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ORIGINAL ARTICLE

Febrile seizure in childhood: A review of the main concepts

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Abstract

Febrile seizure is defined as a seizure that occurs between 6 months and 5 years of age, associated with fever, without signs of central nervous system infection or any other identified cause. Simple febrile seizures are generalized and have a short duration. Complex febrile seizures last longer than 15 minutes, are focal, and might recur within the first 24 hours. Between 2%-5% of children may present at least one febrile seizure up to 5 years of age. The outcome is benign, and there are no associations with cognitive impairment. A few cases may develop epilepsy. The risk factors for recurrence are age below 18 months, family history of febrile seizures, prolonged duration, and fever intensity. The risk factors for epilepsy development are developmental delay and complex febrile seizure. Prophylaxis may be intermittent with benzodiazepines or continuous with phenobarbital or valproic acid. Antipyretics are not effective. In the present article, we review the main concepts about febrile seizures, diagnosis, and treatment.

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INTRODUCTION

A febrile seizure (FS) is any seizure associated with fever, as long as the child does not have intracranial infection or some other neurological disorder, definite metabolic disorders, or a history of nonfebrile seizures[1-6]. It is the most common form of childhood seizures, affecting on an average 2%-5% of children, mostly between 6 and 60 months of age, peaking at 18 months of age[7,8].

FSs are classified into simple and complex. Clinically, the initial presentation may be febrile status epilepticus (FSE)[1,3].

A simple febrile seizure (SFS) is a generalized tonic-clonic seizure lasting less than 15 minutes, with no recurrence within the next 24 hours and full spontaneous recovery[3,9].

A complex febrile seizure (CFS) is defined by one or more of the following features: focal seizures; seizures followed by postictal neurological abnormalities, such as Todd's paralysis; duration over 15 minutes; and recurrence within 24 hours[3,9].

FSE is an FS lasting over 30 minutes and can be characterized by a single prolonged seizure or continued seizures[1], i.e., recurring seizures without full recovery of consciousness between them. It represents 5% of all FSs and is the most common form of childhood status epilepticus.

The vast majority of FSs are simple, corresponding to 70%-75% of all cases, whereas complex FSs account for 9%-35% of the total.

According to Mukherjee, 21% of affected children have febrile seizures within 1 hour after onset of fever, 57% from 1 to 24 hours, and 22% in over 24 hours[3]. Therefore, the period of greatest risk for FS is the first 24 hours of febrile illness.

Epidemiology

FS is the most common form of childhood epileptic seizure, affecting on an average 2%-5% of all children, especially between 6 months and 5 years of age[2,4,7,8], peaking at 18 months of age[3,9].

Its incidence is variable and, according to the literature, relatively higher in Asian countries such as Japan, where an incidence of 7%-8% was found, than in Europe and in the US, which have an incidence of 2%-4%[5].

Etiology

FS is considered to have a multifactorial etiology involving environmental and genetic factors that create a susceptibility to this condition. The genetic inheritance pattern is variable, with family history of FS reported in 25%-40% of cases[10-12]. Monozygotic twins seem to have a higher concordance rate than dizygotic twins, particularly in relation to SFS[13].

An example of predominantly genetic etiology is generalized epilepsy with febrile seizures plus (GEFS+), considered a genetic syndrome with a spectrum of varying severity. Clinically, children have a history of FSs, often complex, persisting after 5 years of age, progressing to generalized epilepsy either in childhood or adulthood. A number of genes, such as *SCN1A* and *SCN1B*, have been linked to this syndrome[14].

Clinical Evaluation and Diagnosis

The diagnosis of FS in emergency is extremely important because different etiologies can be involved, from bacterial meningitis with high morbidity and mortality to common benign conditions such as viral upper respiratory tract infections. Children occasionally undergo invasive procedures, such as lumbar puncture, or are treated improperly due to misdiagnosis.

