Febrile Seizures: a narrative review of the current evidence

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Abstract

Febrile Seizures (FS) are the most common childhood seizures that cause intense anxiety and fear in parents. However, it is a benign condition that does not generally cause brain damage. It mainly affects children aged three months to five years, with peak incidence at 18 months of age. To provide a clinical update on the epidemiology, clinical manifestations, diagnosis, evaluation, and management of children with febrile seizures, major databases comprising of PubMed, ScienceDirect, and Google Scholar were searched. The search contents were 'fever' AND 'convulsion', 'febrile seizure' AND 'clinical features', 'febrile seizure' AND 'management'. Both MeSH and regular keyword search strategies were used. Any form of study on FS was included and any study that was not in English or translated into English was excluded. The overall incidence of FS was estimated to be 460/100,000 in the age group of 0-4 years, the majority of which are simple, but approximately 30% will have some complex features. Although associated with a relatively moderate rate of recurrence, only a small minority of patients with FS will subsequently develop epilepsy. Many risk factors have been attributed to either the initial development or recurrence of FS, with some factors identified as risk for developing epilepsy, and these include positive family history, premature birth, developmental delay, brain disorders, and genetic mutations. Conventionally, FS are classified into simple and complex types, and they typically present with fever, body jerking, or twitching. The management basically involves abortion of the seizure event, control of the fever, airway management, and respiratory and circulatory support.

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Introduction

Febrile Seizures (FS) are the most common childhood seizure disorder and one of the most common pediatric emergency presentations. It is usually benign but a frightening and terrifying experience for most parents and affects about 2-5% of children.[1] It usually occurs in children aged between three months and five years, with peak incidence at 18 months, and onset beyond six years is uncommon.[2] In about 22% of cases, the seizure attack occurs 24 hours after the onset of the fever, and within one hour of the fever onset in 21% of the cases. However, in a few cases, the seizure attack precedes the fever. Nearly one-third of children with FS will have recurrence, and children under one year of age have a 50% chance of recurrence. Usually, a first recurrence tends to occur within a year after the initial FS, and the risk increases when there is a first-degree family history, or when the first seizure occurs at a low degree temperature.[3] Generally, the frequency of recurrence is estimated to be 10% in patients with no risk factors; 25-50% in the presence of 1-2 risk factors; and 50-100% when there are three or more risk factors.

The risk of epilepsy development following a simple FS is 1.5-2.4% and 4-15% for complex FS.[4] FS is a serious pediatric emergency, especially in developing countries that have a very high burden. It has many risk factors that can, in many instances, be prevented. It is not epilepsy and very often has a good prognosis without any neurological complications. Its diagnosis is clinical; however, some supportive investigation can be done. Parents and caregivers play an important role in controlling the condition when they are adequately taught and properly counseled.

This article provides the current evidence and understanding of FS, discusses the various definitions of FS, and comprehensively explores the epidemiologic paradigm, including the risk profile, incidence and prevalence profile, morbidity and mortality profile, and seasonal variation of FS. It also presents the etiopathogenesis of FS in a more understandable and encompassing way, covering a new understanding of the FS evolution. Additionally, the article extensively reviews the evaluation and treatment of FS at various levels, comprising pre-hospital management, acute management in the emergency department, and long-term management, and highlights preventive measures for recurrence. Finally, potential outcomes and FS mimicry were discussed in the articles in order to have a clear view of FS and avoid overzealous and erroneous diagnoses, which will have a negative impact on the child and their caregiver.

