NEUROLOGY

FEBRILE FITS

Kumaresan G

Abstract: *Febrile fits is a common condition seen in day to day practice. The diagnosis is mainly clinical and there is limited indications for investigations. EEG often adds to confusion and is best avoided. The role of genetics is being recognised. Intracranial infections, febrile myoclonus, epileptic syndromes presenting initially as febrile seizures are to be considered in the differential diagnosis. Long term anti-convulsants should be avoided except in rare situations. Intermittent prophylaxis with clobazam is useful in reducing recurrences and parental anxiety.*

Keywords: *Febrile fits, Prognosis, Genetics, Differential diagnosis, Intermittent clobazam.*

Febrile fits is known from the days of Hippocrates. Convulsions occur in children with acute fever and most readily in those who are very young up to their seventh year. Despite the recent advances in genetics and neuroimaging, many questions remain unanswered. The prevalence is reported to be around 3-4% with a higher prevalence in some countries like Japan (7%) and Guam (14%).[1]

There have been differences between pediatricians and neurologists regarding long term prognosis. This is because of varied results based on epidemiological studies and retrospective studies. The most quoted epidemiological study is by Nelson and Ellenberg who followed up 1706 children with febrile fits up to 7 years of age and noted it to be a benign condition.[2] Similar results were noted by many others like Verity (1985) Vandenberg (1969).[3,4] The estimated risk of subsequent epilepsy as per these studies was around 1 in 75,000 children. However, the retrospective studies from neurosurgical centres have the power to detect rare events but not their frequency. It was noted that more than one third cases of intractable temporal lobe seizures undergoing surgery had history of febrile fits in childhood and is termed 'Meyer' hypothesis. This hypothesis suggests that prolonged febrile seizures leads to ischemia which in turn leads on to hippocampal sclerosis many years later.[5]

The advent of MRI has added more information. Fernandez followed up 23 members with family history of febrile fits with MRI. The interesting observation was hippocampal abnormalities were seen in 6 out of 10 children who never experienced febrile fits as compared to 6 out of 13 children with history of febrile fits.[6] Van Landingham study showed 2 out of 6 positive cases in children with complex febrile seizures had pre-existing abnormalities in hippocampus. Four children with prolonged seizures showed acute edema in hippocampus.[7] These studies established two points (i) pre-existing lesions in hippocampus may contribute both to febrile fits and subsequent development of epilepsy and (ii) prolonged seizures (of any etiology) can cause changes in hippocampus leading to epileptogenic focus years later. This was also observed in Febstat study which showed both acute injury and presence of pre-existing abnormalities twice more than in controls.[8]

Hippocampal sclerosis is seen in an epileptic syndrome called 'familial mesial temporal lobe epilepsy'. But this is also seen in their asymptomatic first degree relatives suggesting that hippocampal sclerosis is not related to seizure severity and may occur in individuals who never had seizures, indicating a genetic predisposition and the seizure severity being dependent on interaction of both genetic and environmental factors. So, the question which still needs to be answered is that if the pre-existing hippocampal sclerosis predisposes to both temporal lobe epilepsy and inconsequential febrile fits or childhood febrile status caused the initial damage leading to hippocampal injury. Thus hippocampal injury can be both the cause or effect of prolonged seizures–febrile status being one of the causes. The pre-existing lesions may act in three different ways - (i) hippocampal malformations may themselves cause both febrile fits and temporal lobe epilepsy, (ii) may increase the vulnerability to damage caused by febrile fits and (iii) may increase the vulnerability to damage by fever. There is no mention of febrile fits in 1969 classification in the International classification of

* Professor of Pediatric Neurology (Retd.), ICH & HC, Madras Medical College Chennai.

email: jayalakshmi_kumaresan@hotmail.com

Epilepsy. In 1981 classification, it is classified under special syndromes-situation related. In 2001 classification, it was 'seizures not necessarily requiring a diagnosis of epilepsy' while in 2014 the word "seizure" is replaced by 'epileptic event'.

Definition

National Institutes of Health (NIH) definition of febrile fits – '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'.[9]

Types of febrile fits

1. **Simple febrile fits:** Brief single generalised seizures.

2. **Complex febrile fits**: Focal, prolonged (>15 minutes) and multiple seizure in a single febrile episode.

This differentiation is important in determining the recurrence rate and future epilepsy.

Status epilepticus and febrile fits

Twenty-five percent of status epilepticus in ER is due to febrile status. Five percent of febrile fits may present as status and may be the initial presentation. FEBSTAT study is an important study involving 299 children presenting with febrile status epilepticus. One-third of children with febrile status showed positive PCR or antibody titres for Human Herpes virus (HHV) 6B or 7.[8]

Genetics and febrile fits[10]

Febrile fits was initially considered to be inherited by dominant mode of inheritance with incomplete penetrance. Advances in genetics has led to recognition of many genes like FEB-1(on8q 13-21), FEB-2(19p13.3), FEB-3 (2q23-24), FEB-4(5q14-15) and R43q mutation (CARBG-2) to name a few, leading to recognition of larger role of genetic susceptibility.

There are a few epileptic syndromes associated with initial presentation as febrile fits.

(i) Generalised epilepsy with febrile seizures (GEFS+): This syndrome may continue beyond 6 years of age as multiple febrile fits and by several subsequent types of afebrile generalised seizures – generalised tonic clonic, absence, myoclonic, atonic or myoclonic astatic seizures with variable degrees of severity.

(ii) Dravet syndrome: This may present as early onset febrile fits before six months of age, prolonged febrile seizures and family history of multiple types of seizures. Development of focal or myoclonic seizures and developmental slowing, stagnation or regression in the second year of life suggests Dravet syndrome. Gene defect has been localised to SCN1A, SCN1B and GARBG-2.

(iii) Familial temporal lobe epilepsy: This may be associated with predisposition to febrile fits and other types of seizure.

Febrile seizures are believed to be caused by vagal mediated cerebral ischemic anoxia. This suggests that febrile fits resemble cerebral anoxic seizures and may occur without obvious epileptic mechanism.

Differential diagnosis

1. Benign febrile myoclonus: Myoclonic jerks with fever. This condition may be dramatic enough to be mistaken for other types of seizures including febrile fits and can lead to unnecessary investigations.[11]

2. Afebrile febrile seizures is a newly described entity. It is a distinct entity not related to febrile seizures. It is a provoked seizure lacking objective evidence of fever at the onset of seizures but have definite symptoms and signs of minor infection.[12]

Investigations

Observation of the child over next few hours is more important than rushing into admission to ICU, CT scan or CSF analysis. The combination of fever and seizures may be due to febrile seizures, intracranial infection, metabolic disturbances or initial presentation of an epileptic syndrome like Dravet syndrome or GEFS+ syndrome.

CSF analysis

American Academy of Pediatrics (AAP) has laid down criteria for CSF analysis in febrile fits. In children below 12-18 months of age, it is strongly recommended. However, this is not uniformly agreed. Pediatrician with experience can avoid CSF analysis without missing intracranial infection. Kimia reported no case of meningitis in 271 children of 6-18 months of age presenting with febrile fits.[13] However, one has to remember that the chances of intracranial infection may be as high as 15-18% in febrile fits presenting as status. Other indications for CSF analysis include prior antibiotic therapy and presence of sepsis elsewhere like skin or ear. Though 5% of children with intracranial infection may present with fever and seizures, prolonged duration of seizures, focal neurological deficit and prolonged duration of unconsciousness will be the red flags.

EEG

Though different patterns are described in the EEG of children presenting with febrile fits, none of these are specific for febrile fits, nor are they useful for prognosis. Often many non-specific changes or normal variants are reported as epileptic activity by the less experienced and may confuse the pediatrician.

Neuro-imaging

This is indicated in status epilepticus, focal seizures and presence of prior neurological abnormality but in many series it has been normal. EEG and neuro-imaging done unnecessarily can add to the cost of treating a child with febrile fits.

Prognosis

The recurrence of febrile fits is roughly one in three children. Two aspects are risk of recurrence and risk for subsequent epilepsy. Risk factors for recurrence of febrile fits are young age of onset, prior neurological abnormality, family h/o febrile fits, family h/o epilepsy, occurrence with low grade fever, short interval between onset of fever and seizure and complex febrile fits. The risk for epilepsy varies between 2-7% depending on the number of features of complex febrile seizures.

Treatment

The risk of side effects of long term anti-convulsants outweighs the benefits of treating a benign self limiting condition. Parents have to be counselled about the benign nature of febrile fits. Each episode may appear to them as life threatening event. They should be taught about first aid measures in handling a convulsing child at home and prehospital management of seizures persisting beyond 5 minutes with rectal diazepam (0.3-0.5 mg/kg to a maximum of 5 mg), intranasal midazolam 0.5 mg nasal spray (0.2-0.3 mg per dose divided into half on each nostril) or sublingual (oral soluble) lorazepam though not commonly used. Prompt reduction of fever will add to the physical comfort though its role in prevention of seizures is questioned.

The next most important point to remember is prolonged seizures of any cause which can lead to brain injury and enhance the subsequent risk of epilepsy. The present practical definition of status epilepticus is any child coming to ER convulsing or seizures lasting more than 10 minutes as against the old definition of status as seizures lasting for more than 30 minutes. Hence the best approach is to established an effective emergency management protocol for every convulsing child.[14] Parents and paramedical should be taught about pre hospital therapy with a benzodiazepine. Unfortunately this facility may not be available always. Routine long term maintenance therapy should be discouraged but may be needed in special circumstances like presentation as status every time, lack of accessibility to emergency medical care or frequent recurrences despite intermittent prophylaxis. The use of routine therapy must be discouraged. Phenobarbitone and sodium valproate have been used for continuous therapy. Phenytoin or carbamazepine are ineffective.

Intermittent therapy

During febrile illness initial intermittent therapy with oral diazepam has been used. Clobazam has less sedative effect. Intermittent use of clobazam (0.7mg/kg/day in three divided doses for 3-4 days) has been found to reduce the frequency of recurrences in many studies.[15] This may not be effective if the interval between onset of seizures and recognition of fever is very short or if seizures occur with low grade fever. Sedation and hyperkinesis may be undesirable effect. However, this mode of therapy is not mentioned in many text books. There is a recent article suggesting the use of intermittent melatonin in febrile seizures.[16]

In my practice, I counsel the parents the first aid and use of intra nasal Midazolam if seizures persist for more than five minutes. For prevention intermittent clobazam is useful. Continous anti convulsants is used only for prolonged febrile fits and repeated reccurences occur despite intermittent prophylaxis.

Points to Remember

- ***Febrile fits is a benign age related, self limiting condition.***
- ***Clinical observation to exclude other conditions is most important than investigations.***
- ***Early therapy to stop on-going seizure is important.***
- ***Hippocampal abnormalities can be both cause and effect of febrile fits in different situations.***
- ***Intermittent therapy is useful to minimise recurrences and parental anxiety.***
- ***Restrict use of continuous anti-epileptic drugs.***

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CLIPPINGS

The continuing 2019-nCoV epidemic threat of novel coronaviruses to global health-The latest 2019 novel coronavirus outbreak in Wuhan, China.

Corona viruses (CoVs) are a group of RNA viruses which have posed a global threat to public health. They have an extensive range of natural host. A new corona virus, 2019-nCoV was identified in Wuhan, China after a cluster of cases with symptoms of "pneumonia of unknown cause" were reported. The virus has shown evidence of human-to- human transmission with escalating transmission rate. Now many cases are being reported worldwide. The incubation period of the virus is between 2 to 14 days which is a contagious period. The symptoms include fever, coughing and breathing difficulties; cases of severe infection can result in renal failure and death. Transmission of the virus occurs among close contacts via respiratory droplets.

The virus (2019 n-CoV) was first isolated from a patient in china on 7 Jan 2020 and genome sequencing of the virus was done and it became available to WHO on 12 Jan 2020, now worldwide specific diagnostic PCR tests for detecting the novel infection is available. Like SARS-CoV and MERS-CoV zoonotic infections, 2019 n-CoV was also related to zoonotic spread which was believed to be related to wild animals at the seafood market in Wuhan.

However there is very limited clinical information about the virus, pathogenesis, age range for infections, any treatment response to the virus and any available vaccines. The rapid identification and containment of the infection is reassuring and is a commendable achievement in the capacity to detect, identify and contain the new outbreak globally.

Hui DS, I Azhar E, Madani TA, Ntoumi F, Kock R, Dar O, et al. The continuing 2019-nCoV epidemic threat of novel coronaviruses to global health-The latest 2019 novel coronavirus outbreak in Wuhan, China. Int J Infect Dis 2020; 91:264-266.