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Recent Advances in the Diagnosis and Treatment of Febrile Seizures

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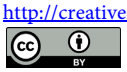

Abstract

Febrile seizures (FS) are the most common convulsive disorders in children, occurring in children between 6 months and 5 years of age, with peak incidence between 12 and 18 months of age. The condition usually has a benign course and rarely leads to brain damage, but it can cause great psychological stress for parents—who often mistakenly believe their child is dying during a seizure. CFS and some SFS carry a risk of recurrent seizures and development of epilepsy, which may affect the child's neurological development, cause harm to the child, and impose an mental and economic burden on parents. This article elaborates on the classification, diagnosis, optimization of treatment strategies, mechanism study and risk assessment of FS.

Keywords

Febrile Seizures, Treatment Optimization, Risk Assessment

1. Introduction

Febrile seizures are the most common cause of seizures in children, and their pathogenesis has not yet been fully elucidated. It is currently believed to be related to a combination of factors, such as immature cerebral development, imperfect formation of myelin sheaths, genetic susceptibility, and inflammatory response. Although most simple febrile seizures (SFS) have a favorable prognosis, the American Academy of Pediatrics guidelines indicate that children with FS may have the following poor prognosis: (1) memory loss; (2) increased risk of epilepsy; (3) risk of FS recurrence; and (4) risk of death. Recurrent seizures not only aggravate parental anxiety, but also increase the financial burden of the family and the consumption of social healthcare resources by frequent medical visits. The aim of this paper is to provide pediatricians and neurologists with the latest diagnostic and therapeutic norms

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of FS, optimize treatment strategies, and guide parents to master the emergency treatment methods in the acute phase, so as to alleviate their psychological pressure.

2. Classification and Clinical Characteristics

FS is categorized into simple FS, complex FS, and Febrile Status Epilepticus (FSE). The classification criteria are based on the following: duration of seizures, number of convulsive recurrences within 24 hours of fever progression, seizure type, and post-seizure status (Table 1). Simple FS accounted for 70% - 80% of cases, with most onset at 6 months of age to 5 years of age, presenting as generalized seizures with a duration of <15 min, one seizure in a single febrile episode, and no abnormal neurologic signs; complex FS accounted for 20% - 30% of cases, with most onset <6 months of age or >5 years of age, with neurologic abnormalities prior to the onset of the attack, and presenting as either a focal seizure or a generalized seizures, seizure duration ≥15 min or ≥2 seizures in one heat session, and seizures may be followed by neurologic abnormalities such as Todd's palsy [1]. Traditionally, FSE has been defined as a sustained convulsive seizure of at least 30 min, or repeated seizures within 30 min with incomplete recovery of consciousness in the interictal period. However, in 2015 the International League Against Epilepsy Task Force10 redefined the time criteria for status epilepticus (including FSE) as (1) generalized tonic-clonic seizures for 5 minutes, (2) focal seizures for 10 minutes, and (3) absence of consciousness for 10 to 15 minutes.

Table 1. Categorical features of simple versus complex febrile seizures (FS) [2].

	Simple FS	Complex FS
Duration.	< 15 min	≥15 min
Number of episodes in a single episode	1 episode	>1 episode
Seizure type	Generalized seizure	Partial seizure
Neurological signs	No abnormal neurological signs	Pre-onset neurologic abnormalities

Although simple febrile seizures usually have a benign course, some children with complex febrile seizures are at risk of developing epilepsy in adulthood [3], with a significantly higher risk of subsequent epilepsy (especially temporal lobe epilepsy), possibly related to hippocampal sclerosis. 2023 ILAE (International League Against Epilepsy) recommended that the term "complex FS" be removed and replaced with "FS with long-term risk factors", emphasizing individualized risk assessment. In 2023, the ILAE (International League Against Epilepsy) recommended that the term "complex FS" be removed and replaced with "FS with long-term risk factors", emphasizing individualized risk assessment.

