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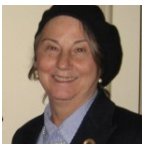
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Febrile Seizures

ARTICLE

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Dr. Shinnar is well known for his research on a variety of topics relating to childhood seizures, including when to initiate and discontinue antiepileptic drug therapy, prognosis following a first seizure, prognosis following discontinuation of medications in children with seizures, status epilepticus, SUDEP and febrile seizures. He has been the principal investigator and co-

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investigator on a variety of NIH-funded research studies. He has also been involved in industry-sponsored trials of new medications. He is currently the principal investigator of the NINDS funded “Consequences of Prolonged Febrile Seizures in Childhood – FEBSTAT” which recently received a Javits Neuroscience award and Co-Principal Investigator of the Einstein NeuroNEXT Center of Excellence for Clinical Trials in Neurology.

Dr. Shinnar is a recipient of the Research Recognition Award of the American Epilepsy Society, the CURE Epilepsy Research Leadership Award and a Javits Neuroscience Award from NINDS. He has authored over 180 peer reviewed papers and over 100 review articles and chapters. He is the Coeditor of the books Childhood Seizures and Febrile Seizures. Dr. Shinnar has served as a reviewer and editorial board member for a variety of journals and is currently on the editorial boards of Pediatric Neurology. He has lectured frequently at both national and international conferences.

SUMMARY

Febrile seizures are a form of acute symptomatic seizures. They occur in 2-5 % of children and are the most common form of childhood seizures. Febrile seizures are most common between the ages of 6 months and 3 years, with peak incidence at approximately 18 months of age. Onset after the age of 7 years is uncommon.

A febrile seizure is defined by the International League Against Epilepsy as a seizure occurring in association with a febrile illness in the absence of a central nervous system (CNS) infection or acute electrolyte imbalance in children older than 1 month of age without prior afebrile seizures. The febrile illness must include a body temperature of more than 101.2 F (38.4 C) although the increased temperature may not occur until after the seizure. The child may be neurologically normal or abnormal.

A febrile seizure is defined by the International League Against Epilepsy as:

- 1) A seizure occurring in childhood after one month of age when a febrile illness is present,
 - a. but that illness is not related to an infection of the central nervous system (CNS);
 - b. nor does the child have an acute electrolyte imbalance;
 - c. nor a history of prior afebrile seizures
- 2) A body temperature of more than 101.2 F (38.4 C)
although the increased temperature may not occur until after the seizure
- 3) The child may be neurologically normal or abnormal

Febrile seizures are further classified as simple or complex. A febrile seizure is complex if it is focal, prolonged (lasting for more than 10 minutes, or multiple (occurrence of more than one seizure during the febrile illness). Conversely, it is simple if it is an isolated, brief, generalized seizure. Although neurologically abnormal children are more likely to experience complex febrile seizures and have a higher risk for subsequent afebrile seizures, the child’s prior neurologic condition is not used to classify the seizure as simple or complex. When a careful history is obtained, approximately 30% of patients with febrile seizures presenting to the emergency department are found to have complex features. The majority of febrile seizures are simple seizures.

The prognosis for febrile seizures usually has been found to be good. Such seizures are not associated with any detectable brain damage and epilepsy will eventually develop in only a small minority of children who have had febrile seizures. It also has been learned that, although antiepileptic drugs can prevent recurrent febrile seizures, they do not alter the risk of subsequent epilepsy. This finding has led to a changing view of the treatment of these common and largely benign seizures.

The one exception to the favorable prognosis is very prolonged febrile seizures lasting more than 30 minutes. These are also known as febrile status epilepticus. These very prolonged febrile seizures which occur in 5-9 % of children with febrile seizures can be associated with injury to the brain structure called the hippocampus and result in subsequent epilepsy. Approximately 30-40% of children with febrile status epilepticus will later develop epilepsy.

