Febrile Seizures: Long-Term Management of Children with Fever-Associated Seizures

Pediatrics in Review 1981;2;209
DOI: 10.1542/pir.2-7-209

Febrile Seizures: Long-Term Management of Children with Fever-Associated Seizures*

Consensus Development Panel

A Consensus Development Conference on Febrile Seizures was held at the National Institutes of Health on May 19–21, 1980. The purpose of the Conference was to bring together practicing physicians, research scientists, consumers, and others in an effort to reach general agreement on the risks of sequelae in children with febrile seizures and to compare them with the potential risks and benefits of prophylaxis with anticonvulsants. This summary is the result of these deliberations.

1. What is a febrile seizure?

A febrile seizure (an abnormal, sudden, excessive electrical discharge of neurons (gray matter) which propagates down the neuronal processes [white matter] to affect an end organ in a clinically measurable fashion) is an event in infancy or childhood, usually occurring between 3 months and 5 years of age, associated with fever but without evidence of intracranial infection or defined cause. Seizures with fever in children who have suffered a previous nonfebrile seizure are excluded. Febrile seizures are to be distinguished from epilepsy, which is characterized by recurrent nonfebrile seizures.

2. What are the risks facing the child who has a febrile seizure?

Children who suffer a febrile seizure generally enjoy normal health after the episode. They are, however, at some risk in several respects. Thirty percent to 40% of children who have one febrile seizure and who do not receive prophylactic therapy will experience a second. Recurrence is more likely if the first seizure occurs during the first year of life. The seizure itself is frightening and frequently may be emotionally disturbing to the family. During a seizure, there is, additionally, a minimal chance of physical injury. The occurrence of a second or subsequent febrile seizure does not, in itself, greatly change the risk of epilepsy.

A small percentage of children who have had a febrile seizure may have nonfebrile seizures, that is, epilepsy. Significant risk factors separate these children. The high risk group, for which one study showed a 13% incidence of epilepsy, is characterized by the presence of at least two of the following risk factors: a family history of nonfebrile seizures; abnormal neurologic or developmental status prior to febrile seizure; an atypical febrile seizure, such as a prolonged (more than 15 minutes) or focal seizure. Only 2% to 3% of children who have none or one of the above risk factors subsequently develop nonfebrile seizures.

The child with febrile seizures may have a neurologic deficit, such as mental retardation, motor deficit, and sensory and perceptual abnormalities. It is generally believed that when present, these central nervous system (CNS) deficits have usually antedated the febrile seizures. There is no convincing experimental or epidemiologic evidence that these deficits reflect neurologic injury occurring at the time of the febrile seizure.

3. What can chronic or intermittent prophylaxis accomplish in reducing those risks?

The only risk demonstrated to be affected by therapy is that of recurrence of a febrile seizure. Numerous studies show that the risk of recurrence of febrile seizures can be reduced by the continuous daily administration of phenobarbital at appropriate dosage to achieve minimum therapeutic blood levels (approximately 15 μg/ml). Preliminary evidence suggests that the frequency of febrile seizures may also be reduced by the prompt administration of diazepam by rectum, or possibly other agents, at the onset of acute febrile illness. There is no evidence to suggest that phenytoin is effective in prophylaxis of febrile seizures.

Maintenance Therapy. While prolonged administration of phenobarbital is an accepted method of reduction of the frequency of febrile seizures, the long-term effects of such management are still poorly understood and require investigation. Valproic acid has been reported to be effective; however, hepatic toxicity following the prolonged use of valproic acid has been reported. Thus, when this drug is used, liver function should be monitored closely.

Intermittent Therapy During Febrile Episodes. Intermittent use of phenobarbital administered orally at the usual recommended dosage (3 to 5 mg/kg) has been shown to be ineffective in promoting therapeutic blood levels. Diazepam, when administered as suppositories (not yet available in the United States), apparently is absorbed rapidly enough to provide immediate protection

EDUCATIONAL OBJECTIVES

94. Appropriate evaluation of the child with febrile seizures, with respect to the need for continuing prophylactic medication (80/81).

12. Appropriate evaluation of the young child with a fever and a convulsion with ability to differentiate among simple febrile seizures, chronic convulsive disorders, and various infectious or metabolic disorders, or drug ingestion, with ability to manage each appropriately (80/81 Topics).

* *This article and the accompanying commentary are being printed in both Pediatrics and Pediatrics in Review to ensure that their important message is available to readers of either publication and to those reviewing for PREP. (R.J.H.)*

from subsequent seizures in a high percentage of febrile children.