The diagnosis of FS is eminently clinical. Mostly, this is a generalized seizure, i.e., with loss of consciousness, that may be tonic-clonic, tonic, or atonic. Other cases are characterized by staring, cyanosis, and focal signs, with or without impairment of consciousness. Recovery is usually immediate. If the child remains drowsy, with an abnormal neurological examination result, the physician should investigate whether there is an underlying disease with potential neurological impairment.

Assessing the patient's overall health status and identifying the cause of the fever are of utmost relevance. The main task in the diagnostic investigation of a child with a recent FS is determining if the fever or the seizure results from a potentially harmful or even fatal disease[9]. Any febrile illness, either viral or bacterial, can cause a febrile seizure, especially viral infections[15], because they are more prevalent. Acute otitis media, upper respiratory tract infection, flu-like illness, pneumonia, and urinary tract infection are common examples of infections that can trigger FSs in the pediatric population[5].

FSE can present as recurrent seizures or as a single and prolonged seizure. In the first case, seizures are intermixed by periods of unresponsiveness, i.e., without full recovery of consciousness, which can make the initial diagnosis difficult. The physician should be aware of this condition because it is a neurological emergency requiring immediate treatment[16].

Diagnostic investigation

A patient who has had a SFS and has undergone complete physical and neurological examinations without any abnormalities does not need to undergo complex additional exams such as neurophysiology and neuroimaging. Thus, diagnostic investigations in a child with seizure and fever should be guided by the clinical presentation and suspected underlying infection[17].

Lumbar puncture

The American Academy of Pediatrics recommends that lumbar puncture be considered for children under 12 months of age who have seizures with fever[18]. In a current review, lumbar puncture is being considered for children aged between 12 and 18 months because the clinical signs of meningitis are unreliable in children aged under 18 months[19,20]. Antibiotic

therapy should be initiated if there are contraindications for lumbar puncture and a diagnostic hypothesis of meningitis[17,20].

However, it is extremely unusual for children to have meningitis without suggestive clinical findings such as petechiae, neck stiffness, altered level of consciousness, and coma[9]. In a study with a population of 455 children hospitalized due to fever and seizures, 30% had a cerebrospinal fluid culture performed, without any growth of pathogenic bacteria[9]. In another study of 839 children with CFS in an emergency department, 260 children had an indication for lumbar puncture upon evaluation, 5 of which (0.7%) had positive cultures, all aged under 12 months. Among the patients who did not undergo lumbar punctures, none presented a clinical examination suggestive of bacterial meningitis[21].

Thus, lumbar puncture should be considered in children aged under 18 months who had their first CFS, prolonged postictal, recent history of antibiotic therapy, or impaired health status.

Electroencephalogram

Practical parameters presented by the American Academy of Pediatrics confirm that no evidence demonstrates that an abnormal electroencephalogram (EEG) after a first FS is predictive of the risk of recurrence or subsequent progression to epilepsy, even in the subgroup with CFS[18,19].

An EEG performed within 7 days of the seizure can indicate brain injury or epileptic activity; however, this finding does not imply a higher risk of developing epilepsy. Generally speaking, there is no indication for EEG in these cases[19]. Thus, the presence of epileptiform abnormalities in the EEG lacks predictive value, makes parents unnecessarily anxious, and may result in a higher probability of these children receiving drug treatment[22].

Therefore, the indications for EEG in FSs are restricted to suspicion of underlying brain disease and the presence of developmental delay and neurological deficit[19].

Neuroimaging

Neuroimaging exams such as computed tomography or magnetic resonance imaging of the head are not routinely indicated and should be considered only for patients with focal neurological signs, FSE, signs suggestive of increased intracranial pressure, potential traumatic brain injury, or suspicion of structural malformations[18,19,23].

Treatment

In the pediatric population, seizure is a situation that makes parents anxious and insecure, especially because of its significance and future implications. Thus, parents should be counseled about the immediate care during a seizure, its benign progression, and the possibility of prophylaxis to reduce the risk of recurrence.

