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Review Article

Clinical review of febrile seizure and updates

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ABSTRACT

Febrile seizure (FS) is one of the most common seizures seen in infant and pre-school age. There are two types of FSs, simple and complex. Simple FS are commonly benign, but complex FS have long-term effects. Most children with FS have normal growth and development after the attack; however, recent evidences suggest that a small group of children presenting fever with seizure may subsequently develop epilepsy or recurrent seizures. Diagnosis is mainly based on clinical presentation, electroencephalogram, lumbar puncture, and neuroimaging, which can be applied based on clinical scenario, but not routinely. Treatment is principally acute management of seizure along with address of underlying etiology and intermediate prophylaxis for preventing further attack. Pediatrician should be familiar with the proper diagnosis and management of this condition. This review will highlight an update on the current diagnostic and management issues of FS.

Keywords: Febrile seizure, Anticonvulsant, Epilepsy, Management, Febrile status epilepticus

INTRODUCTION

Febrile seizure (FS) is one of the most common types of seizure in children. It is usually defined as seizures occurring in children (6 months to 5 years of age) in association with a fever more than 100.4°F (38°C), who have no evidence of any intracranial cause (e.g., head trauma, infection, and epilepsy), or any underlying definable cause of seizure (e.g., hypoglycemia, dyselectrolytemia, and drug withdrawal), or any history of an afebrile seizure.[1-4] ILAE defines FS as a seizure occurring in children aged at least 1 month, associated with a fever which is not originated by any infection of the central nervous system (CNS). A child diagnosed with FS must not have a previous unprovoked seizure, neonatal seizure, or any acute symptomatic seizures.[5] National Institute of Health, USA consensus conference definition of FS illustrates an event typically occurring between 3 months and 5 years of age associated with febrile illness without any evidence of intracranial infection or defined causes.[6] Thus, there is variability of age in different current definitions.

FS is subdivided into two categories: Simple FS and complex FS [Table 1]. Simple FS is more common than complex FS, accounting for more than 70%.[7] Febrile status epilepticus (FSE) is a subgroup of complex FS accounts for 5% of all FS, which are prolonged, continuous, or intermittent seizures without consciousness procured and evolve into status epilepticus.[7,8]

FS is an utmost challenge in pediatric practice due to its high prevalence and tendency to recur. Updated guidelines for diagnosis and treatment of FS have been issued by the American Academy of Pediatrics (AAP) and the Japanese Society of Child Neurology in 2011 and 2015, respectively.[9,10] PubMed search did not find any more guidelines on FS as of publication of this review.

Table 1: Characteristics of simple versus complex FSs.[9]

Character	Simple FS (all of the following)	Complex FS (any of the following)
Age	6 months to 5 years	6 months to 5 years but may be younger age
Types of seizures	Generalized	Focal
Duration of seizure	Less than 15 min	Prolonged, (≥15 min)
Occurrence	Once in 24 h	Recurs within 24 h
Associated neurological condition	No previous neurologic problem	Developmental delay or focal neurologic signs
Post-seizure complication	No postictal pathology	Todd's paresis may be present, seizure may persist for>30 min

FEBSTAT STUDY

Consequences of Prolonged FSs (FEBSTAT) was a prospective multicenter study that assessed the relationship between prolonged FSs and acute hippocampal injury, progress to mesial temporal sclerosis, temporal lobe epilepsy, and hippocampal impairment. The study enrolled 199 children of 1 month to 5 years age who had a FS that persisted more than 30 min.[11,12] Most of the children had focal seizures that were generally first FSs. Human herpes Virus (HHV)-6B infection is commonly associated with FSE and HHV-7 infection was less frequently related with FSE.[13] Younger age and developmental delay were associated with prolonged FS.[14] FSE seldom terminated spontaneously, was fairly resistant to drugs, and even with treatment continued for a significant period of time. Prompt initiation of treatment results in shorter total seizure duration.[15]

