REVIEW ARTICLE

Treatment of febrile seizures

Marilisa M. Guerreiro*

Abstract

Objective: to review basic concepts of febrile seizures and the indications of specific tests. To analyze the prognosis and the medical treatment.

Sources: the author reviewed the literature and presented her published data.

Summary of the findings: the key points are based on the rules of the American Academy of Pediatrics designed according to a consensus about when and how to investigate febrile seizures, and indications of treatment.

Conclusions: febrile seizure is a benign entity and most children will present only one seizure during their lives. There is no indication of complementary tests (electroencephalogram, lumbar puncture and neuroimaging tests) and specific treatment for this group of children. Special indications are revised.


Introduction

Febrile seizure (FS) occurs during childhood, usually in children between 3 months and 5 years of age, associated with fever, in the absence of intracranial infection or any other defined neurological cause, except when children have already presented afebrile seizures.1,4 FS should not be mistaken for epilepsy, which is characterized by recurrent afebrile epileptic seizures.

On average, the first FS occurs between 18 and 22 months. This first FS can be either simple (one sole generalized tonic-clonic seizure, lasting approximately 5 minutes) or complex (partial seizures and/or lasting for approximately 15 minutes and/or recurrent in less than 24 hours and/or with post-ictal neurological manifestations).3,4

The incidence of FS varies from 1% to 14%, according to the study. The only study on FS performed in South America, which took place in Chile, reported a 4% incidence. Perhaps this figure is closest to our reality.5,6

Physiopathology

The low threshold of the developing cerebral cortex, the susceptibility of the child to infections, the propensity for high fever, and the genetic component affecting the convulsive threshold are factors that, if combined, show why FS is a characteristic condition of the first childhood, which is overcome with the child’s development.7

Clinical and experimental studies have demonstrated that the immature brain presents a greater susceptibility to seizures. The low threshold probably derives from the combination between increased excitation and reduced
inhibition, in addition to maturational differences in subcortical circuits.8

Clinical diagnosis

FSs are usually of the simple type, e.g., generalized tonic-clonic seizure, which are fast and occur isolatedly. Parents may refer hypotonicity, but, in these cases, there is usually a fast clonic stage that can go unnoticed. Eighty percent of the FSs match the circumstances described above. The remaining seizures (20% of the cases) are classified as complex FS.

The three characteristics of complex FSs (focality, length > 15 minutes and recurrent seizures in 24 hours) appear to share some underlying common components, since they often occur in association. A strict correlation can be observed between focality and extended length, e.g., focal seizures tend to last long.9 Todd’s paralysis may be observed after a focal seizure.4

The fast increase in the temperature is believed to be a factor that triggers FSs; however, it is still uncertain whether this is more important than the high temperature itself.

A careful history of the patient must be obtained in order to rule out other causes of epileptic seizures, such as trauma or intoxication, in addition to clarifying whether there is a familial history of seizures. A complete description of the seizures is also important. Physical examination must include investigation of possible infections. The presence or absence of meningeal signs and the examination of the fontanelle are two fundamental steps of the neurological exam. Central nervous system infections associated with fever should be discarded, especially encephalitis or meningitis.

Lab diagnosis

A spinal tap is indicated whenever there is a clinical suspicion of meningitis, for example, in the presence of significant lethargy, neck stiffness or bulging fontanelle. Since in infants these clinical signs may be absent, a spinal tap must be more often considered. The American Academy of Pediatrics (AAP) strongly recommends that physicians consider spinal tapping after the first FS in infants under 12 months. This recommendation, albeit not so strong, is also valid for children between 12 and 18 months. For children older than 18 months, a spinal tap is recommended only in the presence of meningeal signs and symptoms, or when there is a clinical suspicion of intracranial infection.10

