Original Article

Febrile Seizures

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ABSTRACT

Febrile seizures are the most common form of childhood seizures, occurring in 2 to 5% of children in the United States. Most febrile seizures are considered simple, although those with focal onset, prolonged duration, or that occur more than once within the same febrile illness are considered complex. Risk factors for a first febrile seizure, recurrence of febrile seizures, and development of future epilepsy are identifiable and varied. Children with febrile seizures encounter little risk of mortality and morbidity and have no association with any detectable brain damage. Recurrence is possible, but only a small minority will go on to develop epilepsy. Although antiepileptic drugs can prevent recurrent febrile seizures, they do not alter the risk of subsequent epilepsy. This has led to a changing view of how we approach the treatment of these common and largely benign seizures. This chapter will review the current understanding of the prognosis and management of febrile seizures. (*J Child Neurol* 2002;17:S44–S52).

DEFINITION AND CLASSIFICATION

The International League Against Epilepsy defines a febrile seizure as "a seizure in association with a febrile illness in the absence of a [central nervous system] infection or acute electrolyte imbalance in children older than 1 month of age without prior afebrile seizures."[1] The temperature associated with the febrile illness must be greater than 38.4°C, although the temperature may not be evident until after the seizure. Prior epidemiologic studies have used either 1 month[2–8] or 3 months[9,10] as the youngest age of occurrence, whereas no specific upper age limit was employed. Febrile seizures have a peak incidence at about 18 months of age, are most common between 6 months and 5 years of age, and onset above age 7 years is rare, although it does occur. The child can be neurologically normal or abnormal.

Febrile seizures can be classified as either simple or complex. A simple febrile seizure is isolated, brief, and generalized. Conversely, a complex febrile seizure is focal, multiple (more than one seizure during the febrile illness), or prolonged, lasting either more than 10[2–6,11] or 15 minutes.[9–11] The child's prior neurologic condition is not used as part of the classification criteria.[1,12]

EPIDEMIOLOGY

Febrile seizures are the most common form of childhood seizures, affecting between 2 and 4% of children in the United States and Western Europe,[4,8,9,13–15] 9 to 10% of children in Japan,[16] and up to 14% of children in Guam.[17] The peak incidence of febrile seizures is at approximately 18 months of age.

Most febrile seizures are simple. In a study of 428 children with a first febrile seizure,[11] at least one complex feature was noted in 35% of children, including focality (16%), multiple seizures (14%), and prolonged duration (>10 minutes, 13%). Five percent of the total group experienced a seizure lasting more than 30 minutes (ie, febrile status epilepticus).[11] Despite febrile status epilepticus representing only 5% of febrile seizures, it accounts for approximately one quarter of all episodes of childhood status epilepticus[18–23] and more than two thirds of status epilepticus cases in the second year of life.[23]

Contrary to traditional beliefs, only 21% of the children experienced seizures either prior to or within 1 hour of the onset of fever; 57% had a seizure after 1 to 24 hours of fever, and 22% experienced their febrile seizure more than 24 hours after the onset of fever.[5,6]

Received Sept 18, 2001. Received revised Dec 3, 2001. Accepted for publication Dec 14, 2001.

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This study was supported by a grant from Elan Biopharmaceuticals.

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Risk Factors for First Febrile Seizure

Two studies have examined risk factors associated with experiencing a febrile seizure (Table 1).[24,25] In a 1993 case-control population-based study, four factors were associated with an increased risk of febrile seizures: (1) a first- or second-degree relative with a history of febrile seizures, (2) a neonatal nursery stay of >30 days, (3) developmental delay, or (4) attendance at day care. There was a 28% chance of experiencing at least one febrile seizure for children with two of these factors.[24] A second case-control study examined the issue of which children with a febrile illness were most likely to experience a febrile seizure using febrile controls matched for age, site of routine pediatric care, and date of visit.[25] Significant independent risk factors, on a multivariable analysis, were the height of the temperature and a history of febrile seizures in a first- or higher-degree relative. Gastroenteritis as the underlying illness appeared to have a significant inverse (ie, protective) association with febrile seizures.

Risk Factors for Recurrent Febrile Seizures

Overall, approximately one third of children with a first febrile seizure will experience a recurrence; 10% will have three or more febrile seizures.[4–10,14,26–29] An assessment of various factors potentially associated with the recurrence of febrile seizures is shown in Table 2. The most consistent risk factors reported are a family history of febrile seizures and onset of first febrile seizure at <18 months of age.[4–7,9,10,14,26–29] This relationship is not attributable to a greater tendency to experience seizures with each specific illness but rather the longer period during which a child with a younger age of onset will be in the age group at risk for febrile seizures.[27,28,30]

Two other definite risk factors for recurrence of febrile seizures are peak temperature[5–7,27,28,31] and the duration of the fever prior to the seizure.[5,6] In general, the higher the peak temperature, the lower the chance of recurrence. In one study, those with peak temperatures of 101°F had a 42% recurrence risk at 1 year, compared with 29% for those with a peak temperature of 103°F, and only 12% for those with a peak temperature of ≥105°F.[5,6] Second, the shorter the duration of recognized fever, the higher the chance of recurrence. The recurrence risk at 1 year was 46% for those with a febrile seizure within an hour of recognized onset of fever, compared with 25% for those with prior fever lasting 1 to 24 hours, and 15% for those having more than 24 hours of recognized fever prior to the febrile seizure.

Children with multiple risk factors have the highest risk of recurrence.[5,27] A child with two or more risk factors has a greater than 30% recurrence risk at 2 years; a child with three or more risk factors has a greater than 60% recurrence risk.[5] In contrast, the 2-year recurrence risk is less than 15% for a child with no risk factors (eg, older than 18 months with no family history of febrile seizures, who experiences a first febrile seizure associated with a peak temperature >40°C after a recognized fever of more than 1 hour).[5,27] A recurrent febrile seizure is also more likely to be prolonged if the initial febrile seizure was prolonged.[11,27]

The relationship between a family history of unprovoked seizures or epilepsy and the overall risk of febrile seizure recurrence appears to be doubtful. Some studies report a modest increase in the risk of febrile seizure recurrence in children with a family history of unprovoked seizures, but a large study in Rochester, Minnesota, found no difference in recurrence risk between children with a family history of epilepsy (25%) and those with no such family history (23%).[4] Other studies have found equivocal results.[5,6,27,28]

The presence of a neurodevelopmental abnormality in the child or a history of complex febrile seizures has not been shown to be significantly associated with an increased risk of subsequent febrile seizures.[4–7,9,11,27,28] Ethnicity and sex have also not been associated with a clear increased risk of recurrent febrile seizures.