Treatment during a febrile seizure

The treatment of SFS primarily consists of keeping the airways open. Most FSs have a duration limited to 5 minutes; therefore, no drug intervention should be carried out at first[5,9,24]. In case it exceeds 5 minutes, a rectal diazepam solution can be administered by the parents, at a 0.5 mg/kg dosage, and repeated, if necessary, after 5 minutes. Oral (0.5 mg/kg) or intranasal (0.2-0.5 mg/kg) midazolam are other treatment possibilities. If the seizure persists, the child should be immediately taken to the hospital for the administration of benzodiazepines, such as diazepam, intravenously (IV) in low consecutive doses of 0.2-0.4 mg/kg/dose. Benzodiazepines are safe drugs, but they may present central nervous system (CNS) side effects when administered in high doses or at a fast infusion rate IV, including respiratory failure (present in 6% of patients with FSE treated IV), or minor side effects such as sedation, ataxia, hyperkinesia, and agitation. However, recommended doses and rectal administration rarely culminate in side effects.

If the seizure still persists, phenytoin 15-20 mg/kg or phenobarbital 15-20 mg/kg IV should be administered gradually to prevent potential side effects such as cardiopulmonary arrest.

Hospitalization should be considered in case of infants, FSE, fever of undetermined etiology, uncertainty of monitoring in the following hours, and for patients of very anxious families[24].

Prophylaxis with antiepileptic medication

FS has a benign progression, which makes long-term prophylactic treatment indicated only for specific situations. Treatment can be continuous or intermittent[3,5,24].

It is indicated when there are 2 or more risk factors for recurrence, such as seizures lasting longer than 15-20 minutes, 2 or more previous seizures, and a short interval between seizures (2 seizures within 12 hours, 3 or more seizures within 6 months, or 4 or more seizures within 1 year)[4]. In these cases, recurrence decreases by 1/3 with prophylaxis[25].

Continuous treatment

Continuous treatment is indicated when there is a history of 2 or more seizures within 24 hours or a prolonged seizure (> 10 minutes). Continuous treatment reduces recurrence effectively but does not prevent epilepsy[19].

In general, continuous treatment is administered with phenobarbital or valproic acid. Phenobarbital, compared to placebo, is effective; nonetheless, it is associated with side effects, e.g., sleep disorders, hyperactivity, irritability, and lethargy[3,5]. Valproic acid is also effective when used continuously[3,5], but side effects should be considered when it is administered to children aged under 2 years[9]. Carbamazepine and phenytoin are not effective in preventing the recurrence of FS[3,5].

Continuous treatment in children aged under 2 years can be achieved with the administration of phenobarbital at a dose of 3-5 mg/kg/day, dividing the daily dose into two. The dosage of valproate is 15-60 mg/kg/day, preferably between 20 and 40 mg/kg/day[3,5]. Treatment should be maintained for a minimum period of 12 months and can be extended until 5 years of age. Medication withdrawal should be gradual, over a period of 3-6 months[3,5].

Regarding CFS, a 2017 systematic review showed the effectiveness of the continuous administration of phenobarbital and valproic acid in reducing the risk of recurrence. On the other hand, carbamazepine increased this risk[19].

Intermittent treatment

Intermittent treatment consists of rectal or oral administration of diazepam at 0.5 mg/kg/dose initially and 0.2 mg/kg/dose every 12 hours while the fever lasts. Another option is oral clobazam at a dose of 2.5 mg (for children weighing less than 10 kg) and 5.0 mg (for children over 10 kg) every 12 hours[26]. These drugs should be given to the child during episodes of fever and for the next 48-72 hours of febrile illness[3,5,24,25]. Although it is not continuous, intermittent prophylaxis is also associated with side effects such as drowsiness and lethargy[3,5].

Antipyretics and temperature control

Antipyretic agents can be used to reduce body temperature; however, they do not reduce the recurrence of FSs[3,5,6,24,28]. In addition, antipyretics are not effective in preventing the occurrence of SFS[6].

