

FEBRILE SEIZURES

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The "febrile seizures" refer to a clinical syndrome of the susceptibility of the young children to experience seizures during a febrile illness. In ancient times, Hippocrates did observe the relationship and susceptibility of some children under the age of 7 years to convulse with fever. Although, the febrile seizures have been described since antiquity, debate continues over their definition and their relationship to epilepsy. Some authors believe, they are a form of epilepsy(1,2), while others think that they represent an entity which is distinct from the other forms of epilepsy(3). These controversies are the outcome of the disagreement of the definition of febrile seizures used among the various workers.

The National Institute of Health Consensus Development Conference on Febrile Seizures (1980) defined febrile seizures as 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 non-febrile seizure are excluded. Febrile seizures are often classified as simple or complex, the latter being characterised by the duration of convulsion more than 15 minutes, focal nature or occurrence of more than a single seizure during 24 hours period(4).

Some use the term of febrile status epilepticus, if seizure continues for more than 30 minutes during which there is no return to consciousness.

Incidence

About 2.0-5.0% of all children experience febrile seizures before the age of 5 years(5-7). Its incidence is 3.5% among white children and 4.2% in black children(8). Tsuboi(9) found a higher prevalence (8.3%) in children in Japan. A higher prevalence of febrile seizures among Asians is perhaps attributed to the Asian culture where parents and children more often sleep in the same room than in the western world, which increases the chance of seizure to be discovered(7).

Febrile seizures occur more frequently in males than females; however, complex febrile seizures, febrile status epilepticus and their sequelae are more frequent among females. The male female ratio of febrile seizures ranges from 1.4 : 1 to 4 : 1(7,10). The more rapid rate of cerebral maturation and myelination in females may be the cause of the rapid decline in

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incidence of febrile seizures in girls after the age of 2 years(10,11).

Age

The majority of febrile seizures occur by the age of 3 years and it is unusual for the first febrile seizure to occur after that age. One to two per cent of the febrile seizures occur in patients under 6 months of age and 1-6% in children over 5 years of age(12,13). The most common age of onset is between 1 and 2 years. Fifty five per cent of the children had their first febrile convulsion during the second year of age, while 20% during the first year, 14% during 3rd year, 9% in fourth year, and 2% in the fifth year of life(7). In boys, the rate of occurrence declines gradually during the first 4 years while among girls there is a marked drop in frequency after 2 years of age(10,11).

Genetics

An increased frequency of febrile seizures has been found among parents and siblings of children with febrile seizures. About 9 to 17% of siblings also experience febrile seizures(5). Siblings of children with epilepsy are also at increased risk for febrile seizures(10-40%). However, the prevalence of epilepsy in relatives of probands with febrile seizures is not clear, some studies have shown an increase in the frequency of non-febrile seizures(12,15), while others have not(13,16). The exact pattern of heredity is not clear. Autosomal dominant inheritance appears to be the most common pattern(13) but there is possibility of recessive trait(17) or polygenic inheritance(18).

Clinical Features

Some data suggest that children with

previous neurologic impairment are more vulnerable to complex febrile seizures, febrile status epilepticus and any seizure associated with fever(19) but the same relationship is not found in simple febrile seizures(4).

The usual child is of good health and normal development, the seizure occurs while the child has a recognizable infection. Most febrile seizures are associated with tonsillitis, otitis media, gastroenteritis of viral origin. Some illness like shigella gastroenteritis and roseola infantum have been associated with an usually high incidence of febrile seizures(20,21).

Fever of extracranial source is always present and is usually above 39°C rectally. The duration of fever prior to the seizure is almost always less than 24 hours, and most seizures occur in the first few hours after the fever has begun. The relative importance of the height of the temperature elevation as compared with its rise remains unclear(10). Many times, the parents will be unaware of the presence of fever until the child begins to convulse.

Most of the febrile seizures are generalised, about 15% are focal. Incidence of focal seizures is high in series which have included children with intracranial abnormalities. Approximately 80% of seizures are clonic, 14% tonic and 6% are atonic(10).

The duration of seizures is usually brief, lasting less than 10-15 minutes. Forty per cent last less than 5 minutes and 75% less than 30 minutes. Most episodes of febrile status epilepticus occur in children of less than 18 months of age and are more common in girls.

Pathophysiology

The exact mechanism that leads to

febrile seizures remain unknown, and equally unknown is the fact why some children are susceptible to the effects of fever, while others are not. There are various studies linking the febrile seizures to circulating toxins, immune reactions, viral and bacterial toxins, relative lack of myelination, increased oxygen consumption(22). Some believe that the occurrence of febrile seizures is linked with the rapid rise in body temperature(23), while others relate it to height of fever(24) or both of these(25). The immaturity of the thermoregulatory mechanism had been held an important factor for the occurrence of febrile seizures(26).

Decreased CSF levels of gammaaminobutyric acid have been reported in patients with febrile seizures, but the exact significance of this is unknown(27). All the reports to date are inconclusive as to whether abnormalities of neurotransmitters are of importance in the causation of febrile seizures(22).

Evaluation of Febrile Seizure

Most children with febrile seizure are seen by a physician after the seizure has already ended. If the child is still convulsing when seen, immediate treatment is required, like any other seizure, *i.e.*, support of vital functions, clinical and laboratory assessment, lowering of fever and intravenous anticonvulsants. After the seizure has ended or stopped, an assessment of the cause of seizure must be undertaken. A few workers(10) advocate routine extensive laboratory tests like blood sugar, urea nitrogen, calcium, electrolytes, blood count, urinalysis, cultures of blood, urine, nasopharynx and CSF, skull and chest X-rays and electroencephalogram. Most of these tests, inclusive of CT scan are not needed in all children with febrile seizures

(depending on the clinical circumstances), exception being the spinal tap. Since the classic signs of meningitis are often absent in children in this age group, a spinal tap is recommended.

Electroencephalography

Electroencephalogram contributes little in the investigation of first febrile seizure. About one third of the patients may have marked delta activity, most prominent posteriorly and may be asymmetrical(28). These changes had a linear correlation with the severity and focal nature of the seizure and tended to resolve within one week(28,29). These EEG findings do not predict the future outcome of febrile seizures, although a small percentage of them do develop spike focus subsequently in the same region of slow activity. This spike wave focus also has no prognostic value as to the occurrence of future epilepsy: however, it has a correlation in the development of benign epilepsy of childhood. On the contrary, EEG has a prognostic significance in the evaluation of first unprovoked idiopathic non-febrile seizure with recurrence upto 52 and 23% with abnormal and normal EEG, respectively(30). Specific epileptiform activity in the first EEG after a febrile seizure is unusual, 1 to 3% (8,31,32). However, in serial EEG studies(28) over long period, up to 29% of the children with febrile seizures develop epileptiform activity; generalised spike wave complexes (13.8%), sharp wave focus (8.7%), and photoparoxysmal response (5.5%).

Treatment

I. Acute Treatment

(a) *Antipyretic Therapy*: Reduction of fever with antipyretic drugs and or physical

cooling of the child (sponging) is of prime importance. Both paracetamol (acetaminophen) and aspirin (10-20 mg/kg/dose), effectively lower the temperature by about 1°C or more within ½ to 1 hour. Medication may be repeated every 4 hours if temperature remains high over 38°C. Physical cooling combined with antipyretic drug is more effective than alone. Both, paracetamol and aspirin are equally effective but paracetamol is preferred over aspirin because of the latter's association with Reye's syndrome.

(b) *Treatment of Seizure*: The child should be placed in semiprone position to minimize the risk of aspiration, airway cleared and maintained, intravenous line started and intravenous medication is indicated. Phenobarbital in a loading dose of 10-15 mg/kg body weight or diazepam 0.3 mg/kg body weight is given intravenously. Both drugs are effective in stopping the seizure. Phenobarbital has the added advantage of use for maintenance therapy, while diazepam has a brief duration of action and so recurrence of seizure may occur. Both of these drugs should not be given together because respiratory arrest may occur.

Although, intravenous antiepileptic medication is preferred, rectal diazepam is an alternative and may be termed "non professional intravenous line". Rectal diazepam (ordinary intravenous diazepam) is administered with an ordinary syringe fitted with a 4 to 5 cm long plastic tube. The drug is administered with the child lying on the side or prone and to avoid discharge of the drug, the child's buttocks should be squeezed together for 3 to 5 minutes after administration. After rectal diazepam, the anticonvulsant plasma concentration of diazepam are attained in 2 to 4 minutes. Diazepam suppositories are not attained in 2 to 4 minutes. Diazepam suppositories are not indicated during seizure, as effective

plasma concentration is not achieved until 15 to 20 minutes after administration.

II. Prophylactic Antiepileptic Drug Therapy

(a) *Intermittent Prophylaxis (at times of fever)*: There are controversies whether or not to treat febrile seizures with anticonvulsant therapy. Those who advocate anticonvulsant therapy argue that doing so will prevent neurological sequelae resulting from recurrent seizures and parental anxiety has also been stated as one of the reasons. Rapid shifts in the treatment pattern have occurred through the years. Campfield *et al.* (33) reported that the use of antipyretic measures alone, did not, appear to reduce the recurrence of febrile seizures. Intermittent oral phenobarbitone therapy is disappointing in the management of febrile seizures (34,36,37), however, use of the intermittent rectal diazepam is encouraging (38,39). Unfortunately, no drug used intermittently can prevent seizures in those where seizures occur prior to the time child is noted to be febrile.

(b) *Continuous Prophylaxis*: Long term use of phenobarbitone decreases significantly the recurrence of febrile seizures (40-43) but not the risk of epilepsy. In prospective studies with chronically administered phenobarbitone, with phenobarbital level about 15 µg/ml, the recurrence rate of febrile seizure was reduced to below 10%, when compared with 19-34%, in controls. Potential problems with long-term use of anticonvulsant drug must be considered before deciding that long-term treatment is indicated. Side effects are seen up to 40% in children receiving phenobarbital and include hyperactivity, irritability, sleep distur-

bances. These effects occur irrespective of the underlying neurologic abnormalities, and are seen within the therapeutic levels of the drug. In several series, the phenobarbital was discontinued in upto 20% of children because of the above said effects(38). Poor parental compliance is relatively common, especially where the patient is otherwise normal between seizures. The concern regarding the effect of long-term use of phenobarbital on cognitive functions in febrile children as in epileptic subjects, appears to be unfounded(33,40). Other anticonvulsant drugs found to be effective in preventing recurrent febrile seizures are primidone and valproic acid. Primidone appears to be as effective as phenobarbital(41). Valproic acid is also equally effective as phenobarbital in preventing recurrent febrile seizures(41,43). Gastrointestinal upset, toxic hepatitis, pancreatitis have been reported with valproic acid, while behavioral effects are rare. Phenytoin(42,44) and carbamazepine(45) are ineffective in the management of febrile seizures.

Although effective anticonvulsant drugs are available, consensus is not to treat all cases of febrile seizures. This is based on the fact that long-term prognosis for febrile seizures is excellent and that subgroups of children at high risk for future epilepsy can be identified. Continuous prophylaxis is indicated for patients with abnormal neurological development: complex and atypical seizures, and history of non-febrile seizures in a parent or sibling. Some would like to treat the cases who had a number of recurrences. Daily therapy, if started, is continued for 2 years or 1 year after the last seizure, whichever is longer period.

III. Education of Parents

Most parents are deeply distressed

when faced with their seizing child and fear impending death or neurological sequelae. Therefore, the communication of proper information to the parents is a crucial part of the treatment. Information to the parents should consist of a brief description of febrile seizures, the favorable prognosis, precautions to be taken at the appearance of fever and seizures, and discussion of the treatment to be given. Parents may practice under supervision, administering the rectal diazepam with a demonstration set containing isotonic saline. Doses of antipyretics and anticonvulsants should be discussed. Failure to do so is bound to result in low compliance and treatment failure.

Prognosis

Following febrile seizure, there is concern regarding development of recurrent febrile seizures, epilepsy, mental impairment, learning and behavior disabilities and mortality.

(a) Recurrent Febrile Seizures

Repeat febrile seizures are common, occurring in 12 to 54% of patients(7,8,10,12,37). The risk of recurrence varies with age of the child at the time of the initial seizure: younger the child, the higher the risk. Without treatment, febrile seizures recur in upto 50% of children, whose first seizure occurred before 1 year of age and in 25%, if first seizure occurred after one year of age. Eighty eight per cent of recurrences occurred within 24 months of the first seizure(8). The recurrence risk of non-febrile seizure (idiopathic, untreated and following first unprovoked seizure) is 24, 33 and 36% at 1, 2 and 3 years, respectively, following the seizure(30). Girls are more likely to have recurrence(21). Only 1.4% of patients with febrile seizures

experience prolonged seizure recurrence, if the initial seizure lasted 15 minutes or less. Seventy five per cent of complex seizures occur as the first seizure of the child's life, and only 8% have a subsequent complex seizure after an initial uncomplicated febrile seizure. The risk for complex seizure remains same for the first as for each subsequent febrile seizure(47). There is no difference in the recurrence rate between previously normal children and those with pre, peri and postnatal abnormalities(34). Knudsen(35) reported 5 risk factors for recurrence of febrile seizures; age upto 15 months, febrile seizures in parents or siblings, epilepsy in parents or siblings, first complex febrile seizure and many episodes of fever. The 18 months recurrence was 80-100% in the presence of 3 to 5 factors, 50% with 2 factors, 25% with 1 factor and 12% if there was no risk factor.

(b) Future Epilepsy

The risk of the occurrence of epilepsy following febrile seizure, irrespective of recurrence is 1.4 to 5%(8,46). This risk is two to three fold higher than that of general population(16,47). The recurrence of febrile seizure does not in itself greatly change the risk of epilepsy(33). After simple febrile seizure the risk for epilepsy is 0.9%(47) to 2.4%(16) while after complex febrile seizures it is 4 to 11%. The period of greater risk for the development of epilepsy following febrile seizures is the first 3 years but the risk continues until the 3rd decade of life(16). The risk factors associated with the development of future epilepsy are: family history of febrile seizures, preexisting neurologic abnormality, complicated initial seizure in 24 hours or seizure longer than 15 minutes in duration. Among the children with one risk factor,

2% developed epilepsy, and among those with two or more of these risk factors, 10% developed epilepsy(44). In neurologically normal children with complex febrile seizures the risk of epilepsy is between 1 to 3% (almost same as for simple febrile seizure), compared with 10 to 15% in neurologically abnormal children. On the other hand, young age at onset, the sex of the child and the total number of febrile seizures do not predict for future epilepsy but do predict the recurrence risk of febrile seizures(16,47).

(c) Complex Partial Seizure

Various reports in the past believed febrile seizure as a predisposing factor in the development of mesial temporal sclerosis and thus complex partial seizures. These retrospective data were based primarily on children with febrile status epilepticus including children whose source of fever was acute neurologic illness. Currently, there is no evidence that febrile seizures carry such risk for complex partial seizure and recent epidemiologic studies strongly indicate that they do not occur(28,47,48).

(d) Intelligence

The relationship of febrile seizures (not associated with neurologic illness) to subsequent intellectual and academic performance, has not demonstrated any difference in mean full scale IQ scores (on Wechsler Intelligence Scales for children) between children with febrile seizures and siblings who were seizure free(49). The status of the child before the first febrile seizure was found to be significantly related to later IQ, but the recurrence, type and duration of the febrile seizure were not.

Behavior and social adjustment of children with febrile seizures has not been found to be different from those who had no seizure(50).

(e) *Neurologic Abnormalities*

The prospective studies have not demonstrated any long term neurologic dysfunction in association with febrile seizures(47).

(f) *Mortality*

In the absence of pre-existing neurologic disturbances, there does not appear to be any significant mortality associated with febrile seizures.

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