3. Diagnostic Progress

The evaluation of a child with febrile seizures generally begins with history taking

and physical examination to determine the cause of the fever. Key elements of history taking include the specific presentation and duration of the convulsive seizure, recent illness or antibiotic use, personal or family history of seizures, record of recent vaccinations, and immunization status for Haemophilus influenzae type B and Streptococcus pneumoniae. Physical examination needs to focus on screening for signs of meningitis, such as depressed state of consciousness, irritability, bulging fontanel, nuchal rigidity, and hypotonia.

Intracranial infections such as meningitis and encephalitis must be excluded as early as possible in infants and young children, as their symptoms may be highly atypical [4]. Aetiologic investigation should be performed in children with fever with seizures, as there are multiple differential diagnostic possibilities. Simple febrile seizures without other symptoms may not warrant additional testing. After a thorough evaluation, complex febrile seizures are usually diagnosed by exclusion [5]. Complete blood counts, serum electrolytes, calcium, magnesium, phosphorus, or glucose testing do not usually change the treatment plan for febrile seizures, but are only indicated when there is a clinical indication such as persistent postictal lethargy or suspected bacteremia. The American Academy of Pediatrics guidelines for screening for first simple febrile seizures recommend that physicians focus on the cause of the fever in children seen within 12 hours of the onset of the seizure. Recent U.S. studies have shown that the probability of bacterial meningitis presenting as a first simple febrile seizure is extremely low, and these recommendations may not need to be strictly enforced. However, in areas with a high prevalence of malaria, these assessment criteria may be more difficult to apply. In children with malaria fever with complicated febrile seizures, clinical identification of the presence of intracranial infection is often extremely challenging [6].

3.1. Lumbar Puncture

Lumbar puncture should be performed when the clinical history is suggestive of meningitis, but contraindications need to be excluded, such as the presence of increased intracranial pressure with altered consciousness, focal neurologic signs, impaired cardiorespiratory fitness, coagulation disorders, or infection at the puncture site. If there is a medical contraindication to performing lumbar puncture, anti-infective therapy should be initiated [7].

3.2. Electroencephalography (EEG)

Routine EEG is usually not required for simple FS, but electroencephalography (EEG) and cranial imaging may be necessary in children with 1) complex febrile seizures, 2) a history of recurrent febrile seizures (FS), and 3) concomitant neurologic abnormalities. EEG is not recommended after febrile seizures in children with a clear source of infection and in good health. If an EEG is performed, it should be performed at least 48 hours after the febrile seizures episode to avoid confusing postictal electrical activity with abnormal activity. It has also been

found that EEG abnormalities are not a reliable indicator of epilepsy. Thus, an early EEG abnormality after a first complex febrile convulsion is unlikely to reveal that a patient is at risk for epilepsy. Variables such as the patient's age, the timing of the EEG, and genetic disorders may influence the development of EEG abnormalities [8]. In children presenting with recurrent simple febrile seizures and a clear source of infection, there is no need to repeat this test, but it is critical to identify the cause of the infection and manage it appropriately [9].

3.3. Neuroimaging

Neuroimaging is not necessary in children with simple febrile seizures (FS). In children with complex febrile seizures but no neurologic abnormalities, there are usually no serious intracranial lesions (e.g., tumor-occupying lesions, hemorrhage, hydrocephalus, abscess, or hydrocephalus) that require immediate neurosurgical or pharmacologic intervention. Children with recurrent complex febrile seizures with other neurologic symptoms (e.g., abnormal head circumference, significant developmental delay, or persistent focal neurologic abnormalities) should be evaluated by magnetic resonance imaging (MRI).

4. Indications for Hospitalization

In children with simple febrile seizures who are clinically well and have a clear source of infection, hospitalization is usually not necessary. They can be discharged after a period of observation in the emergency department (six hours after the onset of the seizure is recommended). The following conditions require hospitalization or inpatient observation: (1) neurological abnormalities: the presence of lethargy, impaired consciousness, focal neurological signs, etc.; (2) the age of the first seizure is <18 months of age, especially those who have been treated with antibiotics; (3) the cause of the infection is not known or the infection is more severe; (4) the children with complex FS or persistent state of seizures; and (5) the children who have no clear family history of febrile seizures or epilepsy, and the cause of the seizure needs to be further investigated. further investigation of the etiology.

