Section A -Research paper

Febrile Seizures: Risk Factors, Evaluation and Management

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Abstract:

A febrile seizure is a seizure occurring in a child six months to five years of age that is accompanied by a fever (100.4°F or greater) without central nervous system infection. Febrile seizures are classified as simple or complex. A complex seizure lasts 15 minutes or more, is associated with focal neurologic findings, or recurs within 24 hours. The cause of febrile seizures is likely multifactorial. Viral illnesses, certain vaccinations, and genetic predisposition are common risk factors that may affect a vulnerable, developing nervous system under the stress of a fever. Children who have a simple febrile seizure and are well-appearing do not require routine diagnostic testing (laboratory tests, neuroimaging, or electroencephalography), except as indicated to discern the cause of the fever. For children with complex seizures, the neurologic examination should guide further evaluation. For seizures lasting more than five minutes, a benzodiazepine should be administered. Febrile seizures are not associated with increased long-term mortality or negative effects on future academic progress, intellect, or behavior. Children with febrile seizures are more likely to have recurrent febrile seizures. However, given the benign nature of febrile seizures, the routine use of antiepileptics is not indicated because of adverse effects of these medications. The use of antipyretics does not decrease the risk of febrile seizures, although rectal acetaminophen reduced the risk of short-term recurrence following a febrile seizure. Parents should be educated on the excellent prognosis of children with febrile seizures and provided with practical guidance on home management of seizures.

Keywords: Febrile Seizures, CNS, Risk.

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Introduction:

The first definition of Febrile Seizures (FS) was published in 1980 by the National Institutes of Health (NIH). It defined FS as an abnormal, sudden, excessive electrical discharge of neurons (gray matter) that propagates down the neuronal processes (white matter) to affect an end organ in a clinically measurable fashion, occurring in infancy or childhood, usually between 3 months and 5 years of age, and is associated with fever but lacks evidence of intracranial infection or defined cause **(1)**.

According to the League for the Fight Against Epilepsy (ILAE), FS has been defined as seizures associated with a febrile disease in previously afebrile children aged six months to five years without central nervous system (CNS) infection or a specific cause (such as acute electrolyte imbalance, metabolic disorder, trauma, intoxication) **(2).** This definition distinguishes "febrile seizures" from "convulsions with fever". A child with FS often loses consciousness, shakes, and moves limbs on both sides of the body. Most FSs occur during the first day of a child's fever **(3).**

More recently, the American Academy of Pediatrics (AAP) has announced a standard definition of febrile seizures as a short (< 15 min.) generalized seizures, with a fever greater than 38°C (100.4°F), not recurring within 24 h which occurring in febrile children between the ages of 6 and 60 months who do not have an intracranial infection, metabolic disturbance, or history of previous afebrile seizures **(4).**

Children with previous afebrile seizures are excluded from the group of children with febrile seizures as the febrile illness is perceived as a trigger of a pre-existing predisposition to epilepsy **(5).**

Etiology febrile seizures:

1- Viral and bacterial infections:

The cause of febrile seizures is multifactorial. It is generally believed that febrile seizures result from a vulnerability of the developing central nervous system (CNS) to the effects of fever, in combination with an underlying genetic predisposition and environmental factors. Febrile seizure is an age-dependent response of the immature brain to fever (**6**).

Viral infections involving the ear, nose, throat, and upper respiratory tract are the most frequent causative events of fever-associated seizures. Viral infection is the cause of fever in approximately 80% of cases of febrile seizures. Roseola infantum (exanthem subitum), influenza A, and human coronavirus HKU1 pose the highest risk for febrile seizures **(7).**

Stokes et al. (8), in a cohort of 276 children with FS identified by the viral analysis of nasopharyngeal secretions and cough/nasal swabs, found viral infections in 49% of the children with influenza A, respiratory syncytial virus (RSV), and adenoviruses, being the most frequent causes of infections. Norovirus gastroenteritis has been reported as a causative event in children with febrile and afebrile seizures.

Recently, children with manifestations of transient generalized seizures have been reported in association with wild gastroenteritis (**9**). A new pathogenetic pathway, the so-called "gut-brain axis", has been reported as a causative event of seizures. Falsaperla et al. (10) have reported a 10-month-old male infant with seizures secondary to cow's milk protein allergy. Neurologic signs disappeared after the suspension of the cow's milk protein (**10**).

2- Genetic factors:

Family and twin studies suggest that genetic factors play an important role. Approximately one-third of children with

febrile seizures have a positive family history (**11**). The risk for febrile seizure for a child is about 20% with an affected sibling and about 33% with affected parents. The concordance rate is about 35–69% and 14–20% in monozygotic twins and dizygotic twins, respectively (**12**). The genes that might increase the risk for a febrile seizure have been mapped to the following loci of chromosomes: 1q31, 2q23-34, 3p24.2-23, 3q26.2-26.33, 5q14-15, 5q34, 6q22-24, 8q13-21, 18p11.2, 19p13.3, 19q, and 21q22. Several modes of inheritance have been suggested, such as an autosomal dominant mode of inheritance with reduced penetrance and multifactorial mode of inheritance (**13**).

