



Review on Febrile Seizures in Children

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Authors' contributions

Author VT designed the article, performed literature survey and wrote the first draft of the manuscript. Authors VT and KD edited the manuscript. All authors read and approved final version of the manuscript.

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Review Article

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ABSTRACT

Background: Febrile seizures are a common, yet benign neurological disorder and characterized by convulsions associated with fever in childhood due to the effect of fever on the immature brain. All treating clinicians must understand the nature and evaluation of this benign condition.

Objective: To provide up-to-date knowledge on febrile seizures and their evaluation.

Methods: A search was conducted with key terms "febrile seizures" or "febrile convulsion" in various databases and writings. The literature included clinical trials, descriptive and observational studies, meta-analyses, and randomized control trials.

Results: Febrile seizures occur between the ages of 6 months to 5 years in all ethnic groups. The exact mechanism has been still unknown although several etiologies have been proposed including genetic and environmental factors. Febrile seizures can be either simple or complex. Febrile seizures generally occur within the first day of fever but rarely happen after 24 hours. Most of the time, febrile convulsions are short-lasting and self-limiting. The diagnosis is mainly based on the clinical description, and investigations have a limited role. Children less than one year of age with suspicion of bacterial infection need lumbar puncture to exclude meningitis. Management mostly depends on control of fever and the treatment of underlying conditions which precipitate fever. Some children can have prolonged convulsions which need anticonvulsants to abort an acute

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attack. Otherwise, long term prophylactic anticonvulsants have an insignificant role in the prevention of recurrences of febrile seizures. Physical methods also play an insignificant role. As the condition commonly carries a favorable prognosis, unnecessary interventions should be avoided. Since febrile seizures recur in a significant proportion of children, they may bring needless fears and anxieties in parents. However, proper health education for parents by health care personnel might alleviate the anxiety and improve the quality of life of children with febrile seizures.

Conclusion: Febrile convulsions are benign and self-limiting. Continuous use of anticonvulsants to prevent the recurrence of febrile seizures is not endorsed. Intermittent prophylaxis at the time of fever is also not routinely recommended. Both physical methods and antipyretics have limited value in the prevention of febrile seizures.

Keywords: Febrile seizure; febrile status epilepticus; phenobarbitone; electroencephalogram.

1. INTRODUCTION

Febrile seizures are also known as febrile fits or febrile convulsions. It is defined as a seizure happening in childhood classically from 6 months to 60 months of age in association with fever which is usually more than 100.4 F (or more than 38 C) [1,2]. The diagnosis of febrile seizure is made after exclusion of central nervous system conditions such as infection, head injury, epilepsy, and metabolic abnormalities such as hypoglycaemia, hypo or hypernatremia, hypocalcaemia, and hypomagnesaemia and other causes such as drug intoxication or withdrawal. Further, there should be no evidence of an afebrile seizure in the past years [3-7]. Although febrile seizures are benign, it is a greater challenge for clinicians as its occurrence seems to be high during early childhood and febrile seizures carry a high probability for recurrence. Referral to a paediatric neurologist might be warranted for patients with complex febrile seizures and background neurological morbidities [4,5]. The Clinician has a dynamic role in educating the parents about the benign nature of this condition and ousting myths and beliefs. The latest recommendations for the assessment and management of febrile seizures were published by the American Academy of Pediatrics (AAP) and the Japanese Society of Child Neurology in 2011 and 2015, respectively [8,9]. This review appraises the up-to-date knowledge and evaluation of febrile seizures.

2. EPIDEMIOLOGY

Febrile convulsions are a common and benign neurologic disorder in childhood occurring between 6 months to 5 years of age. Febrile convulsion seems to occur in all ethnic populations. Although the incidence has been approximately 2-5% in America and Western Europe with a peak between 12 and 18 months

[7,9-11], it is more commonly seen in Asian communities (5-10% of Indian and 6-9% of Japanese) and 14% in Guianese [12,13]. Male children have a slightly high incidence than female [14] and febrile seizures are more common in poor socioeconomic societies which are likely to have poor access to medical care [10].

3. AETIOLOGY AND PATHOGENESIS

The precise primary mechanism underlying febrile seizures is still unknown but thought to be multifactorial. It is believed that febrile convulsions occur due to the susceptibility of either developing or immature brain to the effects of fever in association with environmental and genetic factors [15,16]. A febrile convulsion is an age-related response of the developing brain to a febrile illness. As there is a boosted neuronal impulsiveness to fever during the maturational process of the brain, it lowers the seizure threshold and induces febrile seizures. It is explained by the fact that febrile seizures are more common below the age of 3 years when the seizure threshold is lowest [17]. Further, it has been known that the height of the fever is the utmost significant risk factor than the sudden rise of fever for the development of first febrile convulsion [10,17].