5. Treatment Optimization

5.1. Acute phase Treatment

1) General principles of treatment: Most FS lasts 1 to 3 min and usually does not require immediate use of anticonvulsant drugs. The focus of first aid should include: i) safety protection: keep the airway open, prevent falls or injuries; avoid inappropriate interventions (e.g. pinching, prying open the teeth, pressing or shaking the child). ii) positional management: use the lying head to the side or lateral position; timely cleaning of oral and nasal secretions; preventing accidental inhalation or asphyxiation. iii) life support: continuous monitoring of vital signs, to ensure normal cardiorespiratory function, oxygenation if necessary, establish an intravenous access. Establish intravenous access.

2) Indications for pharmacological intervention: For children with persistent seizures at the time of emergency admission, seizure duration >5 min, accompanied by fever, and recurrent seizures, antitussive drugs should be given [10].

3) Prehospital emergency medication regimen: 1. Diazepam: rectal administration (0.5 mg/kg), oral mucosal administration (0.4 - 0.5 mg/kg); 2. Midazolam: intranasal administration (0.2 mg/kg), etc. [11]. Studies have shown that diazepam given orally or rectally at the beginning of febrile illness, although statistically significant, has a limited clinical effect and only modestly reduces the probability of febrile seizures [12].

4) In-hospital treatment plan: i) First-line drug: diazepam IV: Dose: 0.3 - 0.5 mg/kg (single dose ≤10 mg); speed 1 - 2 mg/min. Precautions: terminate the administration of the drug when the seizure stops; if the seizure is still uncontrolled or recurs after control after 5 min, a dose can be repeated; if it is still ineffective, it is treated as a persistent state of seizures. The drug has an onset of action of 1 - 3 min, but if the injection rate is too fast, respiratory depression, bradycardia, hypotension and other adverse reactions may occur. ii) Alternative options (without the establishment of intravenous access): midazolam intramuscular injection: 0.3 mg/kg (a single dose ≤ 10 mg); 10% chloral hydrate solution enema 0.5 mL/kg. Clinical evidence: randomized controlled trials have confirmed that the efficacy of midazolam is superior to diazepam. Diazepam.

For children with persistent FS, intravenous medication is needed to actively stop the seizures, with close monitoring of postictal vital signs and clinical manifestations, active antipyretic, and searching for and treating the causes of fever and seizures. If the seizures do not stop after 10 minutes, if the child continues to have tremors after the violent twitching stops, or if the seizures recur before the child regains consciousness, emergency care should be called immediately. Antibiotics should be given for bacterial infectious febrile illnesses such as tonsillitis, otitis media, or pneumonia. There is no clear evidence that treating simple febrile seizures prevents subsequent seizures. Complex febrile seizures usually do not stop on their own and therefore require therapeutic intervention [13].

5.2. Prevention Strategies

1) Intermittent prevention

Indications: (1) frequent convulsive seizures (≥3 in 6 months or ≥4 in 1 year); and (2) the development of a persistent convulsive state requiring anticonvulsant medication to terminate the seizure. Diazepam given orally at the onset of fever, 0.3 mg/kg every 8 h, ≤3 times is mostly effective in preventing seizures [14]. Intermittent administration of the new antiepileptic drug levetiracetam has been reported to prevent FS recurrence [15]. Carbamazepine and phenytoin intermittent dosing is not effective in preventing recurrence. A retrospective study in China selected 68 children with febrile convulsion who were treated at the Pediatric Department of Zhongshan Torch Development Zone Hospital from June 2019 to November 2020. The patients were randomly divided into a control group and an observation group, with 34 cases in each group. The control group received diaz-