Definition of Febrile Seizure

There is no consensus definition of FS. The International League Against Epilepsy (ILAE) defines FS as "an epileptic seizure occurring in childhood after the age of one month, associated with a febrile illness not caused by an infection of the Central Nervous System (CNS), without previous neonatal seizures or a previous unprovoked seizure, and not meeting criteria for other acute symptomatic seizures".[5] This definition provides key diagnostic parameters for FS which include excluding potentially harmful conditions like meningitis, encephalitis, serious electrolyte imbalance, or other acute neurological illnesses, as well as prior unprovoked seizures. This implies that diagnosis of FS entails evaluation of the cause of the fever and all other potential causes of the seizure must be excluded.[2] The Joint Working Group of the Research Unit of the Royal College of Physicians and the British Paediatric Association considered FS as "an epileptic seizure occurring in a child aged from six months to five years, precipitated by fever arising from infection outside the nervous system in a child who is otherwise neurologically normal".[6] This definition also emphasizes the fact that diagnosis of FS can only be made if potential CNS causes were excluded. Additionally, it points out that epilepsy should be considered first in a child with fever and convulsion who has background neurologic abnormalities. In a consensus report issued by the United States (US) National Institute of Health (NIH) in 1980, FS was defined as "a seizure in infancy or childhood associated with fever but without evidence of intracranial infection or defined cause for the seizure".[7] This definition does not consider cases of FS in children who previously had afebrile seizures. It also indicates that FS is a diagnosis of exclusion.

Epidemiology

The etiology of FS is still unknown but an association of multiple environmental and genetic risk factors was shown to cause FS in some studies.[8] Generally, about 50% of children have no identifiable risk factors; however, many risk factors have been attributed to either the initial development or recurrence of FS with some factors identified as risk for developing epilepsy in a child with FS as shown in Table 1. Therefore, the risk factors can be categorized into three: i) risk of first FS, ii) risk of FS recurrence, and iii) risk of developing epilepsy.[9]

i) Risk factors for first FS. There are many factors that can be considered as risk factors for development of child's first FS and these include fever as an initial risk of developing seizure. The degree of the fever that could potentially cause FS is controversial among scholars. However, the average value was determined to be 37.8°C, with a range of 37.7°C to 38.0°C.[10] Positive family history within the first-degree relatives has been identified persistently as an important risk factor for FS. The more relatives affected, the greater the risk which could be up to 10-45%.[11] Markers for sub-optimal brain function like premature birth, prolonged stay at the neonatal intensive care unit >30 days, and developmental delay as well as other brain disorders have been shown to be potential risk factors for developing FS.[12] FS has been reported in children following vaccination, however, a genetic mutation of sodium channel has been recognized in these children, a condition called Dravet Syndrome. Therefore, vaccination increases susceptibility of FS in children with Dravet Syndrome.[13] The FS may also be provoked by concurrent viral or bacterial infections like encephalitis or meningitis but more so with viral than bacterial infections.[2] However, gastroenteritis has been shown to have protective effect against FS.[14]

ii) Risk factors for FS recurrence. Nearly one-third of children with FS tend to have a recurrence which occurs within first year in about 75% of cases. Risk factors for the recurrence of FS are age at onset under 18 months, history of FS or epilepsy in a first degree relative, relatively low-grade fever at the onset of the first FS (<39°C), shorter duration of fever before the seizure (<1 hour) and multiple seizures during the same febrile illness.[15]

iii) Risk factors for development of epilepsy. A large body of evidence showed that FS is one of the most commonly identified event preceding epilepsy and children with first FS will have a risk of developing epilepsy four times higher than the general population.[9] In a population based study of children, about 13-19% of children with unprovoked seizure will have had one or more previous FS.[16] The risk was estimated to be 2.4% in children with simple FS and 6-8% among those with complex FS.[15] A positive family history of epilepsy, complex features and the presence of early onset neuro-developmental abnormalities were recognized as important factors increasing the risk of developing epilepsy in children with FS.[17] Other factors include febrile status epilepticus, low Apgar at 5 min, focal epileptogenic discharges on Electroencephalogram (EEG) and age during the first FS: <12 months or >37 months.[4]

In the United States and Western Europe, the incidence of FS is 2-5% in children aged 6 months to 5 years with peak incidence between 12 and 18 months.[18] About 50% of children with FS are in the age range of 12-30 months and uncommon in children above 4 years constituting only about 6-15% of children with FS.[8] It occurs more frequently in some ethnic group than the other with highest incidence of 14% among Guamanians, 6%-9% among Japanese, and 5%-10% among Indians.[19] It is more prevalent among male gender, with about 1.6 to 1 male-to-female ratio, more commonly affecting children of low socioeconomic status.[20] The incidence and prevalence data are poorly reported from the developing nations; however, an incidence of 2.7% was reported from Nigeria, a west African country.[21] The overall incidence of FS was estimated to be 460/100,000 in the age group of 0-4 years, the

Table 1. Risk profile of Febrile Seizure (FS).