Routine exams must be done only as part of the assessment of the patient’s infectious status, and not specifically because of an FS. Radiological and neuroimaging exams, such as computed tomography and magnetic resonance, are rarely useful, and therefore, should not be recommended as routine exams. Electroencephalogram (EEG) does not contribute with prognostic information, although some nonspecific findings (slow waves) may appear up to one week following the FS. Epileptic abnormalities are rare, and undistinguishable between simple and complex FS.11 Recurrence or future seizures can not be predicted by the EEG; there is no definite evidence that an early EEG abnormality will lead to recurrence or future development of epilepsy.12 The AAP recommends that EEG should not be performed for evaluating neurologically healthy children who have presented a first simple FS.10 The AAP consensus adds that an early EEG, or an EEG done in the first month following a simple FS, does not hold any prognostic value. More recently, other authors have evaluated the value of EEG in complex FSs; they also concluded that EEG should not be recommended for healthy children with complex FS.13 Therefore, considering any type of FS, EEGs are only recommended in the following situations: suspicion of underlying brain disorder; delay in psychomotor development; and presence of neurological deficit.

Prognosis

FS is a benign entity. In the most complete study performed on FSs, the National Collaborative Perinatal Project (NCP) assessed and followed up, until the age of seven, 1,706 children who presented FSs.3 Results show that no death could be attributed to FSs, as well as no permanent motor sequelae were found. Also, FSs were not associated with an increased risk of intellectual deficit.

Generally, most children with FSs present only one episode throughout their life.5,6 Other children can present recurrent episodes, and most studies on FSs focus on such cases. Another possible development is epilepsy, which affects a small percentage of children with FS.

Recurrence

Several authors have studied the predictive factors for FS recurrence,3,4,18 in an attempt to identify the group of children who will present more than one episode. Approximately 70% of children will experience only one seizure; 20% will present two FSs; and only 10% will be at risk for several FSs throughout life. The problem lies in finding out who these children who may suffer several seizures are. This is an important aspect, since this is the group to which a prophylactic treatment may be considered.

Data presented in the literature are sometimes inconsistent. However, some consensus factors can be found, such as age of first seizure, familial history and length of seizures.19 With regard to the age of the first seizure, all authors agree that an FS in the first year of life indicates a high risk of recurrence. Some authors, however, believing that this period of high risk of recurrence can not be restrained to the first 12 months, propose that this period be extended to 15-18 months. In relation to familial history, some authors state that only a history of FSs in close family members can be considered a predictive factor, while others
take into account both FS and epilepsy in any family member as an indication of possible future seizures. Concerning the length of the fever, studies demonstrate that the shorter the length, the greater the risk of recurrence. A short length fever is usually associated with low temperature, which denotes the lowest convulsive threshold. In addition, some authors take into consideration the type of FS, stating that complex FS tends to reoccur.9

In face of so many variables, we must decide which factors should be considered as predictive of recurrence. Therefore, we have chosen the following: age under 18 months; familial history of FS; and length of fever less than one hour prior to the first FS. We believe that these are the most consistent and consensual data discussed in the literature. If the child presents one or more of these factors, a prophylactic treatment must be considered.

**Epilepsy**

The risk of epilepsy in the population presenting FS is slightly higher than in the general population, accounting for approximately 2% to 7% in long-term studies.20-22 Annegers et al.20 studied the characteristics of complex FSs individually and observed that the risk of epilepsy is proportional to the number of characteristics presented by the patient. This way, children who presented the three characteristics of complex FS (focal and extended seizures, recurrent within 24 hours) had a 49% risk of developing epilepsy.

In addition to the type of FS, familial history of epilepsy and presence of neurological abnormalities, either at examination or during the development, are predictive factors for late epilepsy in the group of children presenting FSs.20-22 The number of recurrences of FS episodes may be related to a future development of epilepsy.

When analyzing the risk for epilepsy in children with FSs, we can notice that the figures are not significant and that, from this point of view, there is a weak association between FS and epilepsy. On the other hand, when temporal lobe epilepsy (TLE) series are analyzed, the history of previous FS is frequent, possibly representing a positive prognostic factor for surgery. Mesial temporal sclerosis (MTS) is the most frequent cause of TLE in adults. Some authors discuss whether MTS is a cause or a consequence of FSs.