epam treatment, administered intravenously at 0.3 - 0.5 mg/kg once daily, with an infusion rate of 0.3 mg/min. The dosage could be adjusted appropriately based on the patient's condition, but the maximum daily dose did not exceed 4 mg. The observation group received additional phenobarbital treatment on top of the control group's regimen. The dosage and administration of diazepam were the same as in the control group, while phenobarbital was administered intravenously at 10 mg/kg once daily, followed by gradual dose reduction to reach a maintenance dose of 5 mg/kg after 24 hours. The treatment course for both groups lasted one week. The study demonstrated that the combination of diazepam and phenobarbital yielded better therapeutic effects in children with febrile convulsion. On one hand, diazepam, as a benzodiazepine, exhibits anticonvulsant, muscle relaxant, anxiolytic, and sedative-hypnotic effects [16]. Phenobarbital, a long-acting sedative-hypnotic, offers advantages such as prolonged duration of action and shorter onset time for anticonvulsant effects. The combined use of these two drugs produces synergistic effects, helping to reduce glutamate excitation and exert inhibitory effects on multisynaptic and monosynaptic transmissions in the central nervous system, thereby enhancing anticonvulsant efficacy [17]. The results of this study showed that the clinical indicators and treatment outcomes in the observation group were superior to those in the control group.

2) Long-term antiepileptic drugs

Several rigorously controlled trials have demonstrated that barbiturates such as phenobarbital are effective in reducing the rate of febrile seizure recurrence when given daily to achieve a blood concentration of 15 micrograms per milliliter or more. However, chronic phenobarbital regimens are rarely recommended because the risks may outweigh the benefits in most cases. Both human and animal studies have shown that daily valproic acid reduces the risk of febrile seizure recurrence, but this regimen is rarely used because infants and/or children with neurologic abnormalities who require prophylactic treatment are also at the highest risk of fatal idiosyncratic hepatotoxicity. Other prophylactic antiepileptic drugs such as phenytoin sodium and carbamazepine are also available. There is no evidence to support the therapeutic efficacy of newer antiepileptic drugs such as gabapentin, lamotrigine, topiramate, tiagabine, or aminocaproic acid in the treatment of febrile seizures [18].

6. Epilepsy Risk

10% to 15% of patients with epilepsy have a previous history of FS, and the percentage of secondary epilepsy after FS varies; the probability of secondary epilepsy in simple FS and complex FS is 1.0% to 1.5% and 4.0% to 15.0%, respectively [5]. The main risk factors for secondary epilepsy in FS include (1) neurodevelopmental abnormalities, (2) a first-degree relative with a history of idiopathic or hereditary epilepsy, and (3) Complex FS. The more risk factors one has, the higher the risk of secondary epilepsy [19]. Also short duration of fever before convulsive seizures and high number of FS seizures are associated with secondary epilepsy [20].

Some epilepsies and epileptic syndromes can have a FS onset, be characterized by "heat sensitivity" or present early in the course of FS, which should be taken into account. Epileptic syndromes associated with heat sensitivity include Dravet syndrome and hereditary epilepsy with generalized epilepsy with generalized epilepsy with febrile seizures plus (GEFS+). Clinical diagnosis and differential diagnosis should be based on the child's age of onset, seizure manifestations, electroencephalographic features, evolution of the disease course, and family history.

7. Neurological, Cognitive and Memory Dysfunction

It is currently accepted that short-term febrile seizures do not increase the risk of neurologic or cognitive dysfunction, but do slightly increase the occurrence of febrile seizures. This conclusion is more controversial for children with febrile convulsive sustained states (FSE), and as a result this group of children has been specifically studied. A 9-year follow-up study showed that the incidence of epilepsy after FSE was 14% (95% confidence interval) and that most epilepsy diagnoses occurred within two years of FSE.

8. Recurrence Rate

The risk of recurrence of febrile seizures ranges between 15% and 70% within 2 years of the first seizure, especially when the first seizure occurs at less than 18 months of age. The one-year recurrence rate after the first febrile convulsive sustained state (FSE) is 16% (95% confidence interval).