DESCRIPTION

Febrile seizures may start in different ways but less than 90% of them end up as a tonic clonic seizure (also known as a grand mal seizure) or a convulsion. The child may stare, have eye deviation and have shaking of arms and legs; they may stop breathing for a few seconds and have a bluish tint to skin around the lips. After the seizure the child may be irritable and sleepy for some time. People who have not seen a seizure or have little or no medical knowledge about seizures can be very frightened if they witness the event; febrile seizures are however, for the most part, benign events. Most febrile seizures will last less than 5 to 10 minutes in duration and resolve without treatment.

The usual febrile seizure is an isolated brief convulsion lasting less than 10 minutes, typically much less. This is what is called a simple febrile seizure. When there are other features in the beginning, such as a stare or one side only jerking, they are called focal onset. When they last more than 10 minutes they are considered prolonged. If they occur multiple times within a 24 hour period, that is still considered one event. Any of these three features (focal, prolonged or multiple) will then classify the febrile seizure as complex. The special situation of febrile status epilepticus (febrile seizure lasting longer than 30 minutes) is the extreme end of prolonged febrile seizure.

Table 1: Types of Febrile Seizures

Simple Febrile Seizure	Complex Febrile Seizure
A seizure that is isolated, brief, and generalized	<u>Focal</u> : seizure occurs in single area of brain, may begin as a stare or jerking on one side of body
The majority of febrile seizures are simple seizures	<u>Prolonged</u> : lasting for more than 10 minutes
	<u>Multiple</u> : more than one seizure during the febrile illness

SYMPTOMS

The child may or may not have a fever at the onset of the seizure. In many cases, the seizure is the first sign that the child has a fever which is only

diagnosed later in the emergency department. However, most children will first have some symptoms of illness such as an upper respiratory infection, gastroenteritis, an ear infection, or just be “fussy” for a few days before the seizure. Symptoms are further outlined in the above *Description* section.

LABORATORY INVESTIGATIONS & DIAGNOSTIC STANDARDS

By definition, a febrile seizure implies that the cause of the seizure is a fever and the doctor must exclude more serious potential causes of the seizure. These include brain infections such as meningitis or encephalitis, severe electrolyte imbalance which can occur in babies with diarrhea or vomiting, and other acute neurologic illnesses. These exclusions usually are feasible and are based on a detailed history and physical and neurologic examination. Sometimes however, especially in very young children, it is necessary to perform additional tests such as lumbar puncture.

The American Academy of Pediatrics issued guidelines for the testing that should be performed on the child who has experienced a simple febrile seizure between the ages of 6 months and 5 years. For the child younger than 6 months of age, a lumbar puncture is still considered standard. For infants between 6 months and 12 months of age, lumbar puncture should be considered, especially if immunizations are incomplete or if immunization status cannot be determined. Above that age lumbar puncture is not routinely done. At any age if the child looks ill, has persistent lethargy, or there is a clinical suspicion, a lumbar puncture should be performed. It also should be strongly considered in a child who has already received prior antibiotic therapy as these may mask the signs of a more serious infection. While parents are often very concerned about lumbar puncture, in infants who present with what appears to be a febrile seizure, it is a safe and benign procedure.

The following summarizes the AAP Lumbar Puncture guideline recommendations:

1. For the child younger than 6 months of age, a lumbar puncture is still considered standard.
2. For infants between 6 months and 12 months of age, a lumbar puncture should be considered, especially if immunizations are incomplete or if immunization status cannot be determined.
3. Above that age, a lumbar puncture is not routinely done.
4. At any age if the child looks ill, has persistent lethargy, or there is a clinical suspicion, a lumbar puncture should be performed.
5. It also should be strongly considered in a child who has already received prior antibiotic therapy as these may mask the signs of a more serious infection.