The study was established, FSE seldom causes cerebrospinal fluid pleocytosis.[16] The study inferred that electroencephalogram (EEG) findings within 72 h of FSE (focal slowing or attenuation) might be used as a sensitive marker of acute injury linked with FSE.[17] Developmental abnormalities of the hippocampus especially hippocampal malrotation were more frequent in the FSE group.[18] Risk for a subsequent FSE was remarkably increased in FSE versus simple febrile seizure (SFS). Magnetic resonance imaging (MRI) abnormality might increase 3.4-fold ($P < 0.05$) risk of FSE and also increased the recurrence risk when FSE was compared to SFS.[19]

Search strategy

A PubMed, Cochrane, ILAE, and different guidelines searches were conducted in November 2020 using the key terms "FSs" and "febrile convulsions." The search strategy covered meta-analyses, randomized controlled trials, systematic reviews, and observational studies.

EPIDEMIOLOGY

FS is the most frequently found neurological disorder, affecting 2–5% of children between 6 months and 5 years of age in the Western Europe and United States with an optimum incidence between 12 and 18 months.[4,9,20-23] However, most FS (90%) occur within the 1st 3 years of life.[24] Although FS is seen in all ethnic groups, it is more commonly seen in Asian population (5–10% of Indian).[25] The male-to-female ratio is roughly about 1.5–1.8:1.[22,26,27] The majority of FS occur within 24 h of onset of fever. FS often occur in the evening, peaking between 6 pm and 10 pm and most frequently in winter, and least frequently in summer.[28-31]

ETIOLOGY AND PATHOGENESIS

FS is an age-dependent response of immature brain to fever.[32] The exact etiology is still undetermined, though possible causal relationship with genetic and environmental factors have been reported [Figure 1].[33] Releasing high levels of cytokines like interleukin 1 and tumor necrosis factor during a fever may alter normal brain physiology including certain temperature sensitive ion channels, triggering seizures.[34] Developing brain especially under 3 years has inherent increased vulnerability to neuronal excitation and low seizure threshold that explains high fever related seizure burden in children.[31]

Various patterns of inheritance have been demonstrated, for example, an autosomal dominant inheritance with reduced penetrance and a polygenic or multifactorial inheritance.[2,29,35-45] The concordance rate in monozygotic and dizygotic twins is about 35–69% and 14–20%, respectively. The genes and loci of chromosomes that might increase the risk of developing FS have been mapped [Table 2].[33,46]

FS may develop due to mutations in the gene that encodes for the γ-aminobutyric acid A receptor and sodium channels.[36] Mild loss of function or polymorphisms in *SCN1A* gene of $Na_V1.1$ channels may cause a remarkable portion of FS.[47] This mutation depletes peak sodium current for positive shift in the voltage dependent activation when expressed in non-neuronal cells.

Perinatal stress and exposure to nicotine and/or alcohol may potentiate FS due to increase in cortisol level in the offspring.[48-50] Approximately 80% of cases of FS are related with viral infection and the most frequent infections are middle ear infections, tonsillitis, sinusitis, pneumonia, bronchiolitis, tooth infections, and gastroenteritis.[51-53]

Although vaccine is generally well-tolerated, transient adverse events such as FS are rarely experienced after vaccination.[54] FS usually occur within 3 days after Diphtheria, tetanus toxoids and whole-cell pertussis vaccine, 2 days after Pneumococcal conjugate vaccine 7 vaccine, and