Studies showed that approximately one-third of children have a family history and the chance for febrile convulsion in a child is about 20% and 33% with an affected sibling and affected parents respectively [4,18]. The genetic predisposition to febrile seizures can be mediated either through autosomal dominant inheritance with reduced penetrance or multifactorial/ polygenic factors [4,19-21]. The chances of having febrile seizures in monozygotic and dizygotic twins have been 35-69% and 14-20% respectively. This is explained by greater concordance amongst

monozygotic than dizygotic twins concerning all types of febrile seizures [4,22]. The most commonly involved genes are *SCN1A*, *IL-1 β* , *CHRNA4*, and *GABRG2* (19). There are several genetic loci responsible for increased risk of febrile convulsion and they include 1q31, 2q23-34, 3p24, 3q26, 5q14-15, 5q34, 6q22-24, 8q13-21, 18p11, 19p13, 19q, and 21q22 [4, 19-24]. Although several genes and genetic loci have been reported in different groups, the causative genes have not been identified in most patients with febrile seizures. Recently several associations between febrile convulsion and genetic factors have been suggested, however; the results do not show a convincing or consistent relationships with susceptible genes and further research has been ongoing to find out true association based on large populations [25].

Fever due to viral infections accounts for almost 80% of febrile convulsions [26]. Common causes include upper respiratory infections, roseola infantum, influenza A, human coronavirus HKU [16,21,27], otitis media, pharyngitis, and dysentery due to *Shigella* species [28,29]. There is also a risk of post-vaccination fever and febrile seizures following vaccination with combined diphtheria-tetanus toxoids-whole-cell pertussis vaccine (DPT) [30], but the absolute risk is very small [31].

Besides, prenatal acquaintance to nicotine and alcohol, [32] prematurity, intrauterine growth retardation and postnatal treatment with corticosteroids are associated with high chance of having febrile seizures compared to others with no such risk factors [33,34]. Either perinatal or prenatal exposure to stress may affect on febrile convulsions owing to lowered seizure threshold [34].

Deficiency of iron, zinc, selenium, calcium, magnesium, folic acid, and vitamin B12 are also known to be associated with a higher risk of febrile seizures [35-37]. Other contributory factors for febrile seizures include a history of febrile seizures in the past, seizures in first degree relatives, staying in a neonatal unit for more than 4 weeks, neurodevelopmental delay, and attending daycare nursery [10,38].

4. CLINICAL MANIFESTATION

Febrile seizures usually occur on the first day of fever, and a different diagnosis should be suspected if the seizure occurs after 3 days from the onset of fever [29]. Children with febrile

seizures generally have a fever during seizures [14]. It can be classified as simple (80-85%) and (15-20%) complex [10]. A simple febrile seizure occurs with generalized tonic-clonic movements of the limbs, up rolling of eyeballs, and typically lasts for less than 5 minutes, and not more than 15 minutes and is followed by a minimal period of post-ictal drowsiness and no further attacks occur within 24 hours [4,6,14]. Loss of consciousness is a constant feature at the time of convulsion and frothing, difficulty in breathing, pallor, cyanosis, and incontinence of urine and stools might be associated features of simple febrile seizures [39]. A complex febrile convulsion generally persists for more than 10 minutes, usually focal in nature (movement involved to a side of the body), and might reappear within 24 hours and have a long period of postictal drowsiness. It may be accompanied by transient hemiparesis or Todd's paralysis [4,14,40]. Children can have complex febrile seizures following initial simple febrile convulsion [6]. The most severe type of complex febrile seizure is known as febrile status epilepticus which means that febrile seizure occurs either as continuous or intermittent without recovering consciousness for more than 30 minutes. Patients with febrile status epilepticus have a high chance to develop hippocampal lesions in the future [15].

5. CLINICAL EVALUATION

A detailed history should be extracted to identify whether the convulsion is febrile or afebrile; to find out the degree of fever and its relationship to convulsion, duration of convulsion, type of seizure, the extent of postictal drowsiness, and various associated systemic symptoms [14]. Other relevant history includes history of seizure, recent vaccination, attending daycare center, or prior treatment with antibiotics or any drugs during this episode and any other symptoms related to meningitis or encephalitis. Past history and family history of febrile or afebrile seizures, detailed birth and development history are also important [14].