While there is emerging consensus about the role of lumbar puncture in children with a simple febrile seizure and so their use is much less, there is no such consensus in the case of complex febrile seizures. This is because, when meningitis is present, it tends to present with what appears to be a complex febrile seizure although the vast majority of complex febrile seizures are not meningitis. This is especially the case with febrile status epilepticus (febrile

seizure lasting longer 30 minutes) as these children have usually received sedating medications to treat the seizure and it is very difficult to ascertain initially whether their lethargy is simple due to the prolonged seizure or whether there is a more serious underlying cause.

In the absence of suspicious findings in the history (e.g., vomiting, diarrhea) or on physical examination, routine blood cell counts and determination of serum electrolyte, calcium, phosphorus, magnesium, or blood glucose levels are of limited value in the evaluation of a child older than 6 months of age with a simple febrile seizure.

Skull radiographs are of no value. Computed tomography (CT) scans also are of limited benefit in this clinical setting. Magnetic resonance imaging (MRI) scans are not indicated in children with a simple febrile seizure or in most cases of complex febrile seizures. The exception again is the child with very prolonged febrile seizures as MRIs are usually indicated for the diagnostic evaluation of any child with a very prolonged seizure whether febrile or not. Similarly, the electroencephalography (EEG) is of limited or no value in the assessment of the child with a simple or complex febrile seizure. Even though abnormalities may be present, the current view is that they do not help in the diagnosis or management. Once again, the very prolonged febrile seizures are different and an EEG is indicated in the evaluation of the child with a very prolonged one.

CAUSATION AND RISK FACTORS

The precise cause of febrile seizures remains unknown. We do know that the immature developing brain is different than the adult brain. In animals, one can produce seizures with fever at ages that developmentally correspond to the ages that febrile seizures do occur. Therefore, we know that there is a specific age susceptibility. We also know that Interleukin 1b is the chief cytokine that is responsible for producing fever in humans. This molecule also works on specific brain receptors to lower seizure threshold and induce seizures but only in the developing brain.

While the specific causes of febrile seizures are poorly understood, we do know a fair amount about who is at risk for febrile seizures. The major risk factors for having a febrile seizure are:

1. A history of febrile seizures in a first-or second-degree relative
2. A neonatal nursery stay of more than 30 days
3. Developmental delay
4. Attendance at day care.

Children with two of these factors had a 28% chance of experiencing at least one febrile seizure. These factors reflect three different likely risks. The first is genetic predisposition. Even though, the known mutations, of which there are many, account for a tiny proportion of children with febrile seizures, a family history of febrile seizures suggesting a predisposition is very common and is a clear risk factor. Genetic influences clearly play a major role in febrile seizures though the majority of children with febrile seizures will not have such a history; even fewer will have a detectable genetic mutation which is why genetic testing, though an important part of research about febrile seizures, is not a part of the routine evaluation of children with febrile seizures.

Developmental delay and prolonged neonatal stay are both surrogates for

having some brain abnormality. If that abnormality lowers seizure threshold, then when in the age group where the infant is susceptible to febrile seizures, that infant will be more susceptible. Attendance at day care is a risk because febrile seizures are the classic example of the interplay of underlying susceptibility and environmental influence (i.e. having a febrile illness). Children who attend day care are more likely to experience febrile illnesses during the age range (under age 3) of peak susceptibility. This is not a reason to not send children to daycare.

One can also ask: what are the risk factors to experience a febrile seizure during a febrile illness? After all, the majority of children who have a febrile illness do not experience a febrile seizure. In this case the risk factors include the height of the peak temperature (the higher the temperature the more likely it is to have a febrile seizure), a history of febrile seizures in an immediate relative, and the type of illness causing the fever.