Risk factors for first Febrile Seizure	Risk factors for Febrile Seizure recurrence	Risk factors for development of epilepsy
Fever at 37.7-38°C	Age at onset (<18 months)	Family history of epilepsy
Family history in first degree relatives	History of FS or epilepsy in first degree relatives	Complex FS (multiple seizures in 24 h) or Febrile status epilepticus
Children born prematurely, with developmental delays or with brain abnormalities	Low grade fever at the onset of the first FS (<39°C) Low Apgar at 5 min	Early onset neuro-developmental abnormalities or
Vaccination in children with Dravet Syndrome	Fever lasting <1 h before the seizure	Age during the first FS: <12 months or >37 months
Infections like encephalitis or meningitis	Multiple seizures during the same febrile illness	Focal epileptogenic discharges on EEG

FS, Febrile Seizure; EEG, Electroencephalogram.

majority of which are simple, but approximately 30% will have some complex features.[22] The risk of recurrence was reported to be about 30-40% and was related to various factors such as early age of onset, epilepsy or FS in the first degree relative, frequent febrile illness and low temperature at onset.[1]

FS is relatively a benign condition, with extremely low morbidity and mortality, virtually present with no detectable structural brain abnormalities or cognitive impairment. Although associated with relatively moderate rate of recurrence, but only a small minority will subsequently develop epilepsy.[23] The commonly reported morbidity of FS includes development of repeated afebrile seizures, temporal lobe epilepsy, and Hippocampal or Mesial Temporal Sclerosis (HS/MTS) which are commonly reported in complex FS but rarely seen in simple FS.[24] The incidence or risk of mortality in children with FS, including febrile status epilepticus is very low. For example, no deaths recorded from the National Collaboration Perinatal Project, or from the British cohort study.[2] Additionally, no association was found between FS and sudden infant death syndrome.[25]

Etiopathogenesis

The definitive etiology of FS is largely unknown. However, it is thought to develop from the susceptibility of the immature brain to the effects of fever in association with environmental factors, namely the increase in brain temperature (hyperthermia) and genetic predisposition involving genes coding for sodium channels, GABA-A receptors, and interleukins.[26,27] The developing human brain shows an enhanced neuronal excitability, which increases its vulnerability to FS, hence considered as an age-dependent response of the developing brain to fever.[28] There are many theories attributed to the pathophysiology of FS. Firstly, genetic factors have been shown by many studies to play an important role in FS where about one third of the children have positive family history.[29] This genetic vulnerability is thought to have led to many changes in the developing brain, such as alterations in sodium channel expression and hypothalamic dysregulation, resulting in increased cortical and hippocampal excitability making it neurodevelopmentally vulnerable to the effect of fever.[22] Secondly, elevated brain temperature was believed to cause neuronal changes by altering many temperature-sensitive ion channels and cytokines secretions causing neuronal excitability and excessive firing leading to seizures.[12] Thirdly, hyperthermia causes hyperventilation that leads to respiratory alkalosis with consequent brain alkalosis, which provokes neuronal excitability resulting into seizures in susceptible children.[30] Fourthly, inflammatory processes including cytokines secretion have been suggested to play an important role in the genesis of FS. A significantly higher plasma level of fever-promoting pyrogens Interleukin-1β (IL-1β), Interleukin-1 Receptor Antagonist (IL-1RA), Interleukin-6 (IL-6), Interleukin-10, and tumor necrosis factor have been identified in children who have FS as compared to those without FS indicating the role played by these cytokines in the generation of FS.[31] Finally, FS may occur from hot baths-induced hyperthermia, which is provoked during bathing by both tactile and high temperature-dependent stimuli, due to cumulative effects of water temperature over cutaneous stimulation resulting from defective inhibitory pathways of afferent somatosensory fibres.[32] Also, an aberrant thermoregulatory system or an anatomical abnormality of the temporo-insular and parietal networks that are genetically dependent could be the possible causes of the hot water FS.[33]

