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Handbook on EPILEPSY for Physicians



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Foreword
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JAYPEE

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2

Febrile Seizures

Subhas GT, Priyamvada Tatachar

INTRODUCTION

Febrile seizure is a seizure disorder exclusively occurring in childhood.

Febrile seizures are the most common type of seizures affecting 2–14% of children.

Although research supports most febrile seizures as being relatively benign, it is now accepted that a subgroup of children will experience consequences.

DEFINITION OF FEBRILE SEIZURES

A febrile seizure is defined as a seizure which is associated with fever and occurring in infants and children in the age group of 3 months to 5 years. There should not be any evidence of acute intracranial infection, defined cause, metabolic disturbance, or previous afebrile seizure. But the age group of onset may be advanced to 1 month of age (1 month to 5 years).[1]

The definition must be interpreted with caution as at times, especially in infants, seizures may occur even before the fever becomes obvious.

EPIDEMIOLOGY: BURDEN OF PROBLEMS

Although febrile seizure is seen in all ethnic groups, it is more frequently seen in the Asian population (5–10% of Indian children and 6–9% of Japanese children), with an incidence as high as 14% in Guam. The male-to-female ratio is approximately 1.6–1.8. Febrile seizures are more frequent among lower socioeconomic status and show a seasonal predilection to winter months.

ETIOLOGY: PREDISPOSING FACTORS—AGE

Febrile seizures are an age-dependent phenomenon, likely related to a vulnerability of the developing nervous system to the effects of fever in combination with an underlying genetic susceptibility. During the process of maturation there is an enhanced neuronal excitability that predisposes the child to febrile seizures.

FEVER—INFECTIONS

Seizures are usually precipitated when body temperature rises above 38°C rectally and usually occurs during the first 24 hours of febrile illness. But in some cases seizures occur before onset of fever. Extracranial infections like upper respiratory infection (URI), otitis media, gastroenteritis, pneumonia, urinary tract infection, viral infections commonly predispose infants and children to fever with higher temperatures and thereby to febrile seizures.

It is hypothesized that the presence of brain hyperexcitability with reduced seizure threshold and genetic predisposition is a cause for febrile seizure in infants and children.

IMMUNIZATION

Occasionally, febrile seizures may occur after administration of certain vaccines. The highest risk of febrile seizure is within 24 hours of receiving diphtheria, tetanus, and pertussis and 1–2 weeks of receiving mumps, measles, and rubella vaccines. The febrile seizures are the result of the fever, which follows vaccinations and not the vaccination itself. Newer acellular diphtheria/tetanus/pertussis is less reactogenic and there is a marked reduction in febrile seizures after vaccination. Genetic predisposition is also considered as the risk factor for genesis of febrile seizure in these children.

GENETICS

Genetic factors in association with environmental factors play an important role in occurrence of febrile seizures in many families. Polygenic inheritance with autosomal dominant presentation is seen in some families.

Mutations have been identified in sodium channel and in gamma-aminobutyric acid (GABA) receptor genes.

The probability of febrile seizures for a child is about 20% with an affected sibling with febrile seizure and it is more than 30% with affected parents and a sibling. The concordance rate is about 35–69% in monozygotic twins and 14–20% in dizygotic twins.

Generalized epilepsy with febrile seizures plus (GEFS+) syndrome, a familial epilepsy syndrome with variety of causative mutation, and Dravet syndrome [severe myoclonic epilepsy of infancy (SMEI)] though rare have a well-known preponderance for seizures with fever in early childhood and need to be considered in the differential diagnosis.

OTHER ASSOCIATED FACTORS

Premature birth, prenatal exposure to nicotine, and nutritional deficiencies especially iron, zinc, vitamin B12, folic acid, selenium, calcium, and manganese have been linked to development of febrile seizure.

Intrauterine growth retardation, neonatal intensive care unit stay >28 days, neurodevelopmental delay, and daycare attendance (due to predisposition to cross-infection) are considered as precipitating causes for febrile seizures.

CLINICAL FEATURES

Seizures occur early in the course of fever (<24 hours) and usually it is the first indicator of an underlying febrile illness. A febrile seizure occurs in significant proportion of occasions when the temperature is >38°C. Developing febrile seizures is dependent on the child's underlying seizure threshold and also genetic propensity.

CLASSIFICATIONS

Depending on the duration, repetition in the same febrile illness, and type (focal/generalized), febrile seizures are customarily classified as simple, complex, and febrile status epilepticus (FSE).

Simple febrile seizures are of short duration (10–15 minutes) mostly, but are not always generalized convulsions and do not repeat during the same febrile illness (24–48 hours). There is usually a brief postictal period and the child returns to normal without sequelae after the seizure. Simple febrile seizures constitute about 80% of febrile seizures. Children with simple febrile seizures have normal development.