9. Mortality

A retrospective study evaluated the potential role of febrile seizures in sudden unexplained death in children (SUDC). The research team reviewed 622 consecutive pediatric deaths from 18 countries, aged 1 - 17 years, between 2001 and 2017. The study found that the prevalence of febrile seizures was as high as 28.8% (95% CI 23.3% - 34.2%) in the SUDC case group and 22.1% (95% CI 14.8% - 29.3%) in the group of sudden unexplained deaths in childhood, whereas the prevalence of febrile seizures in the general population was only 2% - 5%. It should be noted, however, that the study's definition of febrile seizures was broad and may have included children with other significant neurologic deficits (e.g., 10% of children who were receiving early cognitive intervention). However, the researchers recognize that the finding may be biased and should be considered a hypothesis-generating conclusion. Given the significance of the findings, there is an urgent need to validate these findings with further research to clarify epidemiologic characteristics and risk factor profiles. Such studies, when completed, may have an important impact on current knowledge and treatment options for febrile seizures.

10. Co-Morbidity of Mental Disorders

In a retrospective study based on a Danish population, one researcher found that children who experienced three or more febrile seizures had a 30-year risk of de-

veloping epilepsy as high as 15%, compared with a 2% risk for children who did not experience febrile seizures. As the number of febrile seizures increased, the risk of epilepsy and psychiatric disorders showed a stepwise increase.

11. Progress of Mechanism Research

11.1. Neuroinflammatory Mechanisms

Pro-inflammatory cytokines involved in febrile seizures' pathogenesis frequently reported in the research papers were 1) IL-1β, IL-6, IL-8, IL-12, IL-22, (TNF)-α, 2) IFN-γ (important activator of macrophages involved in autoimmune disorders), 3) transforming growth factor beta (TGF-β) suspected to trigger astrocytes' activity leading to EEG modified patterns toward seizures [20]-[23], and 4) high mobility group box 1 protein (HGMB1) secreted by activated macrophages and monocytes [24] However, the key interleukin involved in febrile seizures pathogenesis was IL-1β. HMGB1, IL-6, TNF-α positively correlated with elevated levels with IL-1 β [20] [24]. The most frequently encountered anti-inflammatory cytokines in the studied papers were IL-1RA, IL-10 and IFN-β. IL-1RA [25] counteracts IL-1 β, IL-10 inhibits TNF-α and IFN-γ, while IFN-β is a marker of Toll-like receptor-3 activation, suggesting a host response to viruses. It modulates the expression of both pro-and anti-inflammatory agents in the brain, reducing the blood–brain barrier permeability to inflammatory cells. Fever activates the thermogenic pathways of the immune system, producing the cytokines interleukin (IL)-1, tumor necrosis factor alpha (TNF-α), IL-6, and interferon. The anti-inflammatory cytokine IL-10 is also produced in response to IL-1, IL-6 and TNF-α [26]. Interleukin-1β (IL-1β) and IL-10 levels are elevated in children with febrile seizures [27]. IL-1β -mediated inflammatory response induces FS by enhancing neuronal excitability, and targeted inhibition of the IL-1 signaling pathway has emerged as a potential therapeutic direction.

11.2. Genetic Factors

GEFS+ syndrome: autosomal dominant inheritance, manifesting as febrile seizure plus (FS+) and multiple epileptic phenotypes, associated with mutations in SCN1A, GABRG2 and other genes. New causative genes: In recent years, gene variants such as HCN1 and STX1B have been found to be associated with FS and epilepsy, providing a basis for precise diagnosis and treatment. Twin and family studies have shown a significant heritability of FS etiology—febrile exacerbation type 1 (FEB1). Parametric linkage analysis of large family lines revealed FEB1 at 8q13-21, FEB2 at 19p13.3, and FEB3 at 2q23-24. Nonparametric analysis of 47 small family lines identified FEB4 at 5q14-15 [28]. The presence of voltage-gated sodium channel α-subunit 1 (SCN1A), α-subunit 2 (SCN2A), and γ-aminobutyric acid (GABA) receptor subunit coding genes are mutated. 25% - 40% of children with FS have a positive family history [29]. The probability of sibling FS correlates with the number of episodes in the child. Several twin surveys have shown that monozygotic twins have a significantly higher concordance rate of FS than dizy-