The child should be monitored at the time of admission. A physical examination needs to be completed to identify the cause of fever and to exclude possible differential diagnoses such as meningitis (bulging fontanelle, neck stiffness or kerning sign and Brudzinski's sign) and encephalitis. A thorough neurological examination includes cranial nerves, motor systems, and fundal examination [14]. There are

neurocutaneous signs which may indicate an underlying aetiology for the seizure and they include unilateral port-wine stain, facial angiofibromas, shagreen or leather patches, periungual fibromas, hypopigmented macules ('ash -leaf sport'), café-au-lait spots, axillary freckling, iris hamartomas (Lisch nodules), and cutaneous or subcutaneous nodules [3,4].

6. DIFFERENTIAL DIAGNOSIS

The first episode of febrile convulsion could be epilepsy precipitated by fever, GEFS+ (Generalized/genetic epilepsy with febrile seizures plus), and FIRES (Febrile infection-related epilepsy syndrome). Thus the diagnosis of epilepsy, GEFS+ and FIRES need to be ruled out in children with atypical presentations of febrile seizures. Table 1 shows important differential diagnosis febrile seizures [21,39-43].

7. DIAGNOSTIC EVALUATION

Blood tests generally are not required when the symptoms and signs are compatible with simple febrile convulsion [8,9,20,40]. A full blood count and other metabolic screening investigations such as serum calcium, phosphorous, magnesium, glucose, electrolyte, urea, nitrogen, and creatinine are generally not required in the evaluation of a child with febrile convulsion [20,40]. These investigations should be individualized depending on the coexisting clinical features and to identify the underlying cause for fever such as urinary tract infection, suspected sepsis, and metabolic derangement in a child with vomiting, diarrhea, and inadequate fluid intake. Lumbar puncture is not necessary for children who are otherwise well once the convulsion has ceased. The AAP intensely recommend to consider a lumbar puncture in patients under one year with febrile seizures and also especially children with incomplete immunization states concerning *Haemophilus influenza* and *Pneumococcus* [7]. Besides, convulsion after first day, and lethargy may also be indications to do a cerebrospinal analysis [4].

Electroencephalogram (EEG) is not routinely recommended and of limited value [36] unless in patients who have complex febrile convulsions, frequent recurrence without a connection with febrile illness, prolong convulsions, and recurrent febrile episodes in a child with neurological abnormalities or developmental delay [44]. Skull radiographs have no value in diagnosis [20]. Computed tomography or Magnetic resonance is not routinely recommended in the absence of coexisting neurologic abnormality such as structural defects in the nervous system, increased intracranial pressure, focal neurological features, history of head trauma, and abnormal size head either macro or microcephaly [6,20]. There are studies which suggested doing imaging either CT or MRI in complex febrile seizures amongst those who had focal seizures, and to identify postictal neurologic deficit and hippocampal lesion following repeated seizures [45,46].

8. COMPLICATIONS

Febrile seizures can cause unnecessary fear and panic to parents as they think their child might develop brain damage and future epilepsy or might die following febrile seizures [47].

Epilepsy risk in later life has been 1% in simple febrile convulsion whilst complex febrile seizures have nearly 4 – 6% [21,37]. There are several risk factors which predispose to epilepsy in a patient with febrile seizures and they include seizures which occur within an hour of onset of fever, the onset of febrile convulsion before 1 year of age or after 3 year of age, several episodes of febrile convulsions, a positive family history, an underlying neurological defect, and an epileptiform discharge on EEG [10,48].

Encephalopathy rarely occurs [49]. Current evidence reveals that missense mutations in sodium channel SCN1A and SCN2A gene might be underlying risk factors for severe febrile seizures [50]. Mesial temporal sclerosis is also a complication following recurrent and prolonged febrile seizures [47] and acts as a triggering factor for future epilepsy.

Table 1. Differential diagnosis of febrile seizures

1. Chills and rigors	5. Breath-holding spells
2. New-onset refractory status epilepticus (NORSE)	6. Febrile infection-related epilepsy syndrome (FIRES)
3. Febrile myoclonus	7. Febrile delirium
4. Generalized/genetic epilepsy with febrile seizures plus (GEFS+)	8. CNS infections (meningitis and encephalitis)

Patients with simple febrile seizures are generally not at higher risk of later neurological deficit including cognitive impairment and intelligence [7]. A population-based cohort study revealed that there is no relationship between febrile seizures and the threat to high functioning and behavioral abnormalities; however, recurrent afebrile convulsions have a significant association with vocabulary overdue as opposed to simple febrile seizures [51]. A study from Sweden targeting parents of twin children showed a significant risk of having developmental coordination disorders, autism spectrum disorders and learning difficulties than in the general population without febrile convulsion after adjusting for epilepsy in the same population [52].