3- Intrauterine risk factor:

In a population-based, prospective questionnaire study conducted by Visser AM, et al., aimed to evaluate the occurrence of FS in 3,372 subjects from early fetal life onward until the age 12 and 24 months. Children in the lowest percentile of transverse cerebellar diameter in the second trimester were at increased risk of developing FS, compared with children in the highest percentile. In the third trimester, children in the lowest percentile of all general growth characteristics (femur length, abdominal circumference, and estimated fetal weight) were at increased risk of developing FS. Children in the lowest percentile of biparietal diameter in the third trimester also were at increased risk of FS. The study concluded fetal growth retardation is associated with increased risk of FS and that adverse environmental and genetic factors during pregnancy may be important in the development of FS (**14**).

4- Vaccination-related FS:

The relationship between childhood vaccines and febrile seizures has attracted attention of the media and medical fields. The risk of febrile seizures is temporarily increased for a few days after the administration of certain vaccines, notably, combined diphtheria-tetanus toxoids and whole-cell pertussis vaccine (**15**). Other vaccines include inactivated poliovirus, Haemophilus influenzae type b vaccine, measles-mumps-rubella-varicella vaccine, conjugated pneumococcal vaccine, and inactivated influenza vaccines (**16**).

Although the correlation between childhood vaccines and febrile seizures is difficult to describe as incidental, researchers have discovered that FS after vaccinations are not different from FS of other causes (**17**). The risk of hospitalization and illness course are not different between vaccination-related and other illness-related FS (**18**). It is worth mentioning that postvaccination FS are quite rare and often occur within the first three days after administration of live attenuated vaccines. Concomitant multivaccination administration is believed to increase the risk of developing FS (**19).**

There is no current evidence of any increased risk of either subsequent seizures or neurodevelopmental affection after the initial seizure. It is thus very crucial to alert the families to the fact that none of the standard vaccinations is currently contraindicated in children with FS. Prescribing fever-lowering

medication around the time of some potentially pyrexic vaccinations can be a reasonable practice in children at risk of FS (**20**).

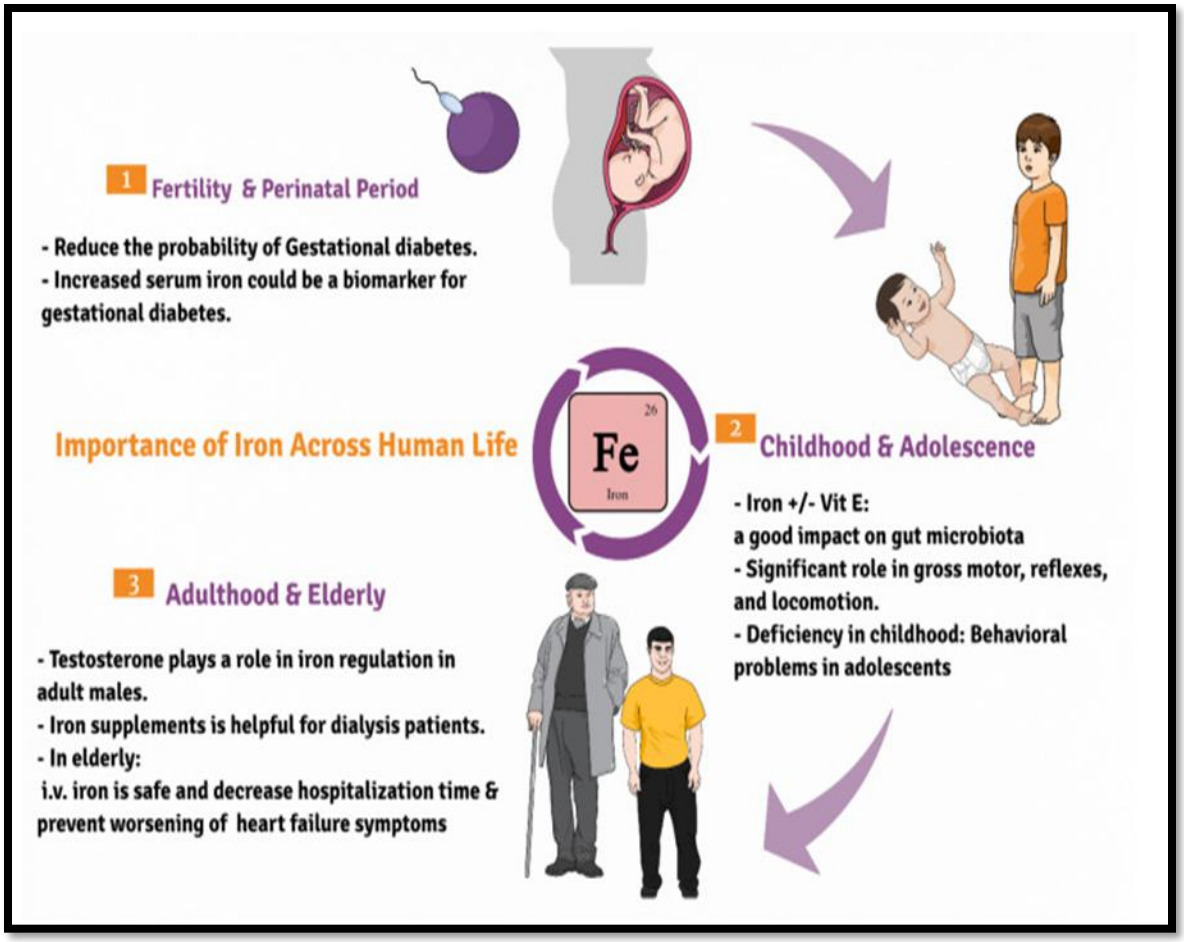
5- Other environmental factors:

Although the role of micronutrients have been largely studied as the predisposing factors, there is still a need to explore their relation to febrile seizures. Iron plays an important role in brain energy metabolism, myelin formation and neurotransmitter metabolism. Iron deficiency affects the regional monoamine metabolism, such as serotonin (**21)**, dopamine and norepinephrine, glutamate and gamma-aminobutyric acid (GABA) (**22**).The fetal brain may be at risk even if the infant is not anemic, because when there is not enough iron supply, the first priority of iron is red blood cells instead of other tissues(**23).**

It has also been suggested that iron deficiency lowers the seizure threshold and increases the risk of febrile seizures (**24**).

Iron deficiency anemia (IDA) is the most common nutritional deficiency in the world. Iron is an important micronutrient which is used by roughly all the cells in the human body (**25**). It is well understood that iron is a cofactor for several enzymes in the body and has a role in the neurotransmitters production and function, hormonal function and DNA duplication (**26**). Iron is essential for the functioning of certain neurotransmitters, such as monoamine oxidase and aldehyde oxidase. Iron-deficiency anemia may predispose to febrile seizures (**27**). Iron deficiency stimulates the function of neurons and, consequently, increases the risk of convulsions.

In a study analyzing Hg. and ferretin level in febrile seizures , the authors concluded that iron deficiency anemia is associated with a moderate increased risk of FC in children, particularly in areas with low and moderate prevalence of anemia (**26**).



Zinc is the most abundant micronutrient in the human body after iron and one of the chief trace elements in the human body detected at approximately 1.4–2.3 g

Zn in the body of an adult. High levels of zinc are present in all body tissues at highest level (85%) in muscles and bones, followed by prostate and the eye. It catalyses the activity of several enzymes involved in both protein structure folding and gene expression regulation. Zinc is also needed structurally for of zinc-containing proteins, namely zinc finger proteins (ZFP), biggest superfamily of nucleic acid-binding proteins. It is also fundamental for cell growth, differentiation and homeostasis, asides from its unique role in connective tissue growth and maintenance and immune system integrity (**28**).

The possible role of zinc deficiency in provoking febrile seizures has been reported in different studies **(29)**. Zinc stimulates the activity of pyridoxal kinase, the enzyme that modulates GABA level, a major inhibitory neurotransmitter.[15] It also modifies the affinity of neurotransmitters and thus prevents the excitatory neuronal discharge (**30**).[2] In addition, zinc significantly reduces the severity of illness and the duration of fever in children with pneumonia and

diarrhea by the activation of immune enhancing T-cells (**31**).

Children are more prone to zinc deficiency due to the lack of adequate nutrition and also due to loss of zinc through excretion as a result of periodic diarrhea (**32)**. Strong association has been found between zinc deficiency and high risk urinary tract infections in children (**33**). Urinary tract infection (UTI) is a prevalent disease among children regarded as the most common infection after common colds, with evidence suggesting that nutrients deficiency might be among the causes of UTI in children.

In a cross sectional study included 100 children from 6 months to 6 years of age presenting with febrile, the authors reported low serum zinc levels in 26% of cases and concluded that Zinc deficiency could be a potential risk factor for febrile seizure in children **(33).**

In another cross-sectional study included 40 children with simple and complex febrile seizures, the authors cocluded that children with febrile seizures had significantly reduced concentrations of serum zinc when compared with fever-matched controls without convulsions **(35).**

In other previous studies, the results revealed that children with simple febrile convulsions had serum zinc levels lower than that of febrile children with the same age (**30**) and (**29**).

There is a considerable body of evidence supports hypozincemia in children with febrile convulsions during an episode of seizure. It is valuable to assess the serum zinc level in children at risk for the occurrence of febrile convulsions during healthy states and before a seizure occurrence (**36**).