Classification

The first attempt to classify FS was made in 1979 by Livingston and colleagues who introduced two forms of FS, namely "simple febrile convulsion" and "epileptic seizures precipitated by fever" based on the age of onset, seizure characteristics, EEG findings, frequency of seizures, and genetic factors.[12] A proposal was made in 2010 by ILAE that FS should be categorized based on the age at onset as either infancy or childhood FS.[15] Conventionally, many clinicians currently classified FS as either simple or complex FS as shown in Table 2. Simple FS are usually benign not associated with any serious neurologic complications commonly seen in children aged 3-5 months with an incidence of 2-5%.[4] Whereas a complex FS is often associated with postictal neurologic abnormalities, most commonly a postictal paralysis (Todd's paralysis) or with previous neurologic deficits.[34] Simple FS is defined as a generalized seizure of short duration, lasting less than 15 mins occurring during the febrile illnesses in a child aged 6 months to 5 years without recurrence within 24 h (single episode), not caused by an acute nervous system disease and with no neurologic deficits.[35] On the other hand, complex FS is defined as a focal seizure lasting more than 15 min which tends to recurs within 24 h of the first episode and commonly associated with postictal neurological abnormalities.[36] When the complex FS last more than 30 mins or involves brief serial seizures, without regain of consciousness in between, it is then referred to as febrile status epilepticus, and occurs in about 5% of FS cases.[1]

Table 2. Classification of Febrile Seizures (FS).

Simple FS	Complex FS
Benign with no post-ictal neurologic abnormalities	There are post-ictal neurologic abnormalities, most commonly a postictal paralysis (Todd's paralysis)
Generalized tonic-clonic seizures without focal Features	There are focal features in which, involving only one side of the body
Seizure is of short duration, lasting less than 15 mins	Seizure lasts more than 15 mins
Single episode within 24 h, i.e. no recurrence within 24 h	Seizure tends to recurs within 24 h of the first episode, i.e. there could be multiple episodes within 24 h
Seizure resolves spontaneously, usually within 1h	Full recovery is not usually observed after 1 h
Do not lead to development of febrile SE	Can lead to development of febrile SE
Anticonvulsant is usually not needed to stop the seizure, stops spontaneously	Anticonvulsant may be required to interrupt the seizure

FS, Febrile Seizure.

Clinical presentation

In the majority of cases, FS occurs within the first 24 h of fever onset, however, it can occur 3 or more days after the onset.[37] Patients present with either generalized or focal tonic, tonic-clonic or clonic jerks with hypotonia in some cases. Myoclonic jerks are never associated with FS, thus occurrence during fever is referred to as febrile myoclonus, and should not mistakenly be diagnosed as febrile seizures.[26,38] Prior to the onset of motor movement, FS is often preceded by auras of confusion, fixed gaze, behavior arrest or unawareness.[27] Depending upon the type, the typical clinical features include body jerking or twitching, which may be associated with unawareness, upward rolling of eyes and clenching of teeth, foaming at the mouth, and post-ictal symptoms such as sleep, drowsiness, loss of sphinteric control, confusion, or irritability that usually resolves within 30 min. Patients may be pale, cyanosed or in respiratory distress.[8] Simple FS usually present as generalized, tonic-clonic seizure associated with upward rolling of eyes. The seizure activity lasts for few seconds to few minutes which is usually followed by short period of postictal drowsiness. On the other hand, complex FS present clinically as multiple episodes of focal seizures, usually associated with loss of consciousness. The seizure activity lasts for more than 15 min with prolonged postictal drowsiness or neurologic sequelae.[37]

