk of illness. It remains unclear why the susceptibility for febrile seizures is age-dependent, however, any other co-existent brain disturbance seems to contribute to this age-dependent risk.

It is also unclear if specific viral illnesses have a particular ability to provoke febrile seizures. Influenza A has been strongly implicated (Chung and Wong, 2007; Hara *et al*., 2007; Frobert *et al*., 2011; Ozkan *et al*., 2011). Human corona virus HKU1 has been associated with a higher rate of febrile seizures than respiratory syncytial virus, parainfluenza virus type 1, or adenovirus (Lau *et al*., 2006). Human herpes virus type 6 (HHV6) has been extensively studied (Suga *et al*., 2000; Laina *et al*., 2010). Infantile roseola is caused by HHV6 and is typically accompanied by a high temperature. HHV6 may invade the nervous system and it remains unclear if the association between febrile seizures and HHV6 is simply the result of high fever or direct cerebral "irritation".

It has been clearly demonstrated that there is an increased risk of febrile seizures shortly after many childhood vaccinations, including cellular pertussis (Hirtz *et al*., 1983). It is now understood that this association is simply based on vaccine-induced fever in a susceptible child (Brown *et al*., 2007).

The role of inflammatory mediators has been explored with a suggestion that certain interleukin alleles are associated with increased susceptibility (Tsai *et al*., 2002; Virta *et al*., 2002; Kanemoto *et al*., 2003; Ishizaki *et al*., 2009; Serdaroglu *et al*., 2009; Kira *et al*., 2010; Chou *et al*., 2010), and others with reduced risk. This is a complex area of research and susceptibility may vary with ethnic group (Wu *et al*., 2012). The serum levels of several interleukins were increased in 41 children with a febrile seizure compared with febrile controls (Haspolat *et al*., 2005), but this study has not been replicated (Tomoum *et al*., 2007; Salam *et al*., 2012). Other genetic factors have been studied. In a study of 100 Egyptian children, a *GABRG2* polymorphism was associated with febrile seizures (Salam *et al*., 2012). Additional factors that have been explored are trace metal serum levels. One Indian study suggested that serum zinc levels were lower in children with febrile seizures (Ganesh and Janakiraman, 2008), with a confirmatory study from Bangladesh (Mollah *et al*., 2008). Lower selenium levels have been noted (Mahyar *et al*., 2010) and several studies have reported decreased serum iron (Idro *et al*., 2010).

In summary, we are still a long way from understanding why an individual child might have a febrile seizure.

Differential diagnosis

Febrile myoclonus should be distinguished from febrile seizures. The age range for this disorder is similar. During fever, these infants have prominent myoclonic jerks, mostly involving the upper extremities. Convulsive seizures do not occur and the disorder vanishes with age. It has not been extensively studied, but is widely recognized (Rajakumar and Bodensteiner, 1996).

Syncope with fever should also be distinguished. A febrile infant suddenly becomes limp, lifeless and pale (Stephenson, 1990; Stephenson *et al*., 2004). This scenario has sometimes been identified as an "atonic" febrile seizure, but we suspect that the vast majority have syncope as the aetiology. The prognosis is equally good.

There are children who have seizures in association with illness (particularly gastroenteritis), but do not have fever at the time of presentation. Their prognosis is also good, but they may have a slightly higher risk of subsequent epilepsy than those with febrile seizures (Lee and Ong, 2004).

Consequences of febrile seizures

Simple versus complex febrile seizures

Through the last 35 or more years, there has been a strong effort in the literature to separate simple febrile seizures from complex febrile seizures (Nelson and Ellenberger, 1976; Annegers *et al*., 1987). The concept is that simple febrile seizures are associated with a very low risk of long-term sequelae, while complex febrile seizures carry a much greater risk. We believe this distinction has been overemphasized. A simple febrile seizure lasts less than 10 minutes, is generalized, and does not repeat in the same illness. A complex febrile seizure may be long (>15-20 minutes), focal, or repeated in the same illness. Subjects with simple febrile seizures have a risk of subsequent epilepsy of 2-3%, which is greater than that in the general population, but clinically unimportant. Complex febrile seizures are followed by epilepsy in 4-15%, depending on the number of complex features (Nelson and Ellenberger, 1976; Annegers *et al*., 1987). While this increased risk is statistically different, the medical significance is not likely very great; even those identified as being at very high risk with several complex features still have an 85% chance of not developing epilepsy. In addition, complex features are very common; up to 40% of children with a first febrile seizure will have at least one complex feature.