The Covid-19 pandemic infection causes serious intense acute respiratory disorder caused by coronavirus 2 (SARS-CoV-2). Due to the lack of therapy for this virus, it is necessary to reach other methods that can aid in disease control. Determination of zinc level and covid-19 infection revealed that Zn anti-inflammatory properties might contribute to the immune function improvement and decreasing the infection risk (**37**). Zinc deficiency is implicated as a risk factor for febrile seizures(**38**).

Extracellular Ca2+ concentration (Ca2+o) modulates core body temperature and the firing rates of temperature-sensitive CNS neurons. Hypocalcemia provokes childhood seizures **(39).**

The Calcium-Sensing Receptor (CaSR) is a member of the class C of G-proteins coupled receptors (GPCRs). It plays a pivotal role in calcium homeostasis by directly controlling calcium excretion in the kidneys and indirectly by regulating parathyroid hormone (PTH) release from the parathyroid glands (**40)**. In turn, PTH controls calcium resorption in the bones, calcium excretion in the kidneys and promotes renal synthesis of the 1,25-dihydroxyvitamin D3 (the active form of vitamin D), calcium absorption in the intestine **(41).**

Calcium ion (Ca) via relative depolarization of neurons sheath and activation of voltage-dependent sodium channels are involved in the

pathophysiology of seizure. Hypocalcemia (Ca <8.5 mEq/L) makes the muscle skips, paresthesia of face and extremities, spasms, stridor, and seizures. Hypercalciuria is defined as calcium excretion higher than 4 mg/kg/day. In these children fever increases the respiratory rate and causes respiratory alkalosis and hypocalcaemia affecting the pathophysiology of febrile seizures (**42)**.

In a study evaluating 160 children aged 6 months to 5 years, including 80 children with febrile convulsion and 80 febrile children without convulsion, the authors reports a significant statistical association between convulsion and hypercalciuria in children (**43**).

The 25-Hydroxy vitamin D is associated with a variety of medical disorders, for example, diabetes, autoimmune disorders, and cardiovascular problems (**44**). The role of 25-Hydroxy vitamin D is also well-defined in epileptic patients (**45**). Vitamin D receptors as well as the 1-alpha-hydroxylase, the enzyme that produces 1,25(OH)D (the active form of vitamin D), are distributed widely in the brain (**46**). Vitamin D level of children was classified according to guideline for 25-hydroxy vitamin D deficiency by Indian Academy of Paediatrics. This criterion defined vitamin D deficiency level below 12ng/mL, insufficiency level at 12–20ng/mL, and normal level above 20ng/mL (**47**).

Some studies reported correlation of 25-Hydroxy vitamin D deficiency and hypocalcaemia with febrile seizures and their recurrence **(48)** and **(49). Abdullah AT, and Mousheer ZT (50)** reported a higher prevalence of vitamin D3 insufficiency in epileptic children receiving valproate monotherapy compared with healthy children and recommended vitamin D3 supplementation to all epileptic children even before initiation of anti-epileptic drugs. In a study conducted on 223 children of age group 7–59 months who presented with simple febrile seizures, 25-hydroxy vitamin D serum level was analyzed, and statistical significance of correlation of vitamin D with the number of recurrent seizure episodes was reported. The authors concluded that vitamin D level is significantly low in simple febrile seizures and also negatively correlated to recurrence of simple febrile seizures. Negative correlation means: as the level of vitamin D concentration increases recurrence of simple febrile seizures decreases and vice versa. So vitamin D therapy is recommended for treatment of simple and recurrent simple febrile seizures **(51).**

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Risk factors for febrile seizures and febrile seizure recurrence:

Positive family history of febrile seizures or epilepsy increases the risk of febrile seizures and has been described in 25–40% of children presenting with febrile seizures **(7).** Generalised epilepsy with febrile seizures plus (GEFS+) is a familial epilepsy syndrome which can manifest as febrile seizures in individuals (**52**). This syndrome may account for part of the observed familial predisposition.

There is a higher prevalence of febrile seizures in children with underlying neurological deficits, such as cerebral palsy or neurodevelopmental delay. Some environmental risk factors have been associated with increased febrile seizure incidence, including maternal smoking and stress (**53**). Low serum zinc and iron levels have also been associated with increased risk of febrile seizures (**29**).

Febrile seizure recurrence occurs in 30–50% of children following the first febrile seizure. Each additional febrile seizure increases the risk of further recurrence, suggesting that experiencing febrile seizures leads to a lower threshold for future seizures (**54**). Also the child who had a febrile seizure has a greater risk of experiencing future afebrile seizures or subsequent epilepsy. Younger children, those with a family history of seizures or epilepsy and those who have complex seizures, have the greatest likelihood of developing further afebrile seizures or epilepsy. The exact relationship between febrile seizures and epilepsy is still uncertain. A correlation between the two may be due to an underlying brain abnormality that predisposes a child to both febrile seizures and epilepsy, or febrile seizures may prime the developing brain, making it more susceptible to later life epilepsy (**55**).