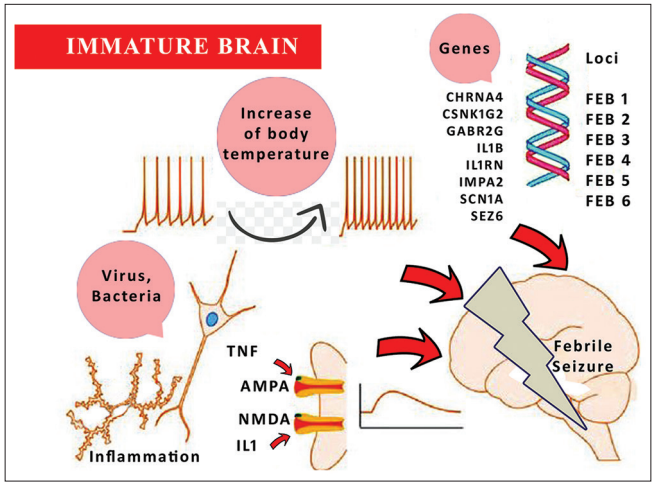

Figure 1: Mechanism of febrile seizure.[33]

Table 2: Different mutations and their clinical correlations.[33,46]

Gene	Loci	Chromosome	Clinical synd romes
GRCH38	FEB1	8q13-q21	FS
	FEB2	19p13.3	FS(Most common)
SCN1A	FEB3A	2q24	Simple FS
ADGRV1	FEB4	5q14-q15	FS
AKAP18		6q22-q24	Simple FS
GABRG2/ C588Tgene gene, encoding the GABA (A) subunit receptor	FEB8	5q34	Febrile convulsion with or without absence seizure
Interleukin 1 beta (-511)		1q31.	Increase frequency of FS (IL-1 beta-polymorphism)
IFI44L		1q31	FS
TMEM16 family gene		12q21.33	FS

FS: Febrile seizure

24 h after Measles Mumps Rubella vaccine.[55-58] Diphtheria, tetanus and acellular pertussis vaccine has fewer chances of FS compared to whole-cell vaccine as it contains minimum number of proteins which does not induce the IL-1â Production (Box 1).[59,60]

RISK FACTORS

The average risk of recurrence is 33%.[61] The major risk factors for recurrence are positive family history, the first FS under the age of 18 months, and 1st episode of complex FS.[4] It has been illustrated that the peak temperature in lieu of the rapidity of the temperature upraise is the most remarkable risk factor for developing first FS.[21,31,62-65] However, the number of FS does not alter the risk of subsequent epilepsy.

Iron is essential for certain neurotransmitters function and thus iron-deficiency anemia may predispose FS.[52,66] In a Bangladeshi study, the authors have showed that mean Zinc concentration in both serum and CSF was significantly lower among children having FS than their matched non-FS peers. Hence, Zinc deficiency is identified as a risk factor for FSs.[67-69] Low serum Vitamin B12 and folic acid level decrease a child's threshold for seizure and may be a risk factor for FS and recurrent FS.[66] Road traffic noise and air pollution during childhood are related with a bit higher risk for FSs, following a compressed exposure–response link.[51] Traffic noise closely associated with stress and sleep disturbance which may be assume mechanisms beyond a relation with increase vulnerability to viral infection. Air pollution exposure is connected with upper airway infection. Some authors mentioned that few risk factors are responsible for developing FS, recurrent FS and also described the chance of subsequent epilepsy in various seizure semiology (Box 2, 3).[70-75]

CLINICAL EVALUATION

In most cases, FS occur within 24 h of the fever.[53] Seizures occurring for more than 3 days after the onset of fever should be suspected for other differentials.[76] Loss of consciousness with breathing difficulty, pallor, or cyanosis at the time of seizure is a common feature.[77] Atonic and tonic spells have also been reported.

A detailed history should be obtained to evaluate the cause and characteristics of fever including fever onset to the occurrence of seizure, duration and the peak temperature of fever, duration of postictal drowsiness, and seizure semiology. The history should also comprise prior seizure and whether the child was recently attended day care, vaccinated, or treated with an antimicrobial agent. Immunization status, developmental milestones, CNS trauma, potential exposures to infection, toxin ingestion, and history of febrile and afebrile seizures among any family member(s) should also be inquired.[23] If postictal drowsiness is unusually prolonged, one should rule out CNS infection in addition to other features that may be related to meningoencephalitis.