gotic twins [30]. Some children with FS develop non-specific types of generalized epilepsy later in life, which can be explained by "FS+". These patients or their family members have a background of FS (usually complex seizures and onset after 5 years of age), and epilepsy can present as multiple seizure types in childhood or adolescence. These families are associated with mutations in the genes SCN1A, SCN1B and GABAA receptor $\gamma 2$ subunit. The clinical phenotypes that constitute the genetic syndrome "generalized epilepsy with febrile seizures plus" (GEFS+) range from mild to severe, with the most severe being myoclonic atonic epilepsy [31]. Two types of mutations associated with genetic susceptibility to FS have been identified: 1) voltage-gated sodium channels, e.g., mutations in the SCN1B and SCN1A genes. 2) hyperpolarization-activated cyclic nucleotide-gated channels, e.g., mutations in the HCN1 and HCN2 genes have been identified in recent years. Provide basis for precise diagnosis and treatment.

11.3. Intestinal Flora

Animal studies have shown that intestinal microorganisms can affect the threshold of fever-induced seizures through the vagus nerve, suggesting that the regulation of bacterial flora may be a new target for intervention.

12. Future Direction

1) Precision prevention: Recent studies have found that elevated levels of cytokines in serum and cerebrospinal fluid are associated with febrile seizures. Ideally, preventive therapeutic drugs can be developed for specific cytokines. Recent studies have also revealed an association between iron deficiency anemia, vitamin D deficiency and febrile seizures. Correcting these deficiencies may play a role in future febrile convulsion prevention. In addition, a clinical trial funded by the National Institute of Neurological Disorders and Stroke is underway to evaluate the value of serum vasculitic hemophilic factor and peptide levels as biomarkers of febrile seizures. These data will be informative in differentiating febrile seizures from non-epileptic events such as chills with fever.

2) Neuroprotection: interventions (e.g., anti-inflammatory and antioxidant treatments) targeting hippocampal damage after FS are being validated in animal models.

3) For children with febrile convulsions, their young age and the symptoms caused by convulsions after acute onset have a significant impact on the psychological state of their families. Excessive worry about the harm of the disease to the children's physical and mental health as well as intellectual development results in heavy psychological burden and obvious negative emotions among family members, which in turn affects their rational judgment and active cooperation [32]. Traditional health education models have the drawback of passive acceptance and fail to consider the educational level and psychological characteristics of the recipients. The content is not comprehensive or systematic enough, and the methods are relatively monotonous, leading to low quality and ineffective outcomes of

health education [33]. Since the introduction of the PRECEDE-PROCEED model, it has continuously adapted to the needs of modern health promotion research and practice, gaining widespread clinical attention. It has been applied to guide health education and achieved certain results [34]. Parental education: standardized educational programs can reduce excessive visits to the doctor, parents and caregivers are often anxious after FS episodes, so it is important to properly educate them about the overall good prognosis and instruct them on how to deal with the child's fever and the acute phase of FS at home to reduce family anxiety.

13. Conclusion

The most common type of convulsion in children is febrile seizures. Most children have a favorable prognosis and only a few develop long-term health problems. Clinical confirmation of FS requires first ruling out intracranial infection, especially in cases of complicated FS. Treatment focuses on symptom control and management of the underlying cause of the fever. The criteria for evaluating children with FS have changed significantly. It is important to categorize FS according to seizure duration and other characteristics, which are relevant to the development of treatment plans and prognosis. To avoid misuse of diagnostic procedures and therapeutic tools, pediatricians and neurologists must have a comprehensive knowledge of FS diagnostic and treatment protocols. The management of febrile seizures has shifted from "watch and wait" to individualized interventions based on risk stratification, and in the future, further integration of multi-omics data is needed to improve predictive accuracy, as well as to explore preventive therapies targeting epileptogenesis.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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