Evaluation and treatment

Most FS are short-lived and self-limiting; therefore do not require long term treatment with anti-epileptic drugs.[8] However, when the seizure lasts for more than 5 minutes, or a child presents with febrile status epilepticus or recurrent FS, antiepileptic drugs should be prescribed.[8] Patient should first be placed in a left lateral semi-prone position to prevent the risk of aspiration.[37] A simple FS in a child with desirable clinical status and well identified source of infection should be observed in a hospital for a maximum of six hours and then discharged unless there is disabling parental anxiety, uncertain home condition or no nearby health facility.[2] Admission should be considered in case of prolonged seizure or persistent neurologic features like Todd's paralysis. Other indications for admission include features of complex FS, significant risk of recurrence, age less than 18 months, features of serious infection or when source of the infection is not well identified. Additionally, presence of red flag signs and symptoms, as shown in Table 3, warrant admission.[39]

ABC of resuscitation should be instituted where patency of patient's airways, adequacy of ventilation and oxygenation, and circulation status should be assessed. When oxygenation is poor, oxygen should be administered via mask, nasal cannula, or oxygen tubing; pulse oxymeter and cardiac monitoring devices should be placed. In case of airway or ventilation problems, non-invasive maneuvers should be started first as might be due to post-ictal or medication effects and condition is likely to improve when the effect is resolved. However, when the patient is not responding to these maneuvers or when he is in respiratory arrest, bag-mask ventilation might be needed. If patient is having persistent or recurrent seizures, intravenous access should be obtained for possible intravenous anticonvulsants. Brief history including history of the presenting complain, past medical history (previous seizures or neurologic condition), drug history and history of any allergy should be obtained during transport. Also, history of any home care or preventive therapy like rectal diazepam should be obtained from the family members. Physical examination should be done focusing on possible sources such as features of infections like petechial rashes or nuchal rigidity; focal neurologic deficits indicating pre-existing neurologic disease; evidence of trauma or exposure to medications or toxins.[40-42] Hypoglycemia should be rule out using blood glucose measurement. Benzodiazepine such as diazepam, midazolam, or lorazepam is given as first-line when the seizure lasts for more than 5 minutes. A typical (simple) FS is usually aborted with a single dose of a benzodiazepine.[40]

The mainstay for the acute therapy involves abortion of the seizure event, control of the fever, airway management, respiratory and circulatory support, and identifying the underlying cause/source of the fever using history and examination as well as laboratory investigations.[26]

In the emergency unit seizures are usually aborted, depending on the center protocol, with benzodiazepines including diazepam, lorazepam and midazolam. Many studies have shown that IV or rectal Lorazepam (LZP) is more effective than Diazepam (DZP). Similarly, oral Midazolam (MDL) was found to be more effective than rectal DZP, and the intranasal form was shown to be as effective as IV DZP. For home or community management, the buccal or nasal MDL is the treatment of choice.[19,43,44] Opinions vary on when to administer the anticonvulsants: some recommend immediate administration while others advice waiting for 5 minutes, especially in case of simple FS, as most seizures spontaneously stops within 2-3 minutes.[16,8,13] If the seizure events ceased before coming to the hospital, child should only be observed and no any anticonvulsant is needed. However, if it persists for a long time more than 5-10 minutes despite first and second dose of benzodiazepines (only two doses are recommended as it can cause respiratory depression), it should be treated as febrile status epilepticus and a full SE protocol should be initiated. This is because prolong seizure is associated with increased risk of complications.[26,45] When patient is stabilized, vital signs are then monitored and recorded including temperature, heart rate, respiratory rate, capillary refill time and serum glucose level.[8]

Fever should be control with antipyretic such as paracetamol or ibuprofen, however, it has not been shown to reduce the risk of

Table 3. Red flag signs and symptoms in a child presenting with Febrile Seizure (FS).

Meningeal signs: a positive Kernig's sign and/or a positive Brudzinski sign and/or neck stiffness
Sustained loss of consciousness for more than an hour after cessation of the FS
Bulging anterior fontanelle
Features of complex FS
Tachycardia out of proportion with body temperature, or persistent tachycardia after fever subsided
Signs of moderate to severe respiratory distress, such as tachypnea, grunting, low oxygen saturation (<92% on air), and chest wall recessions
Evolving non-blanching rashes in an unwell child

FS, Febrile Seizure.