Risk Factors for Subsequent Epilepsy

The risk factors for developing epilepsy after febrile seizures are summarized in Table 3. Following a single simple febrile seizure, the risk of developing epilepsy is not substantially different than the risk in the general population.[2,3,9,13,32,33] Data from five large cohorts of children with febrile seizures indicate that 2 to 10% of children who have febrile seizures will subsequently develop epilepsy.[2,3,9,13,32,33]

In each of these five large studies, the occurrence of a family history of epilepsy and the occurrence of a complex

Table 1. Risk Factors for First Febrile Seizure

In population[24]
First- or second-degree relative with history of FS
Neonatal nursery stay of >30 days
Developmental delay
Attendance at day care
Two of these factors → 28% chance of at least 1 FS
In children with a febrile illness[25]
First- or second-degree relative with history of FS
Height of temperature

FS = febrile seizure.

Table 2. Risk Factors for Recurrent Febrile Seizures

Definite risk factor
Family history of FS
Age <18 mo
Height of temperature
Duration of fever
Possible risk factor
Family history of epilepsy
Not a risk factor
Neurodevelopmental abnormality
Complex FS
>1 complex feature
Sex
Ethnicity

FS = febrile seizure.

Table 3. Risk Factors for Subsequent Epilepsy

Definite risk factor
Neurodevelopmental abnormality
Complex FS
Family history of epilepsy
Duration of fever
Possible risk factor
>1 complex feature
Not a risk factor
Family history of FS
Age at first FS
Height of temperature
Sex
Ethnicity

FS = febrile seizures.

febrile seizure were associated with an increased risk of subsequent epilepsy.[2,3,9,13,32,33] The occurrence of multiple febrile seizures was associated with a slight but statistically significant increased risk of subsequent epilepsy in two studies.[2,33] One study found that children with a febrile seizure that occurred within 1 hour of a recognized fever (ie, at onset) had a higher risk for subsequent epilepsy than those children with a febrile seizure associated with longer fever duration.[33] Two studies have found that very prolonged febrile seizures (ie, febrile status epilepticus) were associated with an increased risk of subsequent epilepsy above that of a complex febrile seizure that was less prolonged.[2,33]

The number of complex features in a febrile seizure may possibly affect the risk of recurrence. Although one study found that patients with two complex features (eg, prolonged and focal) had further increased risk of subsequent epilepsy,[2] another study did not detect this association.[33] A family history of febrile seizures, age at first febrile seizure, and the height of fever at first seizure are not associated with a differential risk of developing epilepsy.[2,3,9,32,33] The only common risk factor for both recurrent febrile seizures and subsequent epilepsy was duration of fever prior to the febrile seizure[5,6,33]; this may be a marker for overall seizure susceptibility.

The types of epilepsy that develop are variable.[2,34,35] In general, the types of epilepsy that occur in children with prior febrile seizures are varied and are not very different from those that occur in children without such a history.[34–36] Febrile seizures can also be the initial manifestation of specific epilepsy syndromes, such as severe myoclonic epilepsy of infancy.[37]

It is controversial whether febrile seizures are simply an age-specific marker of future seizure susceptibility or have a causal relationship with the subsequent epilepsy.[38,39] Two factors support the former, and not the latter, interpretation. There is no increased incidence of epilepsy in populations with a high cumulative incidence of febrile seizures (eg, 10% in Tokyo, Japan).[16] Second, no evidence exists that treatment of febrile seizures alters the risk of subsequent epilepsy.[5,40–43]

MORBIDITY AND MORTALITY

The morbidity and mortality associated with febrile seizures are extremely low. Multiple studies have demonstrated no evidence of permanent motor deficits following febrile seizures or febrile status epilepticus.[8–10,19,21,22,44–47] No reports of acute deterioration of cognitive abilities have been noted following febrile seizures, even in series limited to status epilepticus.[21,22,45,46,48–50] Three large studies have shown that cognitive abilities and school performance of children with febrile seizures were similar to those of controls.[44,45,48,51] Prolonged febrile seizures do not appear to be associated with adverse cognitive outcomes.[45,46,48,50]

No deaths were reported from the National Collaborative Perinatal Project[9,10] or the British cohort study.[8,44,45] The mortality of febrile status epilepticus in recent series is extremely low.[19–22,45–47,49]

GENETICS

Genetic influences are evident in multiple studies. A positive family history of febrile seizures is a definite risk factor for both a first febrile seizure[24,25] and recurrent febrile seizures.[4–7,9,27,28] Tsuboi reported a febrile seizure concordance rate of 56% in monozygotic and 14% in dizygotic twins in a study of 32 twin pairs and 673 sibship cases.[52] Correlation of clinical symptoms, including age of onset and degree of fever, was larger in the twin pairs than in the sibship cases. A separate data set from Rochester, Minnesota, demonstrated similar results.[53] Most likely, all children have some increased susceptibility to seizures from fever at the specific age window. Genetic influences are therefore likely to account for some but not all of the cases.