Risk factors for having a febrile seizure during a febrile illness

- Height of the peak temperature (the higher the temperature the more likely it is to have a febrile seizure)
- A history of febrile seizures in an immediate relative
- The type of illness causing the fever

Lastly, one can talk about the risk factors in a child with a first febrile seizure to experience more febrile seizures. Once again, genetic/familial predisposition is key. Children with a positive family history of febrile seizures are more likely both to experience a febrile seizure and to experience recurrent febrile seizures than children without such a family history. Age at time of first febrile seizure is also key with younger children (under 18 months of age) more likely to experience further febrile seizures. The reason appears to be that the younger children will spend more time in the age susceptibility period than the older child. Finally the characteristics of the febrile illness matter as well. Those with a lower peak temperature and those whose seizure was the first sign of fever are at higher risk for recurrences than those with a high peak temperature and those whose seizure occurred after more than an hour of recognized fever. This has implications for management.

Table 2: Risk Factors

Characteristics with a higher risk for repeat febrile seizure	Characteristics with a lower risk for repeat febrile seizure
Lower peak temperature	Higher peak temperature
Seizure was first sign of fever	Seizure occurred after more than an hour of recognized fever

THERAPEUTIC INTERVENTION

Treatment of febrile seizures falls into several categories. First is the management of the acute seizure if it does not stop. Second is the prevention of further seizures, or at least of further prolonged seizures. Finally, there is the issue of preventing epilepsy which is one of the potential outcomes (*see Prognosis below*).

Treatment of the acute seizure: As previously described, the majority of febrile

seizures are brief and self limited and will stop without any treatment. For these seizures, no medications are needed. The usual first aid for seizures (keeping patient safe and away from sharp objects, do not stick anything in their mouth, etc) are all that is needed.

- Keep patient safe and away from sharp objects
- Do not stick anything in their mouth

For seizures lasting longer than 5 minutes, treatment is generally indicated as these seizures will tend to go on for a long time if not treated and the long seizures are the ones that can have consequences. For the first event, this will be generally done by the emergency medical services or the emergency department. For children at risk, medications for home use are often provided.

If seizure activity is ongoing when the child arrives at the emergency department, treatment to stop the seizure is mandatory. Intravenous medication is effective in most cases. Rectal medication is also appropriate for use in a pre-hospital setting, such as an ambulance, and in cases in which intravenous access is difficult. If the seizure activity continues after an adequate dose of a first medication, then a full status epilepticus treatment protocol should be used.

Home management of a febrile seizure: During a seizure, place the child on his or her side on a protected surface and observe carefully. Keep track of the time; if the seizure lasts longer than 5 minutes, call 911 or take the child to an emergency facility if you can do so safely.

A majority of febrile seizures are brief, lasting less than 10 minutes, and no intervention is necessary. Rectal diazepam has been demonstrated to be effective in terminating febrile seizures. It is widely used in Europe, Canada, Japan and the United States. Use of this agent is a rational therapy in those situations in which acute treatment of a febrile seizure at home is appropriate. This approach has the obvious advantage of minimizing drug exposure. It should be used with caution, however, and only with reliable caregivers who have been trained in its use. Candidates for this treatment include children at high risk for prolonged or multiple febrile seizures and those who live far from medical care. Studies have shown that not all children are at risk for having prolonged febrile seizures. The main risk factor is that the first seizure lasted more than 10 minutes; therefore, not all children with a febrile seizure need to have abortive therapy available at home.

Two steps to remember when managing febrile seizures at home:

1. During a seizure, place the child on his or her side on a protected surface and observe carefully.
2. Keep track of time, and if the seizure lasts longer than 5 minutes, call 911 or take the child to an emergency facility if you can do so safely.

Preventing Recurrent Febrile Seizure: There are several approaches to preventing further febrile seizures. Daily antiseizure medications, including phenobarbital and sodium valproate, can reduce the risk. However, given the benign nature of most febrile seizures and the side effects associated with using these medication, they are used very rarely. A more popular approach is to give medications such as diazepam as soon as the child appears ill to attempt to prevent a febrile seizure. While this approach does somewhat reduce the risk for recurrence, it is not very effective. This is partly because

the children at highest risk are those whose febrile seizure are the first sign of their illness so there is no warning. In addition, as young children tend to sniffle frequently throughout the winter, advising parents to medicate the child at the first sign of illness is likely to result in many days that the child is taking medications.