There is no evidence to support the concept that prolonged therapy with anticonvulsants prevents the development of epilepsy or significant neurologic deficits.

4. What are the potential risks of prophylaxis, using the available forms of therapy?

The potential risks of continuous prophylaxis are those predictable side effects, toxic manifestations, or idiosyncratic reactions that may be peculiar to the anticonvulsant drug selected for therapy.

Drugs currently administered on a long-term basis to prevent febrile seizures are phenobarbital, diazepam, and valproic acid and, to a lesser extent, phenytoin and carbamazepine. Phenobarbital is by far the most commonly used agent.

Side effects and toxic reactions are reported in up to 40% of infants or children receiving phenobarbital. These reactions are usually of the following types: (*a*) behavioral changes—hyperactivity to extreme irritability and, rarely, somnolence; (*b*) sleep pattern disturbances—prolonged nocturnal awakenings; and (*c*) interference with higher cortical or cognitive functions, eg, defect in short-term memory formation, inattentiveness or decreased attention span, or defects in general comprehension.

Disturbances in behavior and patterns of sleep are not predictable. They are the cause for discontinuation of therapy in up to 25% of patients.

Animal and tissue culture studies, which are not at this time conclusive in regard to humans, raise questions as to more serious effects of phenobarbital and certain other anticonvulsant agents on the developing nervous system.

Phenobarbital is capable of enzyme induction and, therefore, may interact with other drugs. The induction of more rapid metabolism of acetaminophen (a major antipyretic) may increase the risks of hepatotoxicity.

Phenobarbital has been used intermittently during febrile episodes to prevent recurrence of febrile seizures. In less than loading doses, this method is ineffective. When given in loading doses (10 to 15 mg/kg), phenobarbital produces somnolence, lethargy, and other behavioral manifestations.

Valproic acid has been shown to be an effective prophylactic agent in preventing recurrent febrile seizures. Few serious side effects and toxic reactions occur; however, gastrointestinal upset, toxic hepatitis, pancreatitis, and other side effects have been reported. Behavioral side effects are rare and disturbances in higher cortical function have not been reported. Liver function studies should be monitored periodically in patients on prolonged valproic acid therapy.

Diazepam, given by rectum, has been reported to be effective in the prophylaxis of seizures during febrile episodes. Side effects and toxic reactions have been rare, although sedation has been observed.

One report, however, did find that antipyretic therapy was not effective in preventing febrile seizures. Acetaminophen and aspirin both produce relatively prompt lowering of temperature and both are relatively free of side effects and toxic reactions.

5. What is a rational approach to management of children with febrile seizures? Which children should be considered for prophylaxis?

A rational approach to the management of febrile seizures should take into account that the long-term prognosis is excellent, that prophylaxis reduces the risk of subsequent febrile seizures, and that there is no evidence that prophylaxis reduces the risk of subsequent nonfebrile seizures.

An initial work-up of febrile seizures should include a complete history and complete pediatric and neurologic examination, including characterization of the febrile illness, degree of temperature elevation, and complete description of the febrile seizure. If a CNS infection is suspected, a lumbar puncture is indicated.

The role of the electroencephalogram (EEG) in the work-up of febrile seizures remains controversial. Most children with simple febrile seizures have normal EEGs. Abnormal EEGs do not reliably predict the development of epilepsy in patients with febrile convulsions.

Other studies, such as a complete blood cell count, measurement of levels of serum electrolytes, calcium, and glucose in the blood, and skull x-rays or computed tomography (CT) scanning of the brain are rarely useful in the uncomplicated febrile seizure.

Febrile convulsions rarely presage complex partial seizures or other forms of epilepsy and are generally benign and self-limited.

Anticonvulsant prophylaxis in therapeutic levels may be considered under any of the following conditions: (*a*) in the presence of abnormal neurologic development (eg, cerebral palsy syndromes, mental retardation, microcephaly); (*b*) when a febrile seizure is: longer than 15 minutes, or focal, or followed by transient or persistent neurologic abnormalities; or (*c*) when there is a history of nonfebrile seizures of genetic origin in a parent or sibling.

The physician occasionally may elect, in certain selected cases, to provide anticonvulsant treatment when a patient has multiple febrile seizures or when seizures occur in an infant under the age of 12 months.

When anticonvulsant prophylaxis is instituted, it is usually continued for at least two years or one year after the last seizure, whichever is the longer period of time. Discontinuation of therapy should be done slowly over a one- to two-month period.