FS recurrence and therefore given only to relieve discomfort caused by the infection.[8] Physical methods of controlling fever such as fanning, cold bathing and tepid sponging do not prevent seizure recurrence and therefore are not recommended.[46] Combination of paracetamol and ibuprofen is not recommended also as it has no added benefit and increases the risk of overdose and administration errors.[8,47] Use of antibiotics is indicated in cases of bacterial febrile infections such as otitis media, pneumonia or tonsillitis.[8]

Supportive measures should immediately be instituted including management of the airways to make sure it is patent; respiratory support by administering oxygen in case of poor oxygenation ($Sa0_2$<90%), non-invasive maneuvers or tracheostomy in case of ventilation problems or respiratory arrest; and circulatory support by ensuring adequate hydration and correcting dehydration or shock using intravenous fluids, preferably 0.9% sodium chloride solution.[8]

The cause of the fever should then be investigated thoroughly through detailed history and thorough examination. CNS infections such as meningitis, encephalitis, meningoencephalitis or cerebral malaria should first be ruled out.[26,40] CNS infections can be ruled out by the presence of meningeal signs and/or evidence of infection from Lumbar Puncture (LP). The Royal College of Physician/British Pediatric Association Joint Working Group has recommended LP in children presenting with fever and seizure if the seizure is complex, there are presence of meningeal signs, child is systematically ill, less than 18 month of age (probable indication) or child is less than 12 month of age (absolute indication).[46] However, the indications of LP to rule out CNS infection in children presenting with fever and seizures, have been the subject of debate over the last many years. Generally, LP is absolutely indicated in the presence of meningeal signs and should be seriously considered if the patient is under antibiotic treatment prior to the seizure events due to the possible masking of signs and symptoms of meningitis.[1] Thus, LP in the absence of meningeal signs is unnecessary, however, this decision can still be made by an experienced doctor.[26] The seizure should be adequately characterized by noting the nature and duration of the convulsions, the presence and duration of the pre-ictal, ictal and post-ictal features. Previous history of FS or diagnosis of epilepsy, past medical history or evidence of developmental delays should be documented. History of other associated symptoms, recent infectious diseases, recent use of antibiotic therapy, history of immunization and vaccination, history of use of antipyretics or anticonvulsants, family history of FS, epilepsy, or neurologic diseases should be sought for.[12] Thorough physical examination should be done noting important clues of neurological or systemic diseases. A complete neurological examination should be performed to identify evidence of focal deficits that may be caused by an intracranial lesion or resultant Todd paralysis from a focal seizure, or increased intracranial pressure evidence by depressed level of consciousness, sunsetting eyes, papilledema, or cranial nerve palsies.[40]

Although routine laboratory investigations are not indicated, especially in simple FS, however, other differentials should be rule out using some tests. These include serum glucose test to rule out hypoglycemia; complete blood count to rule out infectious cause and serum electrolytes to rule out metabolic encephalopathy particularly in patients with severe dehydration, diabetes or other metabolic disease.[48-50] EEG is not routinely indicated in FS for diagnosis or predicting risk of epilepsy. However, some authorities recommend its use in cases of complex or recurrent FS to rule out other neurological abnormalities.[51,52] Additionally, as febrile illnesses lower the threshold of seizure, epileptiform discharges on the EEGs of patients with FS could be important predictive risk

Table 4. Drugs used in the management of Febrile Seizure (FS).