Because febrile seizures, by definition, occur in the context of a febrile illness, aggressive treatment with antipyretic medication could be expected to reduce the risk of having a febrile seizure. In support of use of these agents, studies find that the risk of a febrile seizure is directly related to the height of the fever. Little evidence, however, is available to suggest that antipyretic agents reduce the risk of another febrile seizure. The children in whom the febrile seizure occurs at the onset of the fever have the highest risk of recurrent febrile seizures. Recommendations for antipyretic therapy should recognize its limitations and avoid creating undue anxiety and feelings of guilt in the parents.

The most common and rational approach is based on the epidemiologic data that febrile seizures are by and large benign. Therefore, the only concern is about prolonged febrile seizures. This approach focuses not on prevention of febrile seizures at all costs but trying to prevent prolonged ones. Preventing or aborting prolonged febrile seizures to prevent status epilepticus with its attendant complications is a rational goal. In this approach, parents of children who are at risk for prolonged or repetitive febrile seizures are given abortive medications with instructions of use (*see Home Management above*). For the remaining parents, the vast majority of families, reassurance that while a very frightening event, febrile seizures are benign and counseling of first aid during a seizure is all that is needed.

One reason often given for treating febrile seizures is to prevent future epilepsy. While laudable, our current treatments do not accomplish this goal. They can reduce the chances of having further febrile seizures but do not alter the risk of future epilepsy. In many cases this risk was already present and febrile seizures in infancy are only the marker for that predisposition and not the cause. The only data on febrile seizures causing subsequent epilepsy come from studies of very prolonged febrile seizures. Therefore the rational approach to reduce the risk of future epilepsy focuses on preventing further prolonged febrile seizures as described above.

In a majority of cases, counseling and education will be the sole treatment. Education is key to empowerment for parents who have just experienced a frightening and traumatic event. Many parents are afraid that their child could have died. Keeping the child safe during the seizure generally is the only action that needs to be taken. First aid should be provided during the seizure such as keeping the child safe from injury. The physician should be called after the seizure because treatment may be needed for the cause of fever. The child may need to be taken to the emergency department if the seizure is prolonged.

PROGNOSIS

The prognosis of febrile seizures is generally favorable. Although parents frequently believe their child is dying even during a simple febrile seizure, there are almost no deaths reported in the thousands of cases of febrile seizure (including prolonged seizures) that have been studied. Several excellent studies have followed these children to age 7 and older.

Cognitive and intellectual outcomes are favorable and children with febrile seizure, including those that are prolonged, appear similar to their siblings and to the general population on many measures.

Approximately one-third of children with a first febrile seizure will experience another; 10% will have three or more. The risk factors have been described above. Not surprisingly, children with multiple risk factors have the highest risk of recurrence. 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. In contrast, the child with no risk factors (e.g., older than 18 months with no family history of febrile seizures) who experiences a first febrile seizure associated with a peak temperature less than 104° F (40° C) – after a recognized fever of more than one hour – has a less than 15% chance of experiencing another febrile seizure within 2 years.

The major concern in children with febrile seizure is about the risk of future epilepsy. Data from five large studies of children with febrile seizures indicate that epilepsy develops in 2-10% of children who experience febrile seizures. In most studies, the risk of future epilepsy in a child with simple febrile seizures is very low and not significantly different than in the child without febrile seizures. The risk is higher in those with 3 or more febrile seizures and this is likely a group with a strong family history and an underlying predisposition. The febrile seizures here are a marker for, rather than a cause of, the subsequent epilepsy.

