

# FEBRILE SEIZURES: UPDATE ON DIAGNOSIS AND MANAGEMENT

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## ABSTRACT

Febrile seizures are a benign condition of childhood, and most children will have only one episode in their lifetime. Nevertheless, any seizure is a cause of major concern in the patient's family, and there is much discussion in the literature on when and whether to treat febrile seizures, as well as on what constitutes the best therapeutic approach. This review summarizes the current evidence and recommendations for diagnosis and management of patients with febrile seizures

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## INTRODUCTION

Fever is an elevation of body temperature induced by the thermoregulatory center of the hypothalamus in response to certain situations. This sign is believed to be an adaptive mechanism, developed with the purpose of stimulating the immune system and preserving cell membrane