A thorough physical assessment must be done to evaluate the cause(s) of the fever. A reddish bulging eardrum, exanthem, a beefy red pharynx, swollen, and erythematous tonsils may give hint to the fever etymology. The assessment should look for depressed sensorium, irritability, lethargy, bulging or tense fontanel, nuchal rigidity and Brudzinski's or Kernig's sign to exclude CNS infection such as meningitis or encephalitis.[78] A sequential neurological assessment should also be performed, comprising the level of consciousness, muscle power and tone, and deep tendon reflexes. Any focal sign should pay due attention. Fundoscopy should be done to rule out papilloedema.

LABORATORY INVESTIGATIONS

Blood for complete blood count, electrolytes, calcium, phosphorous, magnesium, glucose, urea, creatinine, and bacterial culture are usually not helpful in evaluating a child with FS but required for identification of cause depending on clinical presentation.[8,79] The laboratory investigations should be individualized based on the history and physical examination.[3,9,80]

Lumbar puncture (LP) is not essential in the majority of well-appearing children who have rapidly returned to quite normal baseline activities, or having no lethargy, neurological deficit after post-ictal period.[4] The AAP strongly urges pediatricians to consider a LP in child with FS in following situtions:[2,3,5,81,82]

1. Less than 12 months of age who present with FS, especially if the vaccination status for *Streptococcus pneumoniae* and *Haemophilus influenzae* is deficient or unknown
2. Younger than 6 months with a simple FS
3. At any age: Altered alertness, lethargy, and/or meningeal symptoms or FSE
4. Occurrence of seizure after the 2nd day of fever, who have taken prior antimicrobial therapy.

EEG has limited value to predict recurrent FS.[5,8,21] A routine EEG is not recommended to evaluate neurologically healthy child with a simple FS.[8,10] A 2017 Cochrane systematic review also found no diagnostic value of EEG and its timing after complex FS.[83]

An EEG should be considered in children with FS who have[4,53,84,85]

1. Complex FSs, especially those with multiple or prolonged seizures
2. Recurrent FSs with developmental delays.

EEG showed bilateral posterior slow wave activity in as much as 80% of cases when done on the same day of the seizure, which usually disappears by 7–14 days.[86] Although EEG abnormalities may persist over several years, yet none of these abnormalities have been associated with increased risk of recurrent FS or future development of epilepsy.[87]

Neuroimaging studies such as computed tomography (CT) and MRI of brain are not routinely indicated in children with FS.[20,21] MRI or CT should be performed in children with signs of-[4,22]

1. Raised intracranial pressure or abnormally large heads
2. Suspected structural defect in the brain, focal neurologic abnormality, and severe head injury
3. Neurodevelopment abnormality
4. FSE.

COMPLICATIONS

FS can be extremely panicked and emotionally traumatic for parents, though no association exists between FS and sudden unexplained death in childhood.[1,4,5,88-90] The seizure may be associated with postictal transient hemiparesis (Todd's palsy) or may have a prolonged period of postictal drowsiness.[2,22,69] Recurrent and prolonged FS may cause persistent alternations of hippocampal neuronal circuits or mesial temporal sclerosis, leading to refractory temporal lobe epilepsy.[1,14,88,91-92]

DISEASES THAT INITIALLY MAY PRESENT WITH SEIZURE PRECIPITATED BY FEVER[93-96]

Rare exceptional cases who presents with fever precipitated seizures should be evaluated critically with clinical evidence and if required by molecular study like clinical Exome sequencing for following diagnostic possibilities:

1. Generalized/genetic epilepsy with FSs plus
2. Dravet syndrome – suspects are prolonged febrile hemiconvulsive seizure and photosensitivity on EEG under 2 years of age.
3. New-onset refractory status epileptics
4. Febrile infection-related epilepsy syndrome
5. Hemiplegia Hemiconvulsive syndrome.