Overall, there appears to be a multifactorial mode of inheritance for febrile convulsions, but there may be a subset of children with an autosomal dominant mode of inheritance.[53–55] To date, no definitive gene or locus for febrile seizure has been established. Some cases of febrile seizures in large families have been linked to genes on chromosomes 8 and 19.[54,56]

INITIAL EVALUATION

Meningitis, encephalitis, serious electrolyte imbalance, and other acute neurologic illnesses must be excluded to make the diagnosis of a febrile seizure. A detailed history and physical and neurologic examinations are essential and can eliminate many of the above. Routine serum electrolytes, calcium, phosphorous, magnesium, complete blood count, and blood glucose are of limited value in the evaluation of a child above 6 months of age with a febrile seizure in the absence of a suspicious history (eg, vomiting, diarrhea, etc) or physical findings.[14,57–60]

The most common evaluation issue is whether a lumbar puncture is necessary to exclude meningitis. The incidence of meningitis in children who present with an apparent febrile seizure is between 2 and 5%.[14,58–65] In each of these

series, the majority had identifiable risk factors. In one series, four features were noted in children with meningitis: a visit for medical care within the previous 48 hours, seizures on arrival to the emergency room, focal seizure, or suspicious findings on physical or neurologic examination.[61] In the absence of risk factors, other authors have found a low yield for routine lumbar puncture.[14,62,63,65]

The American Academy of Pediatrics issued guidelines for the neurodiagnostic evaluation of a child with a simple febrile seizure between 6 months and 5 years of age.[14] A lumbar puncture should be strongly considered in infants less than 12 months of age. Children between 12 and 18 months of age need careful assessment because the signs of meningitis may be subtle. In the absence of suspicious findings on history or examination, a lumbar puncture is not necessary in children above 18 months of age. A lumbar puncture is still recommended in children with a first complex febrile seizure, as well as in any child with persistent lethargy. It should also be strongly considered in a child who has already received prior antibiotic therapy.

Skull radiographs are of no value. Computed tomography (CT) scans are also of limited benefit in this clinical setting and are used when there is concern about increased intracranial pressure or when trauma is suspected. Magnetic resonance imaging (MRI) scans are not indicated in children with a simple febrile seizure.[14] It is unclear whether an MRI study is indicated in the evaluation of a child with a prolonged or focal febrile seizure.[39,66]

Electroencephalograms (EEGs) are of limited value in the evaluation of the child with febrile seizures.[14,67–70] Electroencephalograms are more likely to be abnormal in older children, children with preexisting neurodevelopmental abnormalities, children with a family history of febrile seizures, or children with a complex febrile seizure.[36,67,69,71–74] Even if present, the clinical significance of these EEG abnormalities is unclear. There is no evidence that EEG abnormalities help predict either recurrence of febrile seizures or the development of subsequent epilepsy.[14,36,67,69,71–75]

PATHOPHYSIOLOGY

In general, febrile seizures appear to be an age-specific occurrence, where increased susceptibility to seizures is induced by fever. However, the detailed pathophysiology remains unclear. Decades ago, the key factor was thought to be the rate of rise of the fever[76]; recent data suggest that the key factor is the actual peak temperature.[25,77] Gastroenteritis is associated with a lower incidence of febrile seizures,[25] whereas herpesvirus-6 infections have had a high reported association with febrile seizures.[78–80]

Animal models of febrile seizures also show an age-dependent effect.[81–84] In addition, in vitro preparations show induction of epileptiform activity by temperature elevation in the hippocampal slices in young rats.[85] Recent animal data from Baram and colleagues suggest that prolonged febrile seizures may lead to long-lasting changes in the hippocampal circuits. In a rat model of prolonged febrile seizures, cytoskeletal changes in neurons were evident within 24 hours and persisted for several weeks without leading to cell loss.[86] However, altered functional properties of these injured neurons were evident.[87,88] Nevertheless, even in this model that has produced convincing data for functional changes, a seizure duration of 20 minutes or more was required. Seizures lasting 10 minutes or less were not associated with any anatomic or functional changes.

As may be the case in humans, animals with preexisting neurologic abnormalities are more susceptible to seizures and to their consequences. Young rats with neuronal migration disorders appear more susceptible to hyperthermia-induced seizures[82] and are also more susceptible to hippocampal damage. Interestingly, in this model, hippocampal damage occurs with hyperthermia even in the absence of seizures. The availability of animal models provides a new means of studying the pathophysiology of febrile seizures and their consequences.

FEBRILE SEIZURES AND MESIAL TEMPORAL SCLEROSIS

It remains controversial whether prolonged febrile seizures cause mesial temporal sclerosis.[39,50] Retrospective studies (from tertiary epilepsy centers) report that many adults with intractable mesial temporal lobe epilepsy had a history of prolonged or atypical febrile seizures in childhood.[89–95] However, both population-based studies and prospective studies of children with febrile seizures have failed to find this association.[2,8,9,13,33,38,45]

In those studies that reported an association between prolonged febrile seizures and mesial temporal sclerosis, the duration of the febrile seizures was extremely prolonged. Maher and McLachlan[96] reported on a large family with a high rate of both febrile convulsions and temporal lobe epilepsy. The mean duration of the febrile seizures in those who subsequently developed temporal lobe epilepsy was 100 minutes. VanLandingham et al[66] reported that few children with very prolonged (mean of >90 minutes) focal febrile seizures had acute changes on an MRI, which, in some cases, were followed by later chronic changes. However, these MRI changes occurred only in a small minority of patients. Furthermore, all cases of mesial temporal sclerosis in this study occurred in patients who had focal seizures, some of whom also had focal lesions, which raises the question of preexisting focal pathology.

Overall, febrile seizures are not likely to account for the majority of cases of mesial temporal sclerosis. Febrile seizures lasting more than 90 minutes are very rare and are uncommon, even in series of febrile status epilepticus.[2,9,11,21,22,33,45,46,48,49,66,97] Very prolonged febrile seizures are also usually focal.[66,97] In cases of febrile status epilepticus, imaging abnormalities are relatively uncommon.[66] Mesial temporal sclerosis can also be found in many patients who have no prior history of febrile seizures.[98–103] Recent clinicopathologic studies have also provided evidence for multiple etiologies for mesial temporal sclerosis, as well as the

frequent presence of dual pathology, such as subtle migration defects.[100–103]

TREATMENT

Overview

Two distinct approaches to the treatment of febrile seizures have developed based on the perceived immediate and long-term risks of febrile seizures. One approach is based on the old idea that febrile seizures are harmful and may lead to the development of epilepsy; this approach is aimed at preventing febrile seizures by using either intermittent or chronic treatment with medications.[68,104,105] The second approach is based on the epidemiologic data that febrile seizures are benign; the only concern focuses on aborting febrile seizures to prevent status epilepticus.