The major risk factors of developing epilepsy are the occurrence of complex febrile seizure, a family history of epilepsy, and developmental abnormality. The latter two are risks for developing epilepsy whether or not a child has febrile seizures. In most cases the association is not causal. There are two exceptions to these outcomes. The first is the occurrence of very prolonged febrile seizures or febrile status epilepticus. Between 30% and 40% of these children will eventually develop epilepsy though it may take 10 or more years for the epilepsy to develop. Ongoing research is demonstrating that, in contrast to the benign brief febrile seizures, these very prolonged seizures can cause injury to an area of the brain called the hippocampus and, in some cases, cause subsequent epilepsy. Animal data also suggest that, while brief seizures with fever are benign, prolonged seizures can cause injury and subsequent epilepsy.

The major risk factors for developing epilepsy from febrile seizures are:

- The occurrence of a complex febrile seizure
- A family history of epilepsy
- A developmental abnormality

The other small group of children with a different prognosis are those whose febrile seizure is the first sign of a more severe epilepsy, such as Dravet syndrome (severe myoclonic epilepsy). In these children, the first febrile seizure which is typically prolonged is quickly followed by other seizure types. In this case the febrile seizure is really the presentation of the syndrome, but this can be difficult to establish initially. The reassuring news to parents is that although most cases of this rare syndrome present with prolonged febrile seizures, the vast majority of children with febrile seizures (including prolonged seizures), do not have this entity.

At the moment, with the exception of very prolonged febrile seizures, we are

able to be very reassuring to parents on prognosis. Even with prolonged seizures, cognition and behavior is likely to be fine and the main concern is about future development of epilepsy. This is an area of active research at this time.

GLOSSARY/DEFINITIONS

Acute symptomatic: Seizures that are caused by or related to an acute neurologic or systemic event.

Antipyretic medication: Drugs or herbs that reduce [fever](#), such as acetaminophen or ibuprofen

Electrolyte imbalance: Electrolytes are [minerals](#) in your body that have an electric charge. They are in your blood, urine, and body fluids. Maintaining the right balance of electrolytes helps your body's blood chemistry, muscle action, and other processes. When the electrolytes are too high or low it is called an electrolyte imbalance.

Epidemiologic data: Epidemiology is the study of the patterns, [causes](#), and effects of [health](#) and [disease](#) conditions in defined [populations](#). Epidemiologic data comes from research with collection and [statistical analysis](#) of data and interpretation and dissemination of results.

Febrile seizures: Febrile seizures are events brought on by a fever in infants or small children during which a child may lose consciousness and shake, moving limbs on one or both sides of the body. The child may become rigid or have twitches in only a portion of the body, such as an arm or a leg, or on the right or the left side only. Most febrile seizures last several minutes, although some can be as brief as a few seconds while others last for more than 15 minutes.

Focal seizure: Focal or partial seizures occur when abnormal electrical activity causing the seizure starts and remains in one part of the brain.

Generalized seizure: Abnormal seizure electrical activity affecting the whole brain.

Gene mapping: Also called genome mapping or linkage mapping, can offer evidence that a disease transmitted from parent to child is linked to one or more genes. It also provides clues about which chromosome contains the gene and precisely where it lies on that chromosome. It is the creation of a [genetic map](#) assigning [DNA](#) fragments to [chromosomes](#).

Idiosyncratic hepatotoxicity: A characteristic peculiar to an individual drug that can or does harm the liver.

Lumbar puncture: Lumbar puncture (spinal tap) is performed in your lower back, in the lumbar region. During lumbar puncture, a needle is inserted between two lumbar bones (vertebrae) to remove a sample of cerebrospinal fluid — the fluid that surrounds your brain and spinal cord to protect them from injury.

Prognosis: A prediction of the probable course and outcome of a disease.

Prophylaxis: Prevention of or protective treatment for disease.

Status epilepticus: A prolonged seizure lasting more than 30 minutes. While some newer definitions use 5-10 minutes, they are talking about when to treat. When we worry about prolonged seizures causing injury, 30 minutes remains

the definition.

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