For CFS, a systematic review concluded that the intermittent administration of intrarectal diazepam and oral clobazam was effective in preventing seizure recurrence[19].

Prognosis

Risk of developing epilepsy

The risk of progression to epilepsy after a FS is 6%-7%. Approximately 13% of patients diagnosed with epilepsy have a history of FS[19].

Risk factors for the development of epilepsy include prior neurological deficit, CFS, and family history of epilepsy[1,7,9]. The risk of developing epilepsy is more associated with genetic predisposition than with history of FS[5].

In a British study, the risk of developing epilepsy was 1% after an episode of SFS, 4% after multiple seizures, 6% after prolonged seizures, and 29% after focal seizures. The Rochester study shows the influence of CFS in the development of epilepsy, with a 6.8% risk for children who had one CFS, 17%-22% for two seizures, and 49% for three seizures[1]. It is worth noting, however, that the risk of epilepsy does not differ between groups treated and untreated for CFS[19].

Several studies attempt to demonstrate the relationship between FS and temporal lobe epilepsy associated with mesial temporal sclerosis. The conclusion is that this association is rare[6]. This correlation is recognized but controversial[1,29].

Recurrence

Approximately 30%-40% of children who present one FS have a recurrence[1,3,6]. The probability of a child who had one FS having another one is 32%, another two is 15%, and another three is 7%[7]. Recurrence is more common in the first 6-12 months after the first episode of FS[9].

Progression depends on genetic predisposition, environmental factors, and specific risk factors, which include early age at onset, family history of epilepsy or FS, CFS in the first episode, and short time between the onset of fever and the seizure[1,30]. Studies show that the chances of recurrence increase from 30% to 50% when the first episode occurs before the child turns 1 year old[2,33].

Untreated children without risk factors have a low risk of recurrence (10%). Untreated children with one or two risk factors have a recurrence rate of 25%-50%, whereas having three or more risk factors increases this rate to 50%-100%. Children at high risk of recurrence treated with prophylactic diazepam and having one or more risk factors benefit from a reduction in the risk of recurrence from 75%-100% to 10%-15%[1,6]. Children with moderate and low risk of recurrence have a moderate and low response to prophylaxis with diazepam, respectively[6].

Neurological deficit

Acute brain damage does not occur in SFS, only in rare cases of FSE. Neurological damage seems to be more associated with an underlying brain disease than with seizure[1]. SFS does not cause structural damage and does not increase the risk of developing cognitive deficits[1]. A study conducted by the *National Collaborative Perinatal Project* and another British study reported no evidence that FS can lead to deficits in academic achievement, intelligence, or behavior[1,32]. There are no significant differences regarding cognitive development between children treated with prophylactic diazepam and untreated children[1].

CONCLUSIONS

FSs are seizures precipitated by fever, common in children aged between 6 months and 5 years, usually as a result of infections without CNS involvement. They have an excellent prognosis and a benign progression. The greatest risk in these children is recurrence.

Seizures are usually manifestations of numerous pathological conditions, and identifying them requires careful assessment of clinical history, physical examination, and, occasionally, laboratory tests. The first conduct is to evaluate and identify the underlying infectious process.

Lumbar puncture is indicated when CNS impairment is suspected and for infants under 18 months of age without an identified focus of infection. There is no need to perform an electroencephalogram. Imaging examinations are indicated in case of suspected brain damage.

The use of prophylactic medication should be individualized. FSs are highly prevalent in the pediatric population and are benign in nature; thus, the risk/benefit ratio should be considered because these medications have potential side effects.

When parents are very anxious regarding complex or recurrent FSs, intermittent prophylaxis with benzodiazepines can be justified. Although antipyretics can improve the comfort of the child, they fail to prevent subsequent seizures.

The most important measure is advising the family. This allows adequate management of these children without any need for pharmacological treatment, which poses more risks than benefits to the patient.

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