Stopping a Febrile Seizure

In Hospital

Ongoing seizure on arrival in the emergency department is an indication for initiating therapy. Intravenous diazepam is effective in most cases.[20,106] Rectal diazepam or diazepam gel would also be appropriate for use in a prehospital setting such as an ambulance and in cases for which intravenous access is difficult.[20,107–109] Other benzodiazepines, such as lorazepam, may also be effective but have not been adequately studied.[20,106] If the seizure continues after an adequate dose of a benzodiazepine, a full status epilepticus treatment protocol should be initiated.[20,106]

At Home

The majority of febrile seizures are brief, lasting less than 10 minutes, and no intervention is necessary. Rectal diazepam or diazepam gel has been shown to be effective in terminating febrile seizures and is the therapy of choice for intervention outside the hospital.[107–109] It should be used with caution and only by reliable caregivers who have been trained in its use. Families with children at high risk for, or with a history of, prolonged or multiple febrile seizures[11] and those who live far from medical care are excellent candidates to have rectal diazepam or diazepam gel readily available in their homes. For many families, the availability of a rectal diazepam formulation will relieve anxiety, even after a single febrile seizure, even though they will most likely never have to use it.[110–112]

Preventing a Febrile Seizure

Intermittent Medications at Time of Fever

Antipyretics. Despite the logical assumption that aggressive treatment with antipyretic medication would reduce the risk of having a febrile seizure, and the finding of case-control studies that the risk of a febrile seizure is directly related to the height of the fever,[25,77] there is little evidence to suggest that antipyretics reduce the risk of a recurrent febrile seizure.[64,113] It should be noted that the children in whom the febrile seizure occurs at the onset of the fever have the highest risk of recurrent febrile seizures.[5,6] Any recommendations for antipyretic therapy should take into account its limitations and avoid creating undue anxiety and guilt in the parents.

Benzodiazepines. Diazepam, given orally or rectally at the time of onset of a febrile illness, has demonstrated a statistically significant, yet clinically modest, ability to reduce the probability of a febrile seizure.[26,114–118] In one large, randomized trial comparing placebo with oral diazepam (0.33 mg/kg/dose q8h with fever), 22% of the diazepam-treated group had seizure recurrence by 36 months, compared with 31% of the placebo-treated group.[118] One must weigh this modest reduction in seizure recurrence with the side effects of sedating children every time they have a febrile illness.

Barbiturates. Intermittent therapy with phenobarbital at the onset of fever is ineffective in reducing the risk of recurrent febrile seizures.[119,120] Surprisingly, it is still fairly widely used for this purpose.[68,104,105]

Daily Medications

Barbiturates. Phenobarbital, given daily at doses that achieve a serum concentration of 15 μg/mL or higher, has been shown to be effective in reducing the risk of recurrent febrile seizures in several well-controlled trials.[113,116,117,121–124] However, in these studies, a substantial portion of the children had adverse effects, primarily hyperactivity, which required discontinuation of therapy.[125–127] More recent studies have cast some doubt on the efficacy of the drug and, more importantly, have raised concerns about potential long-term adverse effects on cognition and behavior.[125,128] Chronic phenobarbital therapy is rarely indicated as the risks seem to outweigh the benefits in most cases.

Valproate. Daily treatment with valproic acid is effective in reducing the risk of recurrent febrile seizures in both human and animal studies.[84,117,123,124] However, it is very rarely used since children considered most often for prophylaxis (young and/or neurologically abnormal) are also the ones at highest risk for fatal idiosyncratic hepatotoxicity.[129,130]

Other Antiepilepsy Drugs. Despite evidence of effectiveness when used in intermittent therapy, there is no experience with chronic use of benzodiazepines for treatment of febrile seizures. Even if effective, the toxicity of benzodiazepines and adverse effect profile would likely preclude their widespread use in this setting. Phenytoin and carbamazepine are ineffective in preventing recurrent febrile seizures in humans and in animal models of hyperthermia-induced seizures.[84,121,122,131] There are no published data on the efficacy of the newer antiepilepsy drugs, such as gabapentin, lamotrigine, topiramate, tiagabine, or vigabatrin, in the treatment of febrile seizures.

Preventing Epilepsy

There is no evidence that preventing febrile seizures will reduce the risk of subsequent epilepsy. One rationale for starting chronic antiepilepsy therapy in children with febrile seizures was to prevent the development of future

epilepsy.[68,104,105] In three studies comparing placebo with treatment (either with daily phenobarbital or with diazepam administered at the onset of fever), treatment significantly and substantially reduced the risk of febrile seizure recurrence, but the risk of later developing epilepsy was no lower in the treated groups than in the controls.[26,40–43,120] No difference in the occurrence of epilepsy, or in school performance or other cognitive outcomes, was seen between the treated group and the control group in two of these studies with more than 10 years of follow-up.[40,41]

Therapy Recommendations

Treatment is only rarely indicated for a simple febrile seizure; no treatment is needed in most children with complex febrile seizures or recurrent febrile seizures. A rational goal of therapy would be to prevent very prolonged febrile seizures. When treatment is indicated, particularly in those at risk for prolonged or multiple febrile seizures[11] or those who live far away from medical care, rectal diazepam or diazepam gel used at the time of seizure as an abortive agent would seem the most logical choice.[20,106–109] Daily medications or benzodiazepines at the time of fever are rarely used in the management of febrile seizures.

Counseling and Education

Counseling and education will be the sole treatment for the majority of children with febrile seizures. Education is key to empowering parents who have just experienced a very frightening and traumatic event.[132] Many parents are afraid that their child could have died.[133] Parents need to be reassured that the child will not die during a seizure and that keeping the child safe during the seizure is generally the only action that needs to be taken.

The basic facts about febrile seizures should be presented to the family. The amount of information and the level of content will depend largely on the medical sophistication of the parents and their ability to attend to the information given to them at that particular time. The parents' perception of their child's disorder will be an important factor in their later coping and will ultimately impact on their perception of quality of life.[132]

Parents will usually be interested in information that will help them manage the illness or specific problems; lengthy explanations are usually not helpful. Information should be provided about how to manage further seizures should they occur. This should include what to do during a seizure, when it may be necessary to call the physician, and when the child should be taken to the emergency department.