Above mention differentials should be excluded from FS and manage carefully in suspected scenario.

MANAGEMENT: COMMUNITY SETTING

Parents should be counseled about benign nature and favorable outcome, assure them that treatment is often unnecessary and rare association of simple FS with epilepsy.[26] In this context, organizing effective awareness programs for parents can be helpful.[3,83,88]

MANAGEMENT: AT HOSPITAL SETTING

Treatment should be initiated with intravenous (IV) lorazepam or diazepam if the seizure is still ongoing and repeat the dose if required [Table 3].[2,24,97,98] Per-rectal diazepam and buccal or intranasal midazolam should be administered as safe and effective alternatives, when IV route is unavailable or inaccessible.[3,24]

FSE often requires multiple antiepileptic medications to control as it is rarely stopped spontaneously.[15,24] If the seizures continue for 10–15 min, phenytoin or phenobarbital can be given intravenously [Table 3]. An additional dose of IV phenytoin should be given 10 min after the loading dose, only when seizures fail to stop. Howbeit, IV phenobarbital, valproic acid or levetiracetam can also be given alternatively.[98] In addition, the cause of the fever must be treated accordingly whenever possible.

Table 3: Emergent initial therapy for acute (ictal) management of FS in children.[3,8,35]

Antiepileptic	Administration route	Dose
Midazolam	Oral	0.5 mg/kg BW, repeat in 10 min if necessary
	Nasal	0.20.5 mg/kg BW divided in each nostril, maximum 10 mg
	IV	0.2 mg/kg BW or 0.15 mg/kg BW by infusion
	Intramuscular	0.2 mg/kg BW or 510 mg, buccal dose
Diazepam	Rectal	0.30.5 mg/kg BW, max 10 mg, bolus speed of 5 mg/min, repeat in 10 min if necessary
	IV	0.1–0.2 mg/kg BW, 0.01 mg/kg BW/min by infusion
Lorazepam	IV	0.1 mg/kg BW (maximum 4 mg in children heavier than 40 kg)
Phenytoin	IV	20 mg/kg BW, if required, repeat 5–10 mg/kg BW
Phenobarbital	IV	20 mg/kg BW, if required, repeat 20 mg/kg BW
Valproic acid	IV	20–40 mg/kg BW
Levetiracetam	IV	20–60 mg/kg BW

BW: Body weight

As per AAP recommendation, clinically stable children older than 18 months should not be hospitalized; rather parents should be trained for home management [Box 5].[37,99] Besides, previously diagnosed children with recurrent FS also do not require hospitalization [Table 1].[26,39]

Hospital admission should only be considered to children in following conditions:[24,77]

1. Suspicion of any serious infection
2. Who have prolonged and/or focal seizures, particularly if there is residual neurological findings or delayed recovery to baseline
3. Less than 18 months of age, for observation and possible LP.

PREVENTION OF FURTHER ATTACK

A Cochrane systematic review (2017) stated that daily administration of Phenobarbital, valproic acid or other antiepileptic drugs are effective in the prevention of FS.[2,22] The potential adverse effects of these drugs outweigh their benefits.[5] Therefore, continuous prophylaxis with anticonvulsants is not necessary for simple or complex FS.[5,21,24] Furthermore, the AAP does not recommend continuous antiepileptic therapy with valproic acid or Phenobarbital for recurrent FS prevention.[5]

Box 1: Cause and factors associated with febrile seizures.[35,48-53]