Name	Dosage	Route	Frequency	Maximum dose	Indications	Remarks
Paracetamol	10-15 mg/kg	Oral, rectal or IV	4-6 hourly	Five within 24 h	Fever control	Can cause hepatotoxicity, care should be taken
Ibuprofen	5-10 mg/kg	Oral	6-8 hourly	Four within 24 h	Fever control	Should be avoided in dehydrated children
Diazepam	0.3-0.5 (for rectal) mg/kg/dose	IV, intraosseous, oral, rectal	A second dose may be given 10 min after the first if seizure persists	Only two doses are to be used	Control in seizures that lasted more than 5 min	Can also be used for intermittent FS prophylaxis given for 48 h at onset of fever
Lorazepam	0.1 mg/kg	IV	A second dose may be given 10 min after the first if seizure persists	Only two doses are to be used	Seizure control that lasted more than 5 min	Only two doses of benzodiazepins are to be used, regardless of the agent selected and if they are administered alone or in combination
Midazolam	0.15-0.2 mg/kg	Buccal, intranasal, IV/IM	A second dose may be given 10 min after the first if seizure persists	Only two doses are to be used	Seizure control that lasted more than 5 min	Dripped into buccal area after turning head to one side for buccal route; it is dripped slowly into the nose for intranasal route
Clobazam	1 mg/kg	Oral	Single dose/d	Daily dose for 2-3 days	Intermittent FS prophylaxis	Fewer side effects, lesser sedation than diazepam. Prevents recurrences in 90% cases
0.9% sodium chloride	20 mL/kg	IV	During resuscitation	More than two doses are rarely required	In children with shock, for example, in febrile illness due to gastroenteritis	Correct dehydration as appropriate
Valproate	3-5 mg/kg/d	Oral	Single dose daily	Not more than one dose in 24h	Long term FS prophylaxis	Potentially causes hepatotoxicity
Phenobarb	4-5 mg/kg	Oral	Single dose daily	Not more than one dose in 24h	Long term FS prophylaxis	Associated with behavioural changes and cognitive decline

FS, Febrile Seizure; IV, Intravenous; IM, Intramuscular.

factors for the development of epilepsy with higher risk in patients with frontal paroxysmal EEG abnormalities.[53] Children with FS frequently have epileptiform alteration in EEG and these epileptiform activities can be used in predicting later epilepsy. However, only few retrospective, cohorts and case control studies demonstrated this potential link.[54] When performed, the EEG should be done at least 48h after the FS to avoid confusing post-ictal electrical activities with abnormal electrical activities.[51,55] Similarly, neuroimaging such as Computed Tomography (CT) scan or Magnetic Resonance Imaging (MRI) is not indicated in patients with FS unless clinical picture suggests pathological changes in the brain.[46] It is also recommended in children that do not regain complete consciousness in hours, with prolonged Todd's paralysis and in children with recurrent seizures.[4] Table 4 summarizes various drugs that are used in the management of FS.

The aim of long-term management of FS is to prevent recurrence using prophylactic administration of antipyretics or antiepileptic medications intermittently or continuously.[13,26] Intermittent administration of antipyretics may help in mitigating the fever as in any other febrile illnesses; however, its role in preventing FS recurrence is yet to be established.[56] Studies have shown that adequate doses of intermittent benzodiazepines, such as diazepam and clobazam, given for 2-3 days at the onset of fever prevent FS recurrence in 80-90% of the cases.[57,58] However clobazam has been found to have fewer side effects and maybe preferred over diazepam.[59] Current evidence has demonstrated no effects of intermittent benzodiazepines therapy in the prevention of later epilepsy.[56,60] Prophylaxis can still be given if the benefits outweigh the risks and the child's caregivers are willing to. The duration for the prophylaxis is usually 2 seizure-free years or till 5 years of age, whichever comes first.[26] Giving the serious adverse effects coupled with doubtful effectiveness, long term continuous prophylaxis is no longer recommended for preventing recurrences in FS.[56,61] A Cochrane systematic review by Offringa and colleagues, suggested that neither continuous nor intermittent treatment with zinc, antiepileptics, or antipyretics is recommended for children with FS.[62] On the other hand, a large body of evidence has demonstrated the effectiveness of continuous administration of phenobarbital (4-5 mg/kg/d) and valproic acid in preventing FS recurrence,[1] but horrendous adverse effects whose risks overcome the benefits have contraindicated the administration of these drugs.[1] For example, phenobarbital is associated with behavioural changes and cognitive decline; similarly, valproic acid potentially causes hepatotoxicity and other serious side effects.[26]