In those cases for which rectal diazepam or diazepam gel is being recommended for the next seizure, explicit instructions regarding its use should be given. As it is difficult to absorb all of this information in an emergency department setting, it is usually advisable to see the family again a few weeks later to review the information and answer any additional questions they may have.

CONCLUSION

Febrile seizures are a common and mostly benign form of childhood seizures. An understanding of the natural history and prognosis will enable the physician to reassure the families and provide appropriate counseling and management while avoiding unnecessary diagnostic and therapeutic interventions.

References

1. Commission on Epidemiology and Prognosis, International League Against Epilepsy: Guidelines for epidemiologic studies on epilepsy. *Epilepsia* 1993;34:592–596.
2. Annegers JF, Hauser WA, Shirts SB, et al: Factors prognostic of unprovoked seizures after febrile convulsions. *N Engl J Med* 1987;316:493–498.
3. Annegers JF, Hauser WA, Elveback LR, Kurland LT: The risk of epilepsy following febrile convulsions. *Neurology* 1979;29:297–303.
4. Annegers JF, Blakely SA, Hauser WA, Kurland LT: Recurrence of febrile convulsions in a population-based cohort. *Epilepsy Res* 1990;66:1009–1012.
5. Berg AT, Shinnar S, Darefsky AS, et al: Predictors of recurrent febrile seizures. *Arch Pediatr Adolesc Med* 1997;151:371–378.
6. Berg AT, Shinnar S, Hauser WA, et al: Predictors of recurrent febrile seizures: A prospective study of the circumstances surrounding the initial febrile seizure. *N Engl J Med* 1992;327: 1122–1127.
7. Berg AT, Shinnar S, Hauser WA, Leventhal JM: Predictors of recurrent febrile seizures: A metaanalytic review. *J Pediatr* 1990;116: 329–337.
8. Verity CM, Butler NR, Golding J: Febrile convulsions in a national cohort followed up from birth. I. Prevalence and recurrence in the first 5 years of life. *BMJ* 1985;290:1307–1315.
9. Nelson KB, Ellenberg JH: Prognosis in children with febrile seizures. *Pediatrics* 1978; 61:720–727.
10. Nelson KB, Ellenberg JH: Predictors of epilepsy in children who have experienced febrile seizures. *N Engl J Med* 1976;295: 1029–1033.
11. Berg AT, Shinnar S: Complex febrile seizures. *Epilepsia* 1996;37: 126–133.
12. National Institutes of Health: *Febrile Seizures: Consensus Development Conference Summary*, vol 3, no 2. Bethesda, MD, National Institutes of Health, 1980.
13. Van den Berg BJ, Yerushalmi J: Studies on convulsive disorders in young children, I. Incidence of febrile and nonfebrile convulsions by age and other factors. *Pediatr Res* 1969;3:298–304.
14. American Academy of Pediatrics: Provisional Committee on Quality Improvement: Practice parameter: The neurodiagnostic evaluation of the child with a simple febrile seizure. *Pediatrics* 1996; 97:769–775.
15. Berg AT: The epidemiology of seizures and epilepsy in children, in Shinnar S, Amir N, Branski D (eds): *Childhood Seizures*. Basel, S Karger, 1995, 1–10.
16. Tsuboi T: Epidemiology of febrile and afebrile convulsions in children in Japan. *Neurology* 1984;34:175–181.
17. Stanhope JM, Brody JA, Brink E, Morris CE: Convulsions among the Chamorro people of Guam, Mariana Islands. II. Febrile convulsions. *Am J Epidemiol* 1972;95:299–304.
18. Aicardi J, Chevrie JJ: Convulsive status epilepticus in infants and in children. A study of 239 cases. *Epilepsia* 1970;11:187–197.
19. DeLorenzo RJ, Hauser WA, Towne AR, et al: A prospective population-based epidemiological study of status epilepticus in Richmond, Virginia. *Neurology* 1996;46:1029–1035.