Table (1): Risk factors of febrile seizures, febrile seizure recurrence, afebrile seizures and epilepsy following febrile seizure (5).

Risk factors of first febrile seizures	Risk factors for febrile seizure recurrence	Risk factors predisposing to afebrile seizures and epilepsy following febrile seizure
Family history of febrile seizures Family history of afebrile seizures and epilepsy Developmental delay Viral infection High fever temperature Maternal smoking Neonatal discharge >28 days Low serum zinc Low serum iron	Child younger than 12 months at first febrile seizure Family history of febrile seizures History of febrile seizures Initial complex febrile seizure Febrile status epilepticus Fever <40°C Short fever duration (seizure occurrence within 1 h of fever onset)*	**Risk of Afebrile seizures:** Family history of epilepsy Abnormal neurological status Complex febrile seizures Prolonged seizures and FSE Febrile seizure recurrence Risk of epilepsy: **Prolonged febrile or FSE** **Febrile seizure recurrence** **Family history of epilepsy** **Low APGAR scores at 5 min** **Personal history of cerbral palsy** **Pre-existing neurological abnormality**

Clinical picture:

The classical scenario of simple febrile seizures is a short seizure in the setting of acute febrile illness other than central nervous system infection. It affects children between 6 months and 5 years of age. The seizure is described as generalized, lasting less than 15 minutes. The seizure semiology is either generalized clonic or generalized tonic-clonic. At the time of a seizure, the majority of children have a temperature of ≥39°C (**56**).

Seizures do not recur within the same febrile illness. The child is otherwise neurologically healthy, with no concerning focal neurological deficits. Motor and social development is usually normal (**57**). History and physical examination are vital to determine the cause of the fever. Family history, normal milestone acquisitions, brief resolution of the seizure event, and rapid regain of consciousness are signs indicative of a benign course. There are no routine laboratory tests needed, but a check of electrolytes and blood sugar levels might be warranted, especially with a gastroenteritis illness. CSF studies should be considered for the youngest age group (less than 18 months old), as definitive signs of CNS infections are often difficult to judge (**58)**. Neuroimaging studies are reserved for patients with a history of trauma or unusual residual neurological manifestations (**59**).

Differential diagnosis is made with viral meningitis in the presence of positive neurologic signs, persisting loss of consciousness, and post-ictal drowsiness. In one/third of cases, the seizures tend to reappear with other episodes of fevers. The evolution in epileptic seizures is rare, and almost similar to that of the general

population, and no persistent residual signs of motor, behavioral, and cognitive disturbances are reported. In simple FS, EEG recordings and brain MRI are not necessary, while the lumbar puncture is advised to be performed in children less than 1-year-old and those under antibiotic treatment (**60**).

FS that does not meet the criteria of the simple type are classified as complex FS. Complex (atypical) FS is often focal and may be accompanied by post-ictal paralysis. In contrast to simple FS, complex FS is of longer duration and may recur during the same febrile episode (**61**).

Patients with brain damage are more affected than those without. Differential diagnosis is posed with cerebral abscesses, meningoencephalitis, cerebral vascular malformations, cortical thrombophlebitis, and autoimmune encephalitis. Diagnostic investigations should include routinary analysis, an EEG recording, lumbar puncture, and plasma electrolytes. Brain MRI might also be indicated in patients with focal seizures, and those with episodes that happened after 5 years of age. Brain MRI is advised in an emergency in patients who present focal post-ictal deficit and persisting loss of consciousness, and also in patients with immunodeficiency, or with seizures of particular long durations (**62**). Very prolonged complex FS is thought to be associated with mesial temporal sclerosis and temporal lobe epilepsy, but the direct relationship among these disorders and complex FS remains uncertain(**63**).

Clinical evaluation:

In evaluating a child with FS, it is important to (i) obtain a family history particularly focused on neurological disorders; (ii) conduct a cautious physical examination to exclude direct CNS infections; and, (iii) carry out detailed laboratory analysis, including full blood count, electrolytes, and glucose (**60**).

Detailed history should be taken to find out the cause of the fever, the relationship of the onset of fever to the seizure, the characteristics of fever including the peak temperature and duration, seizure semiology, and duration of postictal drowsiness. The history also should include personal history of prior seizure and whether the child was recently vaccinated. History should be taken about immunization status, potential exposures to infection, toxin ingestion, CNS trauma, developmental milestones, prior seizures, and also history of febrile and afebrile seizures in other family members. Vital signs should be monitored. A thorough physical examination should be done in order to find out the underlying cause of the fever. An erythematous bulging ear drum, a beefy red pharynx, enlarged and erythematous tonsils, may give clue to the source of the fever. The examination should search for signs of meningitis such as irritability, nuchal rigidity, bulging or tense fontanel, and Brudzinski's or Kernig's sign (**64**).