Parents and others who are responsible for the care of young children play a key role in the prevention and management of febrile seizures. Family education and counseling should address: the relatively benign nature of febrile seizures; the recognition of and management of fever; the use of antipyretic agents; medication and compliance; side effects of medication; first aid for a seizure; and when and how to seek emergency assistance, if needed.

Educational materials may be an effective means to complement the

physician's efforts toward family education.

Since nurses and allied health professionals, health educators, and social workers play an important role in family education and counseling, they should receive adequate information in the management of febrile seizures.

Efforts should also be directed to disseminating this knowledge to the public, including day care centers, through mass media and other means.

6. Are further clinical, experimental, or epidemiologic studies necessary to help in answering these questions?

Certain important questions remain unanswered. Studies are needed to address these issues:

A. Determination of risk factors predicting an initial febrile seizure.

B. Continuation of the present efforts to follow into adulthood children who have had a history of febrile seizures. This follow-up should include exploration of any association between febrile seizures and learning disorders, epilepsy, behavior aberrations, intellectual development, and changes in the EEG.

C. Continued efforts to clarify the role of anticonvulsant treatment in febrile convulsions. Can evidence be obtained as to whether anticonvulsant treatment is able to: Alter the probability of developing epilepsy at some later date? Alter the probability of development of other neurologic sequelae, eg, lowered IQ? Alter psychological and behavioral characteristics?

D. Pharmacologic studies: what anticonvulsants are safe and effective in the chronic prophylaxis of febrile convulsions? What is the proper dosage and the therapeutic blood level? What anticonvulsants are safe and effective for short-term prophylaxis of febrile convulsions? What is the proper dosage and the therapeutic blood level? What are the long-term risks of the use of the above anticonvulsants? Does phenobarbital enhance the possible carcinogenic effects of other drugs or chemical agents in humans?

E. Controlled study of antipyretic measures with the onset of febrile illness as a means of decreasing the risk of recurrence of febrile seizures.

F. Continuation of experiments of the effects of drugs on brain growth and development, utilizing animal and tissue culture techniques.

G. Continuation of animal experiments to clarify the effects of single recurrent seizures on brain maturation and development, utilizing both experimental animal models and kindling techniques.

Commentary
Febrile Seizures: A Consensus of Their Significance, Evaluation, and Treatment

The National Institutes of Health recently convened experts from this country and abroad to present current knowledge about febrile seizures and their consequences, and about the risks and benefits of therapy. This information was presented to a panel under the chairmanship of Dr Edwin Kendig, former president of the American Academy of Pediatrics. The panel consisted of both academicians and practitioners. The preceding statement represents the consensus of that panel.

The statement bears reading in its entirety, for it should influence the way that pediatricians think about the child who has had a seizure with fever, how he evaluates and treats that child, and what he tells the parents.

The panel found that there were only two significant risks associated with febrile seizures: a 30% to 40% risk of recurrent febrile seizures and a slightly increased risk of later epilepsy. They found no evidence of mental or neurologic impairment due to the febrile seizure.

The panel concluded that daily phenobarbital in sufficient dosage to produce a blood level of 15 μg/ml could prevent recurrence of febrile seizures, but that there was *no* evidence that either the administration of phenobarbital or the prevention of recurrences prevented later epilepsy.

Phenobarbital was noted to produce side effects or toxic reactions in up to 40% of children. These included behavioral changes, sleep disturbances, and possible interference with learning. Valproic acid was also effective in preventing recurrences, but in view of the rare, but reported fatal hepatitis, liver function tests should be closely monitored.

The consensus panel evaluated the work-up and the usefulness of laboratory tests and concluded that a complete history, physical examination, and neurologic examination should be performed; a lumbar puncture should be performed if a CNS infection is suspected; and blood chemistries, x-rays, and CT scanning, while occasionally useful for diagnosis, were rarely useful in predicting prognosis. Perhaps the most controversial finding was that the EEG, even an abnormal EEG, did not reliably predict the development of epilepsy. Its performance was left to the discretion of the physician, but its prognostic usefulness was questioned.

The panel concluded that in view of the benign nature and outcome of most febrile seizures there was no need for medication. They further concluded that anticonvulsant prophylaxis *may be considered*: (1) in the presence of an abnormal neu-

Febrile Seizures: Long-Term Management of Children with Fever-Associated Seizures

Pediatrics in Review 1981;2;209
DOI: 10.1542/pir.2-7-209