20. Dodson WE, DeLorenzo RJ, Pedley TA, et al: The treatment of convulsive status epilepticus: Recommendations of the Epilepsy Foundation of America's working group on status epilepticus. *JAMA* 1993;270:854–859.
21. Dunn DW: Status epilepticus in children: Etiology, clinical features and outcome. *J Child Neurol* 1988;3:167–173.
22. Maytal J, Shinnar S, Moshe SL, Alvarez LA: Low morbidity and mortality of status epilepticus in children. *Pediatrics* 1989;83:323–331.
23. Shinnar S, Pellock JM, Moshe SL, et al: In whom does status epilepticus occur: Age related differences in children. *Epilepsia* 1997;38:907–914.
24. Bethune P, Gordon KG, Dooley JM, et al: Which child will have a febrile seizure? *Am J Dis Child* 1993;147:35–39.
25. Berg AT, Shinnar S, Shapiro ED, et al: Risk factors for a first febrile seizure: A matched case-control study. *Epilepsia* 1995;36: 334–341.
26. Knudsen FU: Recurrence risk after first febrile seizure and effect of short-term diazepam prophylaxis. *Arch Dis Child* 1985;60: 1045–1049.
27. Offringa M, Bossuyt PMM, Lubsen J, et al: Risk factors for seizure recurrence in children with febrile seizures: A pooled analysis of individual patient data from five studies. *J Pediatr* 1994;124: 574–584.
28. Offringa M, Derksen-Lubsen G, Bossuyt PM, Lubsen J: Seizure recurrence after a first febrile seizure: A multivariate approach. *Dev Med Child Neurol* 1992;34:15–24.
29. Van den Berg BJ: Studies on convulsive disorders in young children. III. Recurrence of febrile convulsions. *Epilepsia* 1974;15: 177–190.
30. Shirts SB, Annegers JF, Hauser WA: The relation of age at first febrile seizure to recurrence of febrile seizures, abstract. *Epilepsia* 1987;28:625.
31. El-Rahdi AS, Banajeh S: Effect of fever on recurrence rate of febrile convulsions. *Arch Dis Child* 1989;64:869–870.
32. Verity CM, Golding J: Risk of epilepsy after febrile convulsions: A national cohort study. *BMJ* 1991;303:1373–1376.
33. Berg AT, Shinnar S: Unprovoked seizures in children with febrile seizures: Short term outcome. *Neurology* 1996;47:562–568.
34. Berg AT, Shinnar S, Levy SR, Testa FM: Childhood-onset epilepsy with and without preceding febrile seizures. *Neurology* 1999;53: 1742–1748.
35. Camfield CS, Camfield PR, Dooley JM, Gordon K: What type of afebrile seizures are preceded by febrile seizures? A population-based study of children. *Dev Med Child Neurol* 1994;36:887–892.
36. Sofianov N, Sadikario A, Dukovski M, Kuturec M: Febrile convulsions and later development of epilepsy. *Am J Dis Child* 1983; 137:123–126.
37. Dravet C, Bureau M, Guerrini R, et al: Severe myoclonic epilepsy in infants, in Roger J, Bureau M, Dravet C, et al (eds): *Epileptic Syndromes in Infancy, Childhood and Adolescence*, 2nd ed. London, John-Libbey, 1992, 75–88.
38. Berg AT, Shinnar S: Do seizures beget seizures? An assessment of the clinical evidence in humans. *J Clin Neurophysiol* 1997;14: 102–110.
39. Shinnar S: Prolonged febrile seizures and mesial temporal sclerosis. *Ann Neurol* 1998;43:411–412.
40. Knudsen FU, Paerregaard A, Andersen R, Andresen J: Long term outcome of prophylaxis for febrile convulsions. *Arch Dis Child* 1996;74:13–18.
41. Wolf SM, Forsythe A: Epilepsy and mental retardation following febrile seizures in childhood. *Acta Paediatr Scand* 1989;78:291–295.
42. Rosman NP, Labazzo JL, Colton T: Factors predisposing to afebrile seizures after febrile convulsions and preventive treatment. *Ann Neurol* 1993;34:452.
43. Shinnar S, Berg AT: Does antiepileptic drug therapy prevent the development of "chronic" epilepsy? *Epilepsia* 1996;37:701–708.
44. Verity CM, Butler NR, Golding J: Febrile convulsions in a national cohort followed up from birth. II. Medical history and intellectual ability at 5 years of age. *BMJ* 1985;290:1311–1315.
45. Verity CM, Ross EM, Golding J: Outcome of childhood status epilepticus and lengthy febrile convulsions: Findings of a national cohort study. *BMJ* 1993;307:225–228.
46. Shinnar S, Pellock JM, Berg AT, et al: An inception cohort of children with febrile status epilepticus: Cohort characteristics and early outcomes, abstract. *Epilepsia* 1995;36(Suppl 4):31.
47. Towne AR, Pellock JM, Ko D, DeLorenzo RJ: Determinants of mortality in status epilepticus. *Epilepsia* 1994;35:27–34.
48. Ellenberg JH, Nelson KB: Febrile seizures and later intellectual performance. *Arch Neurol* 1978;35(1):17–21.
49. Maytal J, Shinnar S: Febrile status epilepticus. *Pediatrics* 1990;86: 611–616.
50. Shinnar S, Babb TL: Long term sequelae of status epilepticus, in Engel J Jr, Pedley TA (eds): *Epilepsy: A Comprehensive Text*. Philadelphia, Lippincott-Raven, 1997, 755–763.
51. Ross EM, Peckham CS, West PB, et al: Epilepsy in childhood: Findings from the National Child Development Study. *BMJ* 1980;1: 207–210.
52. Tsuboi T: Genetic analysis of febrile convulsions: Twin and family studies. *Hum Genet* 1987;75:7–14.
53. Rich SS, Annegers JF, Hauser WA, Anderson VE: Complex segregation analysis of febrile convulsions. *Am J Hum Genet* 1987;41: 249–257.
54. Johnson EW, Dubovsky J, Rich SS, et al: Evidence for a novel gene for familial febrile convulsions, FEB2, linked to chromosome 19p in an extended family from the Midwest. *Hum Mol Genet* 1998; 7:63–67.
55. Wallace RH, Wang DW, Singh R, et al: Febrile seizures and generalized epilepsy associated with a mutation in the Na^+-channel betal subunit gene SCN1B. *Nat Genet* 1998;19:366–370.
56. Wallace RH, Berkovic SF, Howell RA, et al: Suggestion of a major gene for familial febrile convulsions mapping to 8q13-21. *J Med Genet* 1996;33:308–312.
57. Gerber MA, Berliner BC: The child with a "simple" febrile seizure: Appropriate diagnostic evaluation. *Am J Dis Child* 1981;135: 431–433.
58. Heijbel J, Blom S, Bergfors PG: Simple febrile convulsions: A prospective incidence study and an evaluation of investigations initially needed. *Neuropediatrie* 1980;11:45–56.
59. Jaffe M, Bar-Joseph G, Tirosh E: Fever and convulsions—Indications for laboratory investigations. *Pediatrics* 1981;57:729–731.
60. Rutter N, Smales ORC: Role of routine investigations in children presenting with their first febrile convulsion. *Arch Dis Child* 1977;52:188–191.
61. Joffe A, McCormick M, DeAngelis C: Which children with febrile seizures need lumbar puncture? A decision analysis approach. *Am J Dis Child* 1983;137:1153–1156.
62. Lorber J, Sunderland R: Lumbar puncture in children with convulsions associated with fever. *Lancet* 1980;1:785–786.
63. McIntyre PB, Gray SV, Vance JC: Unsuspected bacterial infections in febrile convulsions. *Med J Aust* 1990;152:183–186.
64. Rutter N, Metcalf DH: Febrile convulsions: What do parents do? *BMJ* 1978;2:1345–1346.
65. Wears RL, Luten RC, Lyons RG: Which laboratory tests should be performed on children with apparent febrile convulsions? An analysis and review of the literature. *Pediatr Emerg Care* 1986;2: 191–196.
66. VanLandingham KE, Heinz ER, Cavazos JE, Lewis DV: MRI evidence of hippocampal injury following prolonged, focal febrile convulsions. *Ann Neurol* 1998;43:413–426.