Neurological examination should be performed, including the level of consciousness, muscle tone and power, and peripheral reflexes. Any focal abnormalities should be noted. A fundus examination should be performed to look for increased

intracranial pressure. Neurocutaneous stigmata that might suggest an underlying cause of the seizure should be searched for. A unilateral port-wine stain over the trigeminal area is suggestive of Sturge–Weber syndrome; facial angiofibromas, shagreen or leather patches, periungual/ungual fibromas (Koenen tumors), and hypopigmented macules ('ash-leaf spots') are suggestive of tuberous sclerosis; café au lait spots, intertriginous freckling, iris hamartomas (Lisch nodules), and subcutaneous nodules are suggestive of neurofibromatosis (**11**).

Most FS episodes are short-lived and self-terminating and do not require long-term treatment with antiepileptic drugs. The child with a simple FS should not be hospitalized if the clinical condition is good and the source of the infection is clear. The child can be discharged after a period of observation, preferably six hours after the episode. Antiepileptic drugs are given in cases of seizures lasting more than 5 min, febrile SE, and recurrent seizures. In the evaluation of a child with FS, it is important to recognize red flags, which are useful in deciding if further management is required (Table 2). Such flag signs help to predict the risk of a serious illness. Hospitalization is necessary for observation when the child presents with red flag signs and symptoms, the seizure is prolonged, complex FS, residual neurological findings (i.e., Todd's paresis), a serious infection is suspected, the source of infection is not clearly determined, the child's age is less than 18 months, and if there is a risk of seizure recurrence (**65**).

Table (2): Red flag signs and symptoms in a child presenting with febrile seizures (FS). (66)

The child presents with complex FS
Meningeal signs are observed: a positive Kernig's sign and/or a positive Brudzinski sign and/or neck stiffness
Altered level of consciousness for more than one hour after interruption of the FS
Evolving non-blanching rashes in an unwell child
Bulging anterior fontanelle
Tachycardia out of proportion with body temperature, or tachycardia that persists even after the normalization of body temperature
Signs of moderate to severe respiratory distress, such as tachypnea, grunting, low oxygen saturation (<92% on air), and chest wall recessions

Differential diagnosis:

Febrile seizures should be differentiated from shaking chills (shivering), febrile delirium, breath-holding spells, CNS infection, febrile myoclonus, generalized/genetic epilepsy with febrile seizures plus (GEFS+) (**67**), new-onset refractory status epilepticus (NORSE), and febrile infection-related epilepsy syndrome (FIRES) (**68**).

Shaking chills or shivering is defined as a perception of cold and involuntary muscle tremors that persist for several minutes. In contrast to febrile seizures, there is no loss of consciousness and no involvement of facial or respiratory muscles. Febrile delirium refers to an acute and transient confusional state with high fever. Tonic–clonic movements of the limbs and rolling back of the eyeballs are characteristically absent.

Breath-holding spells are episodes of brief, involuntary cessation of breathing that occur in children in response to stimuli such as anger, frustration, pain, or fear. Two types of breath-holding spells are recognized, the cyanotic type and the pallid type, based on the color of the child during the apneic episode. Typically, the child cries because he/she is upset, frightened, or injured. The child then holds his/her breath, usually for no more than one minute. Loss of consciousness may ensure if the apneic period is prolonged. Spontaneous recovery is the rule. The absence of fever, tonic–clonic movements of the limbs, and rolling back of the eyeballs distinguishes this condition from febrile seizure. Children with CNS infection such as meningitis and encephalitis typically present with fever and seizure. Impaired consciousness, petechial rash, neck rigidity, Kernig's sign, and Brudzinski' sign, if present, give clue to the diagnosis. Febrile myoclonus is a benign disorder affecting children mainly 6 months to 6 years of age. Affected children present with myoclonic jerks, mostly involving the upper limbs during fever. The myoclonic jerks may occur infrequently or several times per minute and may last from 15 minutes to several hours (**69**).

In contrast to febrile seizure, in GEFS+, the seizures with fever continue beyond 6 years of age, and afebrile seizures which could be myoclonic, atonic, or absence seizures also occur (**59**).

NORSE is a clinical presentation, but not a specific diagnosis, in a patient without active epilepsy or other existing relevant neurological disorder. FIRES is regarded as a subset of NORSE that requires a febrile infection between 24 hours and 2 weeks prior to the onset of refractory status epilepticus, with or without fever at the onset of status epilepticus, and with no restriction to the age of the patient. It is difficult to distinguish the first episode of febrile seizure from a seizure resulting from epilepsy, GEFS+, and FIRES in a child with fever. The diagnosis of epilepsy, GEFS+, and FIRES could only be made with evolution of the clinical symptomatology and laboratory investigations (**68**).

Table (3): Differential diagnosis of febrile seizures (FS).