Familial: Genetics [Table 2]	Channelopathies: Sodium (mainly) potassium and calcium channels GABA-A
Viruses: Influenza and Parainfluenza virus, Respiratory syncytial virus, Adenovirus, Herpes viruses, Cytomegalovirus, Chickenpox, Corona virus, Rotavirus, and Entero viruses.	Vaccination: Diphtheria, tetanus toxoids and whole-cell pertussis, Pneumococcal conjugate vaccine 7, Measles Mumps Rubella Cytokines: IL 1, tumor necrosis factor
Bacteria: *Escherichia coli*, *Shigella dysenteriae*, *Streptococcus pneumonia*, and *Salmonella enteritidis*	Vitamin (Vitamin B12) and folic acid
Maternal: Antenatal maternal stress, prenatal exposure to nicotine and/or alcohol Environmental: Exposure to traffic noise and air pollution	Neonatal: Prematurity, hypoxic ischemic encephalopathy, Postnatal treatment with corticosteroids, Neonatal brain injury Cerebral dysgenesis

Intermittent Prophylaxis: Intermittent administration of diazepam (0.3–0.5 mg/kg/dose 8 hourly, maximum 10 mg) or oral clobazam (1 mg/kg once daily, maximum 20 mg) at the onset of fever for initial 3 days has been shown to be effective in recurrent FS prevention in 80% of cases.[5,100,101] Some studies concluded that intermittent clobazam therapy seems more beneficial to diazepam due to similar efficacy, long half life time, and lower side effect such a drowsiness, sedation, and ataxia.[102,103] Besides, intermittent therapy may also be considered in those at high risk for recurrence and in high parental anxiety, especially with a history of multiple and/or prolonged FSs.[3,5,10,24]

Acetaminophen and Ibuprofen are effective antipyretics to relieve fever, though antipyretic agents do not minimize the risk of a FS or a seizure recurrence[2,27,104] Notwithstanding, no evidence was found to be effective to prevent recurrent FS through physical methods of temperature reduction (e.g., direct fanning of the child, tepid sponging, removing clothing, and cooling room).[10,20,29] Universal childhood vaccinations should be strongly encouraged to reduce the risk of FS in the coming years. However, prophylactic antipyretic prior vaccinations are not statistically indicated to reduce the rate of FS recurrences.[100]

PROGNOSIS

The prognosis is favorable in the majority cases as it is typically benign and self-limiting.[24] Usually, children surpass this condition by 6 years of age. About one-third of FS will have a recurrence during early childhood, wherein only <10% will have ≥3 recurrences.[22-24,26] Approximately, 90%

Box 2: Risk factors for the first FS, recurrent FS, and epilepsy after FS.[2,21,31,35,63,65,70-74]

First FS	Recurrence after 1st attack of FS	Epilepsy after FS
In Population i. 1st or 2nd degree relative with history of FS (20% affected sibling and 33% affected parents) ii. Neonatal nursery stay of>28 days iii. Developmental delay In Children with a febrile illness iv. 1st or 2nd degree relative with history of FS v. High peak temperature	i. Age<18 months ii. Family history of FS iii. Low peak temperature iv. Attendance at day care v. Less than 1 h of fever prior the seizure vi. Frequent febrile illnesses vii. Multiple FSs during the same febrile illness viii. Neurodevelopmental delay	i. Shorter duration of fever (<1 h) before the seizure ii. Onset of FS before 1 year or after 3 years of age iii. Neurodevelopmental abnormality iv. Complex FS v. Family history of epilepsy vi. Low Apgar at 5 min at birth vii. Epileptiform discharges on EEG

FS: Febrile seizure

Box 3: Spectrum of febrile seizure and chance of subsequent epilepsy.[8,21,31,53,75]

	Chance of epilepsy
Simple febrile seizure	1%
Recurrent febrile seizures	4%
Complex febrile seizures	6%
Family history of epilepsy	18%
Neurodevelopmental abnormalities	33%

Box 4: Initial management of FS at home.[2,7,8]