Differential diagnosis

Many conditions mimics FS including rigors, febrile delirium, febrile myoclonus, breath-holding spells/attacks, reflex anoxic seizures, evolving epilepsy syndromes and CNS infections (seizures with fever) such as meningitis, encephalitis, and brain abscesses.[20] Rigors (shaking chills or shivering) is just a perception of cold associated with involuntary muscle tremors lasting for many minutes, but unlike in FS, it is not associated with loss of consciousness.[20] Febrile delirium is defined as acute and transient confusion associated with a high fever but no tonic, clonic or tonic-clonic movements of the limbs and rolling back of the eyeballs.[63] Breath-holding spells are defined as episodes of brief, involuntary cessation of breathing that occur in children in response to stimuli such as anger, frustration, pain, or fear.[20] Based on the color of the child during the apneic episode, the spells can be classified into two: the cyanotic type and the pallid type. It is characterized by a cessation of breath for not more than a minute when the child cries because he/she is upset, frightened, or injured. It may be associated with loss of consciousness if the apneic period is prolonged but child recovers spontaneously, and unlike FS, no history of fever, tonic-clonic movement or upward rolling of eyeballs.[20,64] Febrile myoclonus is a condition that affects children between 6 months to 6 year of age characterized by sparse or massive myoclonic jerks, usually involving upper limbs, during episodes of fever lasting from 15 minutes to several hours.[38,65] CNS infections can present like FS, however, impaired consciousness, petechial rash, neck rigidity, Kernig's sign, and Brudzinski' sign, if present, give clue to the diagnosis.[20] Nevertheless, differentiation can be cumbersome in infants as meningeal signs can be subtle or absent. Fever triggers seizures in children with evolving epilepsy syndromes such as generalized/Genetic Epilepsy with Febrile Seizures plus (GEFS+), New-Onset Refractory Status Epilepticus (NORSE), and Febrile Infection-Related Epilepsy Syndrome (FIRES).[66] Differentiating FS and seizures resulting from epilepsy syndromes is usually made based on the evolution of the clinical symptomatology and laboratory investigations.[20] Table 5 summarizes the common differential diagnoses for FS.

Prognosis

FS is common in children but associated with very low risk of subsequent serious adverse outcomes. It is not epileptic in origin and the majority of patients do not progress to develop later epilepsy. The background risk for developing epilepsy is more in children with complex FS than in simple FS.[8] The risk was estimated to be 2.4% in children with simple FS and 6-8% among those with complex FS.[15] Nearly one-third of children with FS tend to have a recurrence which occurs within first year in about 75% of cases. Risk factors for the recurrence of FS are age at onset under 18 months, history of febrile seizure or epilepsy in a first degree relative, relatively low-grade fever at the onset of the first febrile seizure (<39°C), shorter duration of fever before the seizure (<1 hour) and multiple seizures during the same febrile illness.[15] The frequency of FS in children usually reduces as they grow older and these stop completely by six years of age. Parent should be adequately counselled and re-assured that there is no increased risk of

Table 5. Differential diagnosis of Febrile Seizure (FS).

Diagnosis	Clinical features
Rigors	Shaking without a loss of consciousness
Febrile delirium	Acute and transient confusion associated with a high fever
Febrile myoclonus	Sparse or massive myoclonic jerks during episodes of fever
Breath-holding spells	Episodes of brief, involuntary cessation of breathing in response to stimuli such as anger, frustration, pain, or fear
Reflex anoxic seizure	Children suddenly become limp because of painful events or shock
Evolving epilepsy syndrome	Fever triggers seizure episodes
Central Nervous System infections	Meningial signs, impaired consciousness, petechial rash

intellectual delay, school difficulties or behavioral problems in most children who have had febrile convulsions. However, parents need to be counselled about their child's risk, so that they can appropriately manage another episode of febrile convulsion at home.

Conclusions

Febrile seizures are the most common type of seizures in children. The majority of the children do not have any structural brain abnormalities with very low risk of subsequent epilepsy. Diagnoses is clinical in most cases, but CNS infections must be excluded especially in cases of complex FS. Hence some laboratory investigations are offered. The treatment of FS involves abortion of the seizure event, control of the fever, airway management, respiratory and circulatory support, identifying and treating the underlying source of the fever. Parents and caregivers need to be appropriately informed on the usually favourable prognosis of the condition to suppress their anxiety.

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