67. Koyama A, Matsui T, Sugisawa T: Febrile convulsions in northern Japan. A quantitative and qualitative analysis of EEG and clinical findings. *Acta Neurol Scand* 1991;83:411–417.
68. Millichap JG, Colliver JA: Management of febrile seizures: Survey of current practice and phenobarbital usage. *Pediatr Neurol* 1991; 7:243–248.
69. Sofianov N, Emoto S, Kuturec M, et al: Febrile seizures: Clinical characteristics and initial EEG. *Epilepsia* 1992;33:52–57.
70. Stores G: When does an EEG contribute to the management of febrile seizures. *Arch Dis Child* 1991;66:554–557.
71. Doose H, Ritter K, Volzke E: EEG longitudinal studies in febrile convulsions. Genetic aspects. *Neuropediatrics* 1983;14:81–87.
72. Frantzen E, Lennox-Buchthal M, Nygaard A, Stene J: Longitudinal EEG and clinical study of children with febrile convulsions. *Electroencephalogr Clin Neurophysiol* 1968;24:197–212.
73. Millichap JG, Madsen JA, Aledort LM: Studies in febrile seizures. V. Clinical and electroencephalographic study in unselected patients. *Neurology* 1960;10:643–653.
74. Tsuboi T: Correlation between EEG abnormality and age in childhood. *Neuropediatrics* 1978;9:229–238.
75. Kuturec M, Emoto SE, Sofianov N, et al: Febrile seizures: Is the EEG a useful predictor of recurrences? *Clin Pediatr* 1997;36:31–36.
76. Livingston S, Bridge EM, Kajdi L: Febrile convulsions: A clinical study with special reference to heredity and prognosis. *J Pediatr* 1947;31:509–512.
77. Rantala H, Uhari M, Hietala J: Factors triggering the first febrile seizure. *Acta Paediatr* 1995;84:407–410.
78. Barone SR, Kaplan MH, Krilov LR: Human herpesvirus-6 infection in children with first febrile seizures. *J Pediatr* 1995;127:95–97.
79. Hall CB, Long CE, Schnabel KC, et al: Human herpesvirus-6 infection in children: A prospective study of complications and reactivation. *N Engl J Med* 1994;331:432–438.
80. Kondo K, Nagafuji H, Hata A, et al: Association of human herpesvirus-6 infection of the central nervous system with recurrence of febrile convulsions. *J Infect Dis* 1993;167:1197–1200.
81. Baram TZ, Gerth A, Schultz L: Febrile seizures: An appropriate-aged model suitable for long-term studies. *Brain Res Dev Brain Res* 1997;98:265–270.
82. Germano IM, Zhang YF, Sperber EF, Moshe SL: Neuronal migration disorders increase susceptibility to hyperthermia-induced seizures in developing rats. *Epilepsia* 1996;37:902–910.
83. Holtzman D, Obana K, Olson J: Hyperthermia-induced seizures in the rat pup: A model for febrile convulsions in children. *Science* 1981;213:1034–1036.
84. Olson JE, Scher MS, Holtzman D: Effects of anticonvulsants on hyperthermia-induced seizures in the rat pup. *Epilepsia* 1984; 25:96–99.
85. Tancredi V, D'Arcangelo G, Zona C, et al: Induction of epileptiform activity by temperature elevation in hippocampal slices from young rats: An in vitro model for febrile seizures? *Epilepsia* 1992; 33:228–234.
86. Toth Z, Yan XX, Haftoglou S, et al: Seizure-induced neuronal injury: Vulnerability to febrile seizures in immature rat model. *J Neurosci* 1998;18:4285–4294.
87. Chen K, Baram TZ, Soltesz I: Febrile seizures in the developing brain result in persistent modification of neuronal excitability in limbic circuits. *Nat Med* 1999;5:888–894.
88. Dube C, Chen K, Eghbal-Ahmadi M, et al: Prolonged febrile seizures in the immature rat model enhance hippocampal excitability long term. *Ann Neurol* 2000;47:336–344.
89. Abou-Khalil B, Andermann E, Andermann F, et al: Temporal lobe epilepsy after prolonged febrile convulsions: Excellent outcome after surgical treatment. *Epilepsia* 1993;34:878–883.
90. Bruton CJ: *The Neuropathology of Temporal Lobe Epilepsy*. New York, Oxford University Press, 1988.
91. Cendes F, Andermann F, Dubeau F, et al: Early childhood prolonged febrile convulsions, atrophy and sclerosis of mesial structures, and temporal lobe epilepsy: An MRI volumetric study. *Neurology* 1993;43:1083–1087.
92. Cendes F, Andermann F, Gloor P, et al: Atrophy of mesial structures in patients with temporal lobe epilepsy: Cause or consequence of repeated seizures. *Ann Neurol* 1993;34:795–801.
93. French JA, Williamson PD, Thadani M, et al: Characteristics of medial temporal lobe epilepsy: I. Results of history and physical examination. *Ann Neurol* 1993:34:774–780.
94. Sagar HJ, Oxbury JM: Hippocampal neuron loss in temporal lobe epilepsy: Correlation with early childhood convulsions. *Ann Neurol* 1987;22:334-340.
95. Taylor DC, Ounsted C: Biological mechanisms influencing the outcome of seizures in response to fever. *Epilepsia* 1971;12:33–45.
96. Maher J, McLachlan RS: Febrile convulsions. Is seizure duration the most important predictor of temporal lobe epilepsy? *Brain* 1995;118:1521–1528.
97. Chevrie JJ, Aicardi J: Duration and lateralization of febrile convulsions. Etiological factors. *Epilepsia* 1975;16:781–789.
98. Falconer M: Genetic and related etiological factors in temporal lobe epilepsy: A review. *Epilepsia* 1971;12:13-31.
99. Falconer MA, Serafetinides EA, Corsellis JAN: Etiology and pathogenesis of temporal lobe epilepsy. *Arch Neurol* 1964;10:233–248.
100. Mathern GW, Babb TL, Mischel PS, et al: Childhood generalized and mesial temporal epilepsies demonstrate different amounts and patterns of hippocampal neuron loss and mossy fibre synaptic reorganization. *Brain* 1996;119:965–987.
101. Mathern GW, Babb TL, Vickrey BG, et al: The clinical-pathologic mechanisms of hippocampal neuronal loss and surgical outcomes in temporal lobe epilepsy. *Brain* 1995;118:105–118.
102. Mathern GW, Pretorius JK, Babb TL: Influence of the type of initial precipitating injury and at what age it occurs on course and outcome in patients with temporal lobe seizures. *J Neurosurg* 1995; 82:220–227.
103. Mathern GW, Babb TL, Pretorius JK, et al: The pathophysiologic relationships between lesion pathology, intracranial ictal EEG onsets, and hippocampal neuron losses in temporal lobe epilepsy. *Epilepsy Res* 1995;21:133–147.
104. Hirtz DG, Lee YJ, Ellenberg J, Nelson KB: Survey on the management of febrile seizures. *Am J Dis Child* 1986;140:909–914.
105. Millichap JG: Management of febrile seizures: Current concepts and recommendations for phenobarbital and the electroencephalogram. *Clin Electroencephalogr* 1991;22:5–12.
106. Maytal J, Shinnar S: Status epilepticus in children, in Shinnar S, Amir N, Branski D (eds): *Childhood Seizures*. Basel, S Karger, 1995, 111–122.
107. Camfield CS, Camfield PR, Smith E, Dooley JM: Home use of rectal diazepam to prevent status epilepticus in children with convulsive disorders. *J Child Neurol* 1989;4:125–126.
108. Knudsen FU: Rectal administration of diazepam in solution in the acute treatment of convulsions in infants and children. *Arch Dis Child* 1979;54:855–857.
109. Morton LD, Rizkallah E, Pellock JM: New drug therapy for acute seizure management. *Semin Pediatr Neurol* 1997;4:51–63.
110. Knudsen FU: Practical management approaches to simple and complex febrile seizures, in Baram TZ, Shinnar S (eds): *Febrile Seizures*. San Diego, Academic, 2002, 274–304.
111. O'Dell C. What do we tell the parent of a child with simple or complex febrile seizures? in Baram TZ, Shinnar S (eds): *Febrile Seizures*. San Diego, Academic, 2002, 305–316.
112. O'Dell C, Shinnar S, Ballaban-Gil K, et al: Home use of rectal diazepam gel (Diastat), abstract. *Epilepsia* 2000;41(Suppl 7):246.
113. Camfield PR, Camfield CS, Shapiro S, et al: The first febrile seizure—Antipyretic instruction plus either phenobarbital or placebo to prevent a recurrence. *J Pediatr* 1980;97:16–21.