1. Remain calm, no panic, loosen clothes, secure the child from injury
2. Do not introduce fingers or objects to open the mouth or to give any drugs or fluids
3. Do not recommend to wet the child during the seizure
4. If unconscious, to decrease the risk of aspiration, place the child in lateral position
5. Once the seizure is controlled, make sure that child is in lateral position to quicken recovery without obstructing airway
6. In recurrent FS, administer initial rescue therapy if seizure lasts>5 min
7. Administer per-rectal diazepam or nasal/buccal midazolam as first line treatment [Table 3]
8. Seek hospital admission if the seizure lasts>5 min or more
9. A medical intervention is crucial in the following cases: (a) Seizures duration of>15 min or not revoking after treatment, (b) Recurrent seizures, (c). Focal seizures, (d) presence of prolonged consciousness and/or postictal palsy

FS: Febrile seizures

recurrences occur within 2 years wherein 75% happen within 1 year.[26,53] Children without any of the above mentioned risk factors are accounted for only 4% chance of recurrence, whereas those with all of the risk factors have up to 80% chance of recurrence (Box 2).[21,24] The majority of children with simple FS have normal growth and development but complex FS and FSE may turn into epilepsy.

Box 5: Febrile status treatment in a hospital environment.[80,100]

1. Open the airway, aspirate secretions, maintain adequate ventilation, and ensure perfusion
2. Obtain venous access
3. Monitor vital signs
4. Oxygen supplementation, if necessary (SpO_2 < 92%)
5. Administer diazepam intravenously or per-rectal
6. Monitor arterial blood gas analysis, electrolytes and blood glucose
7. If convulsion does not subside, ask pediatrician to determine treatment options
8. FSE should be treated under the same treatment guideline for pediatric a FSE
9. The measures for fever reduction must be taken after benzodiazepine administration.

COUNSELING

FS in children can give rise to significant parental anxiety and fear of the death of their child. It can be alleviated by regular educational programs by specialized health workers to explain the benign nature of the condition and lack of any significant association with future epilepsy.[24,44] It is important to teach about home management and basic resuscitation measures to every parent who has children with febrile convulsions.[5,24]

CONCLUSION

Worldwide, FS is one of the most common age-dependent seizures, especially in South Asia. FS has genetic predisposition with a notable vulnerability of the developing brain to the effects of fever. Almost one-third of children have chances of recurrence, but they outgrowth the condition after 5 years of age. Although continuous anti-epileptic therapy can prevent recurrent FS and surpass the few risks of FS, yet it cannot prevent subsequent epilepsy. Besides, it has high potentiality for adverse effects. Hence, long-term therapy

is not recommended. However, intermittent therapy with diazepam or clobazam at the onset of fever may be advised to prevent recurrent FS in high parental anxiety and/or multiple recurrences of FS. Prolong seizure must be treated acutely. Parental counseling on home treatments and about the risks associated with FS is the greatest contribution that the pediatrician can make for the care of children with FS.

Key message

- FS has slightly male preponderance.
- Usually autosomal dominant in inheritance.
- Low age at onset for FS has appeared a crucial predictor for a repeated FS.
- Simple FS are common, benign, and self-limited.
- Children with complex FS are at risk of developing epilepsy.
- FS usually does not cause intellectual or neurologic damage.
- EEG and neuroimaging are not indicated in the routine evaluation of simple FS.
- Acute treatments are indicated when seizure is prolonged.

Limitations

While the review contains updated clinical recommendations, still there are many unanswered or controversial problems. Many limitations might be due to the lack of conclusive clinical evidences, particularly regarding the prophylactic use of intermittent drug in FS, and FSE. Future clinical research is required to explain these unanswered questions. Howbeit, this review may play a role in raising issues in the treatment of FS and in prompting further investigations or research.

Author contributions

Hossain MM. wrote the first draft of the manuscript; Saha N critically revised the text and made substantial scientific contributions. Both the authors approved the final version of the manuscript.

Declaration of patient consent

Patient's consent not required as there are no patients in this study.

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Conflicts of interest

There are no conflicts of interest.

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