A number of studies from other settings revealed different findings regarding the association of attention deficit hyperactivity disorders (ADHD) and febrile convulsion [5,14,20]. The latest findings from population-based cohort studies revealed a significant association between febrile seizure and ADHD [53,54]. There is also an increased risk of developing Tourette syndrome (TS) according to data based on a retrospective study performed in Taiwan. The study found that other risk factors for TS include male gender, children with rural residence, and manual working-class or blue-collar workers [55].

Current evidence reveals those children with complex febrile convulsion and febrile status epileptics can die suddenly and unpredictably similar to a sudden unexpected death in adult epilepsy [56,57] which contrast with the findings of previous studies that revealed no association between febrile seizures and sudden death [3,7,57]. Further, children with febrile seizures have high chances of developing atopic diseases [6,58], stress-induced hyperglycemia [59], and rarely can have pulmonary oedema [60].

9. MANAGEMENT

Routine interventions to prevent recurrent seizures are not necessary as febrile seizures self-abort with time. During an acute attack whilst monitoring of vital signs, the patient may be commenced on intravenous (IV) either lorazepam with a dose of 0.05- 0.1 mg/kg or diazepam with a dose of 0.1-0.2mg/kg to abort the convulsion. [4,15,28,48]. Rectal diazepam can be considered in the absence of an intravenous route with a dose of 0.5mg/kg. In addition, there are other safer routes including

intranasal route (0.2 mg/kg) and buccal mucosa (0.5mg/kg) [15,28,48].

Febrile status epileptics might require more than one medication to control as it rarely resolves spontaneously [6]. The first choice would be IV lorazepam (0.1 mg/kg), followed by additional IV phenytoin (dose - 5-10 mg) if the seizure persists. The next option would be IV phenobarbitone at the dose of 20 mg/kg, valproic acid at the dose of 20-40 mg/kg, and levetiracetam at the dose of 20-60 mg/kg guided by availability and institutional practices [61]. Also, the child needs to be monitored with pulse oxymetry while oxygen being delivered to maintain SaO₂ > 92%. An antipyretic may be given to control fever and clothes can be removed to make the child more comfortable [39]. Parental advice should be mandatory to alleviate fears about febrile convulsion given that it is a benign disease and generally, associated with favorable outcomes [28]. Further, the parents should be advised to keep the child in an either left lateral or semi-prone position to reduce the risk of aspiration [4].

10. PREVENTION

10.1 Continuous Prophylactic Treatment

Although there is risk of recurrence and very low chance of epilepsy, the current consensus is that prophylaxis for febrile convulsion is not necessary [10,15,28] as chronic antiepileptic treatment does not reduce the risk of epilepsy and recurrence. Cochrane review revealed that routine use of Sodium valproate and Phenobarbitone seemed to be beneficial in the prevention of febrile seizures [4,62,63], however unacceptable side effects [64,65,Table 1] of these medications do not provide significantly benefits over disadvantages [7]. Almost 30-40% of children exhibited side effects during chronic anticonvulsant therapy [15,62]. The AAP also disagrees with long term anticonvulsant therapy with any of the drugs as a recommended prevention method of febrile seizures [7,11].

10.2 Intermittent Prophylactic Treatment

The recent accord does not recommend the routine use of intermittent prophylactic treatment in the prevention of febrile seizures due to its benign nature and considering potential adverse effects of anticonvulsant drugs overhead benefits [7]. A single-blind the randomized clinical trial failed to demonstrate the effectiveness of continuous oral phenobarbitone versus intermittent oral

Table 2. Adverse effects of anticonvulsants [7,64,65]