Rigors: shaking without a loss of consciousness
Febrile delirium: acute and transient confusion associated with a high fever
Febrile syncope
Breath holding attacks: children voluntarily hold their breath and may transiently lose consciousness
Reflex anoxic seizures: children suddenly become limp because of painful events or shock
Evolving epilepsy syndrome: fever triggers seizure episodes
Central nervous system infections: meningitis, encephalitis, and brain abscesses

Diagnostic evaluation:

Blood tests usually are unnecessary if the history and physical examination are typical that of a febrile seizure. A complete blood cell count and blood tests for glucose, electrolytes, urea nitrogen, creatinine, calcium, phosphorous, and magnesium are usually not helpful in evaluating a child with febrile seizure. 6, The basic laboratory workup should be individualized, guided by the history and physical examination results(**70**).

Complete blood cell count should be considered in children who appear ill. Children with bacteremia have a higher rate of febrile seizures. Determination of serum glucose, electrolytes, creatinine, and urea nitrogen should be considered if there is a history of insufficient fluid intake, vomiting, or diarrhea or if there are physical signs of dehydration or edema. Urine analysis should be considered if the cause of the fever is obscure. Urine culture would be in order if the urine analysis is abnormal (**71**).

Lumbar puncture is not necessary in the majority of well-appearing children who have returned rapidly to a normal baseline after the seizure. Lumbar puncture should be performed in children with any symptoms or signs of meningitis or febrile status epilepticus (**53**). The procedure should also be considered in children who have the seizure after the second day of fever, who have had prior antimicrobial therapy, or who do not ‘look right’. Lumbar puncture is not recommended in simple and complex febrile seizure unless the child's clinical examination is suggestive of meningitis **(72).**

If lumbar puncture is performed, it is advisable to obtain blood culture and serum glucose determination concurrently. Pleocytosis, low glucose level, and high protein level in the cerebrospinal fluid are indicative of bacterial meningitis, necessitating the need for culture of the cerebrospinal fluid (**11**).

Table (4): Indications for lumbar puncture after a febrile seizure

1- Any child with physical examination findings suggestive of meningitis
2- Simple febrile seizures
a- Children between 6 and 12 months old if immunization status is unknown or incomplete
b- Children on antibiotics
3- Complex febrile seizures if under 12 months old
4- All children with febrile status epilepticus

There are no febrile seizure–specific electroencephalogram (EEG) findings, and EEGs are of limited value to predict recurrence of a febrile seizure. A routine EEG is not helpful and is not recommended in the evaluation of a neurologically healthy child with a simple febrile seizure (**2**). An EEG should be considered in children who have prolonged or complex febrile seizures, have a recurrence not associated with fever, or in children with recurrent febrile seizures who have developmental delays or neurologic deficits (**73**).

Skull radiographs are useless in the evaluation of a child with febrile seizure. Neuroimaging studies such as magnetic resonance imaging (MRI) or cranial computed tomography (CT) are not routinely indicated in children with febrile seizures. MRI or CT should be considered in patients with signs of increased intracranial pressure, focal neurologic abnormality, suspected structural defect in the brain, abnormally large heads, and severe head injury (**74**).

Complications:

Febrile seizures are extremely frightening and emotionally traumatic for parents. The condition can cause undue anxiety and panic to parents who may be under the impression that their child might die during the seizure and brain damage is inevitable if their child is going to survive(**75**).

It is the seizure type that defines risk of future epilepsy. It is generally believed that children with simple febrile seizures are not at increased risk for the later development of a neurologic deficit, and their intelligence and cognitive function are not affected (**76**). Other reports stated that children with simple febrile seizures have a slightly higher risk of subsequent epilepsy of around 1% compared with the incidence in the general population of approximately 0.5% (**77**).

The risk of future epilepsy in children with complex febrile seizures is around 4–6%, depending on the number of complex features. Other risk factors for the development of epilepsy include shorter duration of fever (<1 hour) before the seizure, an onset of febrile seizures before the age of 1 year or after the age of 3 years, multiple episodes of febrile seizures, an underlying neurodevelopmental abnormality, a positive family history of epilepsy, and epileptiform discharges on EEG. Generally, the number of febrile seizures does not alter the risk of subsequent epilepsy (**78**).

If Febrile seizures, are recurrent, severe, and prolonged, may induce persistent alternations of hippocampal neuronal circuits in balance between excitatory and inhibitory responses as well as mesial temporal sclerosis, leading to epileptogenesis following febrile seizures(**79**).

In contrast to single febrile seizures, recurrent febrile seizures were significantly associated with an increased risk of delayed vocabulary development. Early symptomatic syndromes eliciting neurodevelopmental clinical examinations (ESSENCE), refers to autism spectrum disorder, learning difficulty, developmental coordination disorder, and attention-deficit/hyperactivity disorder. It is found that the rate of ESSENCE in febrile seizures and epilepsy was significantly higher than in the total population without febrile seizures. Also a significant association was found between febrile seizures and developmental coordination disorder, autism spectrum disorder, and intellectual disability (**80**).