With regard to the relation between MTS and FSs, there are three possibilities25: patients are born with a normal brain and the FSs cause MTS; patients are born with MTS and, because of that, they present an increased susceptibility to epileptic seizures, including FSs; or patients are born with hippocampal abnormalities that are aggravated by extended FSs.

Recent studies26-29 have tried to elucidate this discussion and, today, there is evidence supporting the idea that previous hippocampal pathology is responsible for focal and extended FSs, by making the brain more susceptible to damage induced by the seizure itself.

**Treatment**

Several authors believe that there is no need to consider a prophylactic treatment in cases of FSs. However, among authors who consider that only children presenting predictive factors for FS recurrence should be treated, there is some doubt with respect to which the best therapeutic method would be: a continuous prophylactic treatment with phenobarbital and valproate, or an intermittent treatment with benzodiazepine drugs.

The prophylactic treatment with phenobarbital presents some inconvenient side effects, such as hyperactivity, irritability and sleep disorders, affecting up to 60% of users.30,31 In addition, although most studies demonstrate the efficacy of phenobarbital, some studies suggest that it is not an appropriate agent for the treatment of FS. An apparent risk of reducing the intelligence quotient (IQ) must be further evaluated, as demonstrated in one randomized study.32

Valproate presents a risk for rare side effects, fulminant hepatitis, which limits its use, particularly in small children presenting benign entity such as FS.33 In addition, valproate can cause gastric intolerance, weight gain and hair loss.

At present, there is only one clear condition for indicating a continuous prophylaxis: when the increase in the temperature happens so fast that the mother or caretaker can not detect the fever until the seizure has started. In these cases, which are fortunately uncommon, the fast increase of the temperature restrains the use of an intermittent medication, which depends on detecting the onset of the febrile status.

Despite being rare, whenever there is an indication for continuous prophylaxis, the option for a specific medication must take into consideration the side effects that are most likely to occur in each age group, especially because phenobarbital and valproate have comparable levels of efficacy.35 In children under the age of two, we suggest the use of phenobarbital in a 3 mg/kg/day to 5 mg/kg/day dosage, divided into two doses. Over the age of two, we recommend the use of valproate. Suggested dosages vary from 15 mg/kg/day to 60 mg/kg/day, split into two or three doses, maintaining them within a scope of 20-40 mg/kg/day.

Lately, the use of benzodiazepine drugs has been the most accepted option for the treatment of FSs, as well as the most prudent in these cases. Several studies have demonstrated the efficacy of benzodiazepine drugs in the prophylactic treatment of recurrent FSs.34-41 Some recent works even compare a continuous and an intermittent prophylaxis, suggesting that the latter has a similar or superior efficacy in comparison to the chronic use of phenobarbital. Tolerance to benzodiazepine drugs is
positive: 20% to 30% of patients present light to moderate side effects, which are transient and do not affect the use of the medication.

We suggest the use of oral diazepam in a 0.5-1 mg/kg/day in two doses. In our experience,35-36 oral diazepam is efficient in the prevention of recurrent FSs and is well tolerated and easy to be administered, two characteristics that are not necessarily true in the case of rectal diazepam, the route of administration suggested by some authors. Nevertheless, we suggest that its use be restricted to cases presenting some risk factor for recurrence. We also recommend family members to begin with the treatment at any sign of sickness. Medication must be suspended approximately 24 hours after the last peak temperature.

It is important to stress that all pediatric care, such as, administration of antifebrile drugs and the casual use of antibiotics, must be maintained.

Another benzodiazepine drug that presents efficacy and tolerance levels similar to those of diazepam is clobazam,39 which can be used as follows: 5 mg/day for children weighing up to 5 kg; 10 mg/day for children weighing between 5 kg and 10 kg; 15 mg/day for children weighing between 11 kg and to 15 kg; and 20 mg/day for children whose weight is over 15 kg.

References

Corresponding author:
Dra. Marilisa M. Guerreiro
Departamento de Neurologia - FCM - UNICAMP
Caixa Postal 6111 - CEP: 13.083-970 - Campinas, SP
Telephone: +55 (19) 3788.7372 - Fax: +55 (19) 3871.6715
E-mail: mmg@fcm.unicamp.br