It is also very likely that complex features are poorly recognized by distressed parents. Confusion with the postictal state makes an estimate of seizure length inaccurate. Postictally, some children with febrile seizures continue to have tonic posturing or eye deviation - who knows when the seizure stopped! (Yamamoto, 1996). Focal features are inconsistently noted based on video recordings of seizures that have been reviewed by physicians and family members, and the emotionally charged time during a first febrile seizure leads to even less accuracy (Rugg-Gunn *et al*., 2001). We suspect that repeated seizures within an illness are more accurately recalled.

Recurrences

About 20-40% of children with a first febrile seizure will have a recurrence. The risk of recurrence after a second febrile seizure is similar (Nelson and Ellenberg, 1976; Verity *et al*., 1985; Annegers *et al*., 1987). Very few children have more than three febrile seizures. Some of the predictive factors for recurrence are noted in *table 1*. The most consistent and powerful predictor of recurrence is a first febrile seizure at age <12-16 months. Berg and coworkers attempted to identify additional independent factors that could be used to predict recurrence (Berg *et al*., 1997). These included "young age at onset, a history of febrile seizures in a first-degree relative, low degree of fever while in the emergency department, and a brief duration between the onset of fever and the initial seizure". Children

Table 1. Statistically significant predictive factors of aspects of febrile seizures -who has a first seizure, who recurs, and who later develops epilepsy?

	Prediction of an incident febrile seizure	Prediction of recurrence after a first febrile seizure	Prediction of epilepsy after a first febrile seizure
Family history of febrile seizures in a first degree relative	+	+	-
Developmental delay or neurological problems	+	-	+
Complex febrile seizure (focal, prolonged, repeated)		-	+
Age at onset <18 months		+	-
Level of temperature at first seizure		+	-
Duration of illness before seizure		+	-
Attendance at day care centre	+	+ (possible)	-

with all four of these factors had a recurrence risk of 70%, while those with no factors had a recurrence risk of only 20%.

Brain injury

There is very strong evidence from multiple studies that febrile seizures do not damage the brain (Ellenberg and Nelson, 1978; Verity *et al*., 1998; Sillanpää *et al*., 2011). Children who have had febrile seizures have the same cognitive skills as their unaffected siblings or population-based controls. The NCPP study recruited 55,000 mothers before they delivered, and followed the children to age 7 years. There were 431 sibling pairs, discordant for febrile seizures: one child had ≥1 febrile seizure, the other had none. At age 7, their scores on the WISC (a general measure of intelligence) and the WRAT (a measure of scholastic achievement) were identical, unless they were known to be neurologically abnormal prior to the febrile seizure (Ellenberg and Nelson, 1978). The British study followed a cohort of 14,676 children in the UK who were all born during the same week (Verity *et al*., 1998). During follow-up at age 10 years, those with febrile seizures had identical scores on standardized intellectual and behavioural tests to those without febrile seizures. A cohort of 900 newborns in Finland was followed to age 18, and again those with febrile seizures did not differ from controls in intellectual outcome (Sillanpää *et al*., 2011).

The particular issue of mesial temporal sclerosis following a prolonged febrile seizure requires a separate discussion. The duration of febrile seizures seems to be divided into two populations; those with a febrile seizure that lasts a few minutes up to 5-10 minutes and those that continue well beyond 15 minutes (Hesdorffer *et al*., 2011). There is no doubt that a small number of children will have a very prolonged febrile seizure, usually focal, followed eventually by intractable temporal lobe epilepsy. The risk appears to be about 1 in 75,000 children (Camfield *et al*., 1994). The MRI in many of these patients shows mesial temporal sclerosis and their response to epilepsy surgery is typically very good. Some of these patients have dual pathology, for example, mesial temporal sclerosis in conjunction with a localized cortical dysplasia. MRI shortly after a prolonged febrile seizure, and then later, has suggested that hippocampus swelling in some is followed subsequently by MTS, although the hippocampal swelling may be bilateral and MTS is usually unilateral (VanLandingham *et al*., 1998; Scott *et al*., 2006).