Children with febrile seizures, mainly those with complex febrile seizures and febrile status epilepticus, can die suddenly and unexpectedly in a manner reminiscent of adult sudden unexpected death in epilepsy. It is suggested that febrile seizures could potentially contribute in a risk-stratification model for sudden cardiac death (**81**).

Management:

Intervention to stop the seizure usually is unnecessary as the seizure has typically resolved by the time the child is evaluated by a physician. On the other hand, treatment should be initiated if the seizure is still ongoing by the time the child arrives at a medical facility. If that is the case, the child can be treated with intravenous lorazepam (0.05–0.1 mg/kg) or diazepam (0.1–0.2 mg/kg) which is very efficient in terminating the seizure. When the intravenous route is unavailable or inaccessible, diazepam administered rectally (0.5 mg/kg), buccally (0.5 mg/kg), or intranasally (0.2 mg/kg) (**82**).

It is important to ensure adequate hydration by encouraging the child to drink, and paracetamol or ibuprofen can be administered to relieve discomfort caused by the infection. Parents should be made aware that administration of antipyretic drugs is to relieve the discomfort caused by the infection, not to reduce the risk of FS (**83)**. Table (5) shows a list of drugs commonly used in the Emergency Room for children presenting with FS. In the case of bacterial, febrile infections, such as tonsillitis, otitis media, or pneumonia, antibiotics should be administered.

Table (5): Drugs commonly used for children with febrile seizures (FS) who present to the Emergency Room (66).

Name	Dosage	Administration Route	Frequency	Maximum Dosage	When Used
Paracetamol	15 mg/kg	Oral, rectal or intravenous (IV) during resuscitation	Every four to six hours	Five within 24 h	For pyrexia in children with FS
Ibuprofen	5–10 mg/kg	Oral	Every six to eight hours	Four within 24 h	For pyrexia in children with FS unless they are dehydrated
Diazepam	0.25 mg/kg 0.5 mg/kg	IV or intraosseous Rectal	A second dose may be given ten minutes after the first	Only two doses of benzodiazepines are to be used, regardless of the agent selected and if they are administered alone or in combination	For an actively convulsing child whose seizures have lasted more than five minutes
Lorazepam	0.1 mg/kg	IV	A second dose may be given ten minutes after the first	Only two doses are to be used	For an actively convulsing child whose seizures have lasted more than five minutes
Midazolam	0.15–0.2 mg/kg	IV	A second dose may be given 10 min after the first	Only two doses are to be used	For an actively convulsing child whose seizures have lasted more than five minutes
0.9% sodium chloride solution	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

Febrile status epilepticus rarely stops spontaneously and often requires more than one antiepileptic medication to control. The initial treatment consists of intravenous administration of lorazepam (0.1 mg/kg) or diazepam (0.2 mg/kg). If the seizures continue after 5 minutes, the dose of lorazepam (0.1 mg/kg) or diazepam (0.2 mg/kg) can be repeated intravenously (**84**). If the seizures continue for 10–15 minutes, second-line antiseizure medications such as levetiracetam, fosphenytoin, valproate, or phenobarbital may be necessary (**85**). Table (6),shows a list of Medications used to treat febrile status epilepticus-

Table (6):Medications used to treat febrile status epilepticus-(68)

First-line medications (may repeat dosing after 5 minutes)	**Second-line medications**
Lorazepam 0.1 mg/kg IV. Maximum dose 4 mg.	Levetiracetam 60 mg/kg IV. Maximum dose 4500 mg.
Diazepam 0.2 mg/kg IV. Maximum dose 10 mg.	Fosphenytoin 20 mg phenytoin equivalents IV. Maximum dose 1500 mg.
If IV access not available:	Valproate 20–40 mg/kg IV.
Midazolam 0.3-0.5 mg/kg buccally, OR 0.2 mg/kg intranasally, OR 0.1–0.2 mg/kg IM. Maximum dose 10 mg.	Phenobarbital 20 mg/kg IV. Maximum dose 1 gram.
Diazepam 0.5 mg/kg buccally, OR 0.2 mg/kg intranasally, OR 0.5 mg/kg rectally. Maximum dose 20 mg.	

Vital signs such as temperature, heart rate, respiratory rate, and blood pressure should be monitored during a seizure. Children admitted to hospital should be monitored with continuous pulse oximetry. Hypoxic children should be given supplemental oxygen through nasal cannulae, head box, face mask, or high-flow delivery device to maintain SaO_2 >92%. Removal of excessive clothing and blankets may help to bring down the fever. An antipyretic may be given if the fever is high enough to cause discomfort in the child. Normalization of the body temperature might not prevent further febrile seizures; but the use of an antipyretic may make the child more comfortable. The cause of the fever should be treated whenever possible(**2**).

Hospital admission should be considered to those suspicious to have a serious infection and those with prolonged and/or focal seizures, especially if there is delayed recovery to baseline or residual neurological findings (**87**).

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