114. Autret E, Billard C, Bertrand P, et al: Double-blind randomized trial of diazepam versus placebo for prevention of recurrence of febrile seizures. *J Pediatr* 1990;117:490–494.
115. Knudsen FU: Effective short-term diazepam prophylaxis in febrile convulsions. *J Pediatr* 1985;106:487–490.
116. Knudsen FU, Vestermark S: Prophylactic diazepam or phenobarbitone in febrile convulsions: A prospective, controlled study. *Arch Dis Child* 1978;53:660–663.
117. McKinlay I, Newton R: Intention to treat febrile convulsions with rectal diazepam, valproate or phenobarbitone. *Dev Med Child Neurol* 1989;31:617–625.
118. Rosman NP, Colton T, Labazzo J, et al: A controlled trial of diazepam administered during febrile illnesses to prevent recurrence of febrile seizures. *N Engl J Med* 1993;329:79–84.
119. Pearce JL, Sharman JR, Forster RM: Phenobarbital in the acute management of febrile seizures. *Pediatrics* 1977;60:569–572.
120. Wolf SM, Carr A, Davis DC, et al: The value of phenobarbital in the child who has had a single febrile seizure: A controlled prospective study. *Pediatrics* 1977;59:378–385.
121. Anthony J, Hawke S: Phenobarbital compared with carbamazepine in prevention of recurrent febrile convulsions. *Am J Dis Child* 1983;137:892–895.
122. Bacon C, Mucklow J, Rawlins M, et al: Placebo-controlled study of phenobarbital and phenytoin in the prophylaxis of febrile convulsions. *Lancet* 1981;11:600–603.
123. Herranz JL, Armijo JA, Arteaga R: Effectiveness and toxicity of phenobarbital, primidone, and sodium valproate in the prevention of febrile convulsions, controlled by plasma levels. *Epilepsia* 1984;25:89–95.
124. Newton RW: Randomized controlled trials of phenobarbitone and valproate in febrile convulsions. *Arch Dis Child* 1988;63: 1189–1192.
125. American Academy of Pediatrics Committee on Drugs: Behavioral and cognitive effects of anticonvulsant therapy. *Pediatrics* 1995;96: 538–540.
126. Camfield CS, Chaplin S, Doyle AB, et al: Side effects of phenobarbital in toddlers: Behavioral and cognitive aspects. *J Pediatr* 1979;95:361–365.
127. Wolf SM, Forsythe A: Behavior disturbance, phenobarbital and febrile seizures. *Pediatrics* 1978;61:728–731.
128. Farwell J, Lee YJ, Hirtz DG, et al: Phenobarbital for febrile seizures—Effects on intelligence and on seizure recurrence. *N Engl J Med* 1990;322:364–369.
129. Dreifuss FE, Langer DH, Moline KA, et al: Valproic acid hepatic fatalities. II. U.S. experience since 1984. *Neurology* 1989;39:201–207.
130. Dreifuss FE, Santilli N, Langer DH, et al: Valproic acid hepatic fatalities: A retrospective review. *Neurology* 1987;37:379–385.
131. Camfield PR, Camfield CS, Tibbles JA: Carbamazepine does not prevent febrile seizures in phenobarbital failures. *Neurology* 1982; 32:288–289.
132. Shinnar S, O'Dell C: Treating childhood seizures: when and for how long, in Shinnar S, Amir N, Branski D (eds): *Childhood Seizures*. Basel, S Karger, 1995, 100–110.
133. Baumer JH, David TJ, Valentine SJ, et al: Many parents think their child is dying when having a first febrile convulsion. *Dev Med Child Neurol* 1981;23:462–464.