The aetiology of MTS is more complex than just an effect of febrile seizures. There are people with MTS who have never had a febrile seizure and some without any seizures at all. This means that the cause and effect relationship between prolonged febrile seizures and MTS is complex. Children with Dravet syndrome have repeated, very long, focal febrile seizures in the first year of life. Much to our surprise, it appears that the majority do not develop MTS (Guerrini *et al*., 2011) - why, is unknown. In addition, there appears to be an association between a polymorphism of the *SCN1A* gene and the combination of febrile seizures with MTS and temporal epilepsy that is not associated with other types of epilepsy following febrile seizures (Kasperaviciute *et al*., 2013).

The USA Febstat study is addressing some of the issues about prolonged febrile seizures. From multiple emergency rooms, this study recruited 191 patients with a very prolonged febrile seizure (longer than an hour). Ten percent showed mesial temporal T2 changes on MRI within 72 hours, although it remains unreported how many went on to develop MTS and temporal lobe

epilepsy (Shinnar *et al*., 2012). This study also showed that children with a very prolonged febrile seizure, compared with controls, were at an increased risk of a partially malrotated hippocampus, a minor developmental anomaly. Surprisingly, the malrotation was most often contralateral to the side with the T2 MRI changes.
Another very important study regarding the consequences of prolonged febrile seizures is that of a population-based epidemiological and clinical study of children from a geographical area in North London, England. Febrile status epilepticus was documented to be the most common "cause" of status epilepticus in small children. MRI findings included reversible changes in white matter (Yoong *et al*., 2013a). Hippocampal volume loss was documented over time in 80 children, in 20-30% of children with status epilepticus, regardless of the aetiology (Yoong *et al*., 2013b). Neuropsychological testing of a subgroup of the patients with febrile status showed a significant, possibly permanent, decrease in recognition memory compared with controls when testing was carried out shortly after the febrile status and a year later. Memory loss was related to loss of hippocampal volume (Martinos *et al*., 2012).
Because of the concern about long-term effects of prolonged febrile seizures, it is prudent to treat febrile status as promptly as possible. It is also relevant that those with a first prolonged febrile seizure have perhaps a 20-30% risk of a prolonged recurrence. The families of these children may be candidates for learning how to deliver at home a "rescue" benzodiazepine, such as buccal midazolam or rectal diazepam.

Epilepsy

Febrile seizures are followed by epilepsy (recurrent afebrile seizures) in 2-4% by age 7 years; a longer follow-up period appears to reveal a higher risk of epilepsy, possibly up to 6% (Nelson and Ellenberg, 1976; Annegers *et al*., 1987).
As mentioned above, the risk of epilepsy after a simple febrile seizure is only about 2% and after a complex febrile seizure, perhaps 2-3 times as high. This difference is statistically significant but of doubtful clinical significance. The majority of children who develop epilepsy after a febrile seizure do so after a simple febrile seizure, not a complex febrile seizure; this seeming paradox is explained by the fact that simple febrile seizures are more common and that the chance of subsequent epilepsy is not all that much greater after a complex febrile seizure.
Based on data from Olmstead County (Rochester, Minnesota), it appears that if epilepsy follows a simple febrile seizure, it is more likely to be generalized epilepsy, and if the febrile seizure is complex, the epilepsy is more likely to be focal (Annegers *et al*., 1987). These findings have not been replicated and are based on a very small sample size, although the population-based methodology is very sound.
When population-based cohorts of children with epilepsy are questioned, about 15% have had a previous febrile seizure which leads to the conclusion that febrile seizures rarely lead to epilepsy, but epilepsy is fairly frequently preceded by febrile seizures (Camfield *et al*., 1994). The type and cause of epilepsy does not seem to correlate with the incidence of previous febrile seizures, suggesting that the genetic predisposition that leads to febrile seizures is a fundamental determinant of an individual's seizure threshold.