Complex febrile seizures are febrile seizures with prolonged duration (most of the time) with focal features at the onset, recurring within 24 hours or within the same febrile illness (24–48 hours).

Transient hemiparesis following a febrile illness (Todd's paresis) may occur but is relatively rare. Children with complex febrile seizure are often younger (usually less than 1 year of age) and more likely to have abnormal development.[2]

There are a few criterias to differentiate simple and complex febrile seizures (Table 1).

Table 1: Differences between simple and complex febrile seizures.

Simple febrile seizures	*Complex febrile seizures*
• Constitutes 80–85%	• Constitutes 15–20%
• Generalized tonic-clonic motor activity	• Focal seizures manifestation
• Seizure activity lasts <15 minutes with rapid return of consciousness	• Recurs more than once within 24 hours
• No postictal neurological abnormalities	• Postictal neurological abnormalities may be present
• Child having normal neurological and developmental status.	• Likely to have abnormal neurological status.

Febrile status epilepticus (FSE) is a continuous seizure or an intermittent seizure without neurological recovery lasting for 30 minutes or more, majority generalized tonic-clonic. Most seizures terminate spontaneously and the end is evidenced by a deep breath and closed eyes. Children with persistently open and deviated eyes might still be seizing despite cessation of convulsive activity. If the seizures fail to stop within 5 minutes, it is considered as prolonged seizure and if it continues in spite of acute therapy, it is also considered as FSE. FSE is rare but form significant proportion of the status epilepticus in children.

DIAGNOSTIC EVALUATION

A detailed history about the description of the seizures from the eyewitness and search for the cause of fever constitute the mainstay in the clinical evaluation of children with febrile seizures.

Clinical history includes questioning about:

- Seizure characteristics
- Duration of seizure
- Focality
- Personal or family history of seizure
- Immunization status and developmental status of the child.

A formal, general, and detailed neurological examination is done to identify the cause of fever and to detect the neurological abnormalities.

Neurological examination includes assessment of consciousness, muscle tone and power, deep tendon reflex, signs of meningeal irritation like neck stiffness, Kernig's signs, Brudzinski signs to rule out central nervous system (CNS) infection (meningitis, encephalitis), and check for impending sign of raised intracranial pressure like examination of fontanel (tense) and optic fundus (papilledema). Frequently meningitis initially presents with fever and seizure; however, in infants, these signs may not be present. Signs of head injury and markers of epilepsy (neurocutaneous markers) must be looked for. It is mandatory to evaluate neurological status serially.

DIFFERENTIAL DIAGNOSIS

This includes chills (shivering), febrile delirium, breath-holding spells, CNS infections (meningitis, encephalitis), febrile myoclonus, GEFS+ syndrome, Dravet syndrome (SMEI), and febrile infection-related epilepsy syndrome (FIRES).

Generalized epilepsy with febrile seizures plus is a familial epilepsy syndrome (SCNAIA, SCN2A, SCN1B, and GARBG2). It is an autosomal disorder with at least six phenotypes delineated by their causative genes. Initially seizures appear with fever but subsequently frequent febrile and afebrile

seizures develop, which could be myoclonic, atonic, absence, or generalized tonic-clonic seizure (GTCS). Seizures with fever in GEFS+ continue beyond the age of 6 years.

Dravet syndrome is an autosomal dominant disorder due to de novo mutation. To start with, this epileptic syndrome of the infancy presents with prolonged febrile seizures, which may be unilateral. Subsequently, multiple prolonged afebrile seizures appear, which may be GTCS, myoclonic, partial, and are associated with psychomotor retardation. It is rare and described as SMEI.

A FIRES is a febrile infection-related epilepsy syndrome. A clinical entity present with status epilepticus following an infective event may be mistaken for FSE.

It is difficult to distinguish the first episode of the febrile seizure from a seizure resulting from epilepsy, GEFS+, SMEI, and FIRES in a child with fever. The diagnosis can only be made with evaluation of clinical symptomatology and laboratory investigations.

Investigative workup depends directly on the provisional diagnosis of febrile seizures. Basic workup is necessary to find out the causes of fever during the first simple febrile seizure, other investigations like metabolic workup, urine analysis (in case fever is obscure) are done. Depending upon the results of the clinical examination, lumbar puncture (LP) is mandatory in infants with first febrile seizure, when CNS infection is suspected or in those who are on prior antibiotic therapy and in FSE. LP should be considered in complex febrile seizures if neuroinfection is suspected. LP is not required in majority of the children with first simple febrile seizures.[3]

Electroencephalogram (EEG) is not useful in simple febrile seizures. It is rarely considered in complex febrile seizures when epilepsy is suspected.

Neuroimaging studies are not required in simple febrile seizures. Magnetic resonance imaging (MRI) (less preferably CT scan) should be considered in patients with signs of increase in intracranial pressure, with focal neurological abnormalities, suspected structural defects in the brain, abnormally large head, and in severe head injuries.

Genetic testing is not indicated in preliminary evaluation of febrile seizures. It should, however, be considered in patients where a genetic syndrome like Dravet syndrome is being considered on the basis of multiple prolonged febrile seizures.

TREATMENT OF FEBRILE SEIZURES IN ITS ACUTE PHASE

The majority of the febrile seizures end spontaneously by the time the child is first evaluated and the child usually returns quickly to normal baselines. In such cases, active treatment with benzodiazepines is not necessary. Fever should be treated symptomatically and causes of fever should be investigated.

There is no need for hospitalization. As with afebrile seizure, treatment should be started if the duration of seizures last for more than 5 minutes. Majority of the prolonged seizures are terminated by intravenous administration of lorazepam 0.1 mg/kg body weight at the rate of 2 mg/min or diazepam 0.2 mg/kg body weight at the rate of 1 mg/min to a maximum dose of 5 mg.

Close watch on breathing, arterial pulse and blood pressure should be monitored. If the seizure fails to stop, drugs may be repeated twice at 5 minutes interval.

If the intravenous route is inaccessible or unavailable in acute therapy, rectal administration of the diazepam (rectal preparation) in a single dose of 0.5 mg/kg body weight with option to repeat after 10 minutes or intranasal midazolam 0.2 mg/kg body weight (two puffs to each nostril) or 0.5 mg/kg body weight of midazolam is buccally recommended, and also in situations when the seizures are prolonged and no immediate medical care is available. These rescue medicines can be administered by parents at home and is safe and effective.

If immediate treatment of acute phase fails, the patient should be hospitalized and antiepileptic drugs (AEDs) should be administered. The line of management is the same as for afebrile status epilepticus and intravenous phenytoin/fosphenytoin, phenobarbitone, valproate, levetiracetam, and lacosamide are the preferred AEDs.

Hospital admission is considered when febrile seizures are prolonged and not terminated with acute therapy, when the seizures are focal, if there is delayed recovery to normal baseline status or when residual neurological defects are detected, and in all FSE. Hospitalization is also required to those suspected to have serious infections or other comorbidities.

RECURRENCE RISK

After the first febrile seizure, about one-third of the children in their early childhood will experience one or more recurrences but is relatively rare after 3 years of age.

The predictors for recurrences are:

- Age of onset in infancy or early childhood (<12–18 months)
- Low-grade fever during first febrile seizure
- Brief interval between seizure presentation and fever onset
- First febrile seizure presenting with features of complex febrile seizures
- Family history of febrile seizure (parent/siblings).

If none of the above predictive factors represent, the risk of recurrence of fever seizure is <15%.

In the presence of all the risk factors, the chances of recurrence febrile seizure may reach 80%. In spite of recurrence, simple febrile seizures are

benign and will not have any effect on the growth and development in the affected children.[4]

PROPHYLAXIS

There are two types of prophylactic treatments:
1. Intermittent therapy
2. Continuous therapy.

Indications for Intermittent Therapy

Use of AEDs as prophylactic treatment is not justifiable when the natural history of febrile seizure is considered vis-à-vis when compared with risk following the use of AEDs.

But in a country like India where medical facilities in remote areas are not adequate or inaccessible, prophylactic treatment may have a role to play in children with prolonged febrile seizure or with a past history of complex febrile seizures.

In such situations, oral benzodiazepine (normally diazepam) is administered orally during febrile episode for 48 hours (0.33 mg/kg body weight, 8th hourly) and also may be given rectally (0.5 mg/kg body weight, 8th hourly). Other drugs commonly advised are oral preparation of clobazam during the first 48 hours of febrile episode (1 mg/kg body weight in two doses).

Indications for Continuous Therapy

Application of continuous AED treatment is not justifiable. Recurrences of febrile seizures are reduced with continuous therapy but are generally not considered worth the potential adverse effects of treatment.

The incidence of morbidity and mortality including FSE is rare without AED and has no impact on risk of latter epilepsy.

However, continuous AED therapy is rarely considered in patients with failed intermittent therapy or compulsion from anxious parents even after adequate counseling. If continuous AED is to be used, oral phenobarbitone is advocated (4 mg/kg body weight per day in two divided doses) and valproic acid is used very rarely. However, the risk and adverse effect of AEDs in personality development and behavioral disturbance with phenobarbitone and hepatotoxicity (hyperammonemia) of valproate outweigh the benefits. Unless barring compelling reasons, generally there is no role for prophylactic intermittent or continuous AED treatment in the management of febrile seizures.

Antipyretic drugs have no role in reducing the risk of febrile seizures or its recurrence. However, it may minimize the discomfort of the child during febrile episode. Oral paracetamol is the preferred antipyretic drug (20 mg/kg

body weight in three doses) or ibuprofen (5 mg/kg body weight per dose) till the fever subsides (aspirin and nimesulide should be avoided). Tepid sponging to reduce the fever gives more discomfort to the child and is not recommended. An oral benzodiazepine and an oral antipyretic should be started at the onset of fever and have to be administered in every febrile episode till the child is 5 years of age.

PROGNOSIS

Neurologic sequel including new neurological defects, intellectual impairment, and behavioral abnormalities are rare following febrile seizures.

The risk of epilepsy in simple febrile seizure (about 2.5%) is marginally higher than in normal children.

The chances of development of epilepsy in febrile seizure under special circumstances like complex febrile seizure, FSE, with prior abnormal neurologic status or developmental impairment, family history of complex febrile seizure, or afebrile epilepsy are definitely more (>4%).

Febrile seizures do not appear to cause temporal lobe epilepsy. The association may represent an inherent susceptibility in some children who are predisposed to prolonged febrile seizures and epilepsy simultaneously.

Febrile status epilepticus is a rare event in febrile seizure, but forms a significant proportion of overall status epilepticus in children. FSE may present as first febrile seizure episodes or is more frequent in complex febrile seizures. Management of febrile status epilepsy with AEDs is in the same line as in the management of afebrile status epilepticus in children. Response to therapy is favorable. Subsequent development of epilepsy and mortality is rare.

To consider the abnormalities noticed in EEG and acute hippocampal injuries seen in MR imaging, postictally in FSE as the biomarker for future epilepsy is still to be confirmed.

PARENTAL COUNSELING

It is necessary to provide all the information about the natural history of febrile seizures to the parents soon after the first episode. Benign nature of the illness should be explained and parents should be properly counseled.

The importance of taking preventive measures to protect the child from contracting frequent infections should be highlighted.

At times, prolonged febrile seizures or multiple complex seizures may occur in short intervals and immediate medical aid may not be available. To face such situations, parents should be taught about administration of rescue medicines at home properly. They should be told to store thermometer, AEDs like diazepam (preferably rectal preparations), midazolam (nasal or

buccal preparations), and antipyretic drugs (paracetamol oral) at home or while traveling.

They should also be sensitized about cardiopulmonary resuscitative procedures as first aid treatment and holding the child in semi-prone position to avoid aspiration during seizure episode.

The routine information about Do's and Don'ts during the seizure episode should be made available. Parents' doubts regarding subsequent neurological sequelae including appearance of new neurological deficits, intellectual impairment, and behavioral disorders following febrile seizures should be cleared.[5]

SUMMARY

Febrile seizures exclusively occur in infants and early childhood and are the most common seizure disorder in that age group.

Febrile seizures are genetically predetermined, age-dependent response to fever and are self-limited, prognosis is excellent, and risk of recurrence occurs in small proportion.

Risk of brain damage is extremely rare and simple febrile seizures do not adversely affect neurological status or mortality.

Severe recurrent attacks occur in less than 10% of febrile seizures and fewer than 5% develop epilepsy. Risk factors are identified to predict the recurrence after first febrile seizure and subsequent epilepsy. Application of diagnostic procedures depends upon the clinical assessment.

Treatment is initiated on selective basis. If a febrile seizure lasts for more than 5 minutes, it must be treated as a medical emergency.

Prophylactic therapy reduces recurrence and allays parental anxiety but does not prevent epilepsy. Parental counseling forms an important part of management of febrile seizures.

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Handbook on Epilepsy for Physicians

Epilepsy is not only a common neurological disease but one which can be eminently treated with high rate of success mostly by antiepileptic drugs and partly through neurosurgery. There is, however, an unequal ratio between the number of people with epilepsy (PWE) in India and the availability of neurologists, particularly in the rural areas. On the other hand, drug treatment and social management of PWE can be very well done by the primary care physicians, taking the help of specialists only for a few of the complicated cases.

Handbook on Epilepsy for Physicians is compiled to give up-to-date information on the management of PWE by experienced Neurologists/Epileptologists and specialists of other disciplines from the Indian Epilepsy Association Bangalore Chapter. The Authors have taken much trouble to give practical guidance in various aspects of epilepsy treatment and social management, so that majority of PWE can be very well-managed at the level of general physicians.

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