Sodium valproate	Phenobabitone	Diazepam
Headache, nervousness, insomnia, Ataxia	Dizziness, sleep disturbances, day time insomnia, disturbances in memory, cognitive dysfunction, loss of balance, aggression, attention deficit, Hyperactivity irritability, hyperactivity.	Headache, drowsiness, slurred speech, ataxia irritability, respiratory depression, bradycardia lethargy
Nausea, vomiting, increase appetite, pancreatitis, diarrhoea	Nausea, vomiting, loss of appetite	Dry mouth, constipation
Flu like symptoms		
Liver toxicity		
Bone marrow suppression including thrombocytopenia		
Renal toxicity		
Hair loss, thinning and discoloration of hair		

diazepam [7,66]. However, side effects have been less in intermittent oral diazepam compared to continuous phenobarbitone therapy. The use of diazepam intermittently with the episode of fever either by oral or rectal route (dose 0.3-0.5mg/kg, maximum 10mg) was effective in the prevention of febrile seizures [7,67], however, it was not useful in patients who developed seizures before fever appeared [7]. At the same time, treatment with intermittent oral or per-rectal diazepam is also not routinely recommended due to its potential side effects (Table 2) over benefits [7] and adverse effects may mimic clinical features of meningitis. In certain conditions where parental anxiety, presence of numerous seizures with or without lengthy febrile seizures (particularly febrile status epileptics) and those who have exponential risk of recurrence, prophylactic intermittent therapy with oral or rectal diazepam or nasal/ buccal midazolam with the onset of each fever may be suggested [4,5,7,15]. Oral clobazam and levetiracetam has also been used for intermittent prophylaxis [42,56,68].

11. CONTROL OF TEMPERATURE

Antipyretics have been used to control fever which in turn may prevent the occurrence of seizures. Both acetaminophen at a dose of 15mg/kg/dose every 6 hourly and ibuprofen at a dose of 5mg/kg/dose every 8hourly seem to be effective antipyretics at any age [4,12,42]. Ibuprofen may be used with caution in areas where dengue has been endemic. Controlled studies failed to demonstrate the effectiveness of

antipyretic in the prevention of recurrences [7,11-13,28] and also analysis of systematic review on three randomized control trials did not show a significant difference in using antipyretic for reducing recurrence during follow up of one to two years amongst children with previous febrile seizures between the age of 6 months to 6 years [69].

Physical methods such as tepid sponging, direct fanning, cooling, and removing clothes also failed to reduce the occurrence of febrile seizures and their recurrence [8,9,13].

As there is no effective method to prevent febrile convulsion and its recurrence, prevention of infectious disease is the only option to reduce morbidity and mortality. National vaccination programs prevent most of the childhood infectious diseases [70,71]. There is no recommendation to give antipyretic before vaccination and further prophylactic antipyretic might decrease the effectiveness by suppressing the immune response to the certain vaccine [72].

12. PSYCHOSOCIAL ASPECT OF PARENTS

Febrile convulsions in children can give rise to significant parental anxiety and fear of the death of their child. Most of the time, it is due to a lack of sound knowledge. It can be alleviated by regular educational programs [5,28] by specialized health workers to explain the benign nature of the condition and lack of any significant association with future epilepsy [11,28]. Routine

treatment with anticonvulsants is rarely necessary and parents need education on how to manage their children at home when they develop seizures [5,11,47]. It is important to teach basic resuscitation measures to every parent who has children with febrile convulsions

13. PROGNOSIS

A favorable outcome is a norm as febrile seizures are benign and self-limiting by the age of 6 years [15]. About, 30-35% of febrile seizures recur during early childhood whilst 75% of children will have recurrence by one year after the first seizure. Nearly 90% recurs by the second birthday. Recurrences are common among patients having risk factors for febrile convulsion including early-onset seizures before the age of 15 months, seizures that occur with the lowest temperature rise, a shorter time between the onset of fever and the initial seizure (less than 1 hour), presence of epilepsy and febrile seizures in the first degree relatives, attending daycare, frequent febrile illnesses, several seizures within the same febrile illness, complex febrile seizures and co-existing neurological abnormalities [21,28]. Most children with simple febrile seizures have normal growth, and development [38].

14. CONCLUSION

Febrile seizures affect approximately 2-5% of children between the ages of 6 months to 60 months and are the most common type of seizures in children. Eight percent of them have simple seizures whilst the rest have complex convulsions. Febrile convulsions generally carry a good prognosis except in a minority of those who have complex convulsions, and therefore, a higher the risk of future epilepsy. About one-third of them have a chance to recur especially in early childhood. None of the prophylactic treatment methods either anticonvulsant medications or non-pharmacological methods have been effective in the prevention of recurrence of febrile convulsions according to the review of available literature. Naturally, children with febrile seizures grow out of seizures by 5- 6 years of age. Although various aetiologies have been put forward, more research is needed to identify the genetic implications of this disease and novel treatments to control recurrences.

CONSENT

It is not applicable.

ETHICAL APPROVAL

As per international standard or university standard written ethical approval has been collected and preserved by the author(s).

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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