Effect on the family

Several studies have reported interviews with parents shortly after their children had a febrile seizure. Parents nearly always indicate that they thought their child was dying during the seizure, a fright that probably leads to disrupted sleep for parents and changes in family routine for quite some time (Bethune *et al*., 1990; van Stuijvenberg *et al*., 1999).
Despite this fright, it is interesting that, at the end of a Finnish prospective study of children followed from birth through the teenage years, parents sometimes had forgotten the febrile seizure and some parents reported febrile seizures when comprehensive medical reports failed to document them (Sillanpää *et al*., 2008).
In Nova Scotia, we studied 75 children who presented to an emergency room with their first febrile seizure compared to 75 age-matched controls with fever and no seizure, and 75 without fever (Gordon *et al*., 2000). Because all Canadians are automatically covered equally by a national health care system, there is no financial barrier to medical care. We used provincial administrative databases that document all physician visits and hospitalizations to show that the children with febrile seizures consumed equal amounts of health care over the next 7-10 years. These findings suggest that even though parents are very distressed initially, they do not translate this fear into excessive doctor visits; they seem to "get over it".

Investigations

At acute presentation

There has been a seemingly endless series of reports addressing the question of the necessity for a lumber puncture (LP) when a child presents with a febrile seizure. The issue is to exclude meningitis. The American Academy of Pediatrics Practice Parameter indicated that if the child is older than 12 months and

looks "well", an LP is not required (American Academy of Pediatrics, 1996, 2011). If the child is younger than a year, there is a sense that the physical findings of meningitis may be more subtle and therefore an LP should be strongly considered. Overall, our sense is that experienced physicians do very few LPs, while less experienced doctors are safer doing more (Offringa and Moyer, 2001).

There is apparently little reason to measure blood electrolytes. Several years ago, one study suggested that if the serum sodium was decreased, the risk of a recurrent febrile seizure within that illness was considerably increased. Subsequent studies failed to confirm this finding (American Academy of Pediatrics, 1996, 2011). Blood glucose and complete blood count are not routinely recommended.

If the child recovers promptly from a febrile seizure, there is no value in a head CT scan. Radiation from the current generation of CT scanners is significant (American Academy of Pediatrics, 1996). MRI has not been systematically studied as an acute investigation, but there would seem little justification.

Investigations during follow-up

A controversy swirls around the value of EEG after a febrile seizure. Within a few days, even up to two weeks, after a febrile seizure, the EEG background may show diffuse slow wave activity. If repeated at a later date, this abnormality resolves, so its identification is of little value.

A spike discharge may be found in children who have had a febrile seizure -does this mean that they are at increased risk of subsequent epilepsy? A very careful protocol, reported in 1968 by Frantzen, mandated repeated EEGs over several years in children who had experienced a febrile seizure (Frantzen *et al*., 1968). Those with a spike discharge were no more likely to develop epilepsy than those without. About 8% of normal children without seizures of any kind will have a spike discharge during a sleep EEG and yet never have a seizure -the child with a febrile seizure and EEG spikes is similarly unlikely to have a further seizure (Eeg-Olofsson *et al*., 1971).

In summary, beyond a careful examination to exclude meningitis, no acute or later investigations are justified, other than those that seem appropriate to address the cause of the fever. We strongly endorse a follow-up visit within a week or two to help the family come to grips with what has been a traumatic situation.

Treatment

Acute management of febrile status follows the usual protocol for status of any kind. An intravenous, buccal or rectal dose of a benzodiazepine will stop most episodes of febrile status. Buccal midazolam is apparently more effective than rectal diazepam (McMullan *et al*., 2010).

Long-term AED treatment is rarely, if ever, indicated. Daily phenobarbital may be effective, although a meta-analysis has shed some doubt (Camfield *et al*., 1980; Newton, 1988). Behavioural and cognitive side effects of phenobarbital should discourage its use. Valproic acid may be effective, but has not been extensively studied and is associated with rare fatal toxic hepatitis.

Intermittent medication given just at the time of fever will often fail because the seizure may be the first indication of fever. Oral intermittent diazepam at 0.1 mg/kg was ineffective in a randomized clinical trial (Uhari *et al*., 1995). In a larger study, a dose of 0.3 mg/kg diazepam was marginally effective, although the number needed to treat, to prevent a single recurrent febrile seizure, was 12 (Rosman *et al*., 1993; Camfield *et al*., 1995). In addition, about 25% of those treated had significant side effects, including somnolence and ataxia; symptoms that might interfere with the assessment for meningitis (Rosman *et al*., 1993). We have concluded that oral intermittent diazepam should not be used to attempt to prevent recurrent febrile seizures (Camfield *et al*., 1995).

Oral intermittent clobazam has been the subject of several randomized clinical trials in India. It seems to have fewer side effects than diazepam and may be an alternative, if treatment is deemed essential because of parental anxiety; there seems to be little other advantage for the child (Khosroshahi *et al*., 2011; Offringa and Newton, 2012).

Antipyretic medications and treatments

Since fever is a critical part of a febrile seizure, it seems intuitively correct that antipyretic treatment should reduce recurrences. Alas, this has not turned out to be correct. Patients for study are those with one or more febrile seizures and the goal is to try to prevent recurrences. Well constructed randomized trials of appropriate doses of acetaminophen (Uhari *et al*., 1995), ibuprofen (van Stuijvenberg *et al*., 1998) and diclofenac (Strengell *et al*., 2009) have failed to show any benefit. In addition, sponging with tepid water does not reduce the temperature (Newman, 1985).

In a very real way, parents whose child has had a febrile seizure need to know that there is no reasonable way to prevent a recurrence. They need to know that over the next few years, the problem will vanish and there will be no sequelae.

GEFS+

Scheffer and colleagues described several Australian families with a remarkable disorder that they initially

called "generalized epilepsy with febrile seizures plus (GEFS+)" (Scheffer and Berkovic, 1997). The name has been changed to "genetic epilepsy with febrile seizures *plus*" (still GEFS+) because the associated epilepsy may be focal.

This disorder is typically inherited with autosomal dominance and variable penetrance. About one third of affected family members only have febrile seizures, although the febrile seizures tend to recur well beyond 5-6 years of age, even up to the teenage years. About one third develop a few afebrile generalized tonic-clonic seizures in childhood with remission in adolescence. The remaining one third may have a variety of generalized epilepsies, including childhood absence and myoclonic astatic epilepsy. In addition, some families include patients with focal epilepsy, particularly temporal lobe epilepsy, of varying severity. A rare member of a GEFS+ kindred may develop Dravet syndrome, although most Dravet patients have *de novo SCN1A* mutations and are not members of GEFS+ families (De Jonghe, 2011).

Genetic studies of GEFS+ families have found that many, but not all, have a mutation in *SCN1A*, typically a missense mutation. Clearly, these mutations are inherited with autosomal dominance and about 80% of those with a mutation will have some form of seizure disorder, as outlined above. It remains unclear why affected members may have such a variety of seizure disorders. A few families with GEFS+ have been reported to have mutations in the neuronal sodium channel voltage-gated genes *SCN2A* and *SCN1B*. A few others have been demonstrated to have mutations in GABA(A) receptor subunit genes (*GABRG2* and *GABRD*). Therefore, the syndrome of GEFS+ may arise from a variety of different mutations even though mutations in *SCN1A* predominate and the genetic aetiology for many families presently remains unknown. The exact proportion of families with GEFS+ without a known mutation is not easily studied, particularly because the diagnosis of GEFS+ in small families may be difficult.

Speculation

It is interesting to speculate about the biological importance of febrile seizures. They are common and typically benign which is not surprising. Any disorder that affects 4% of the population early in life must be relatively benign or should vanish with natural selection. Febrile seizures arise due to many causes, including multiple gene mutations or polymorphisms, but also represent a complex interaction between genes and environment. We have speculated that the genes involved in the febrile seizure tendency are very important determinants of the seizure threshold for an individual. As humans, we appear to pay a price for our complex brains and all are capable of having a seizure with the "correct" combination of factors. The febrile seizure tendency plays a large role in this "correct," but individual, combination. □

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TEST YOURSELF

(1) What are complex febrile seizures and to what extent do they predict subsequent epilepsy?

(2) Which children with febrile seizures are candidates for home rescue benzodiazepines (rectal diazepam or buccal/nasal midazolam)?

(3) If a child has a parent with GEFS+, what is the chance that this child will have febrile seizures?

(4) If a child has a prolonged febrile seizure and MRI shortly afterwards shows T2 changes in the hippocampus, what are the chances that this child will develop mesial temporal lobe sclerosis and intractable temporal lobe epilepsy?

(5) Which child has the highest risk of a recurrent febrile seizure?
A. The first seizure was at 12 months of age with a temperature of 38.5°C. The child's father had febrile seizures as an infant.
B. The first seizure occurred at 36 months of age, was short and left-sided. There was no family history of febrile seizures.
C. The first seizure occurred at 24 months of age and was "simple". The child attends a day care centre.

Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, www.epilepticdisorders.com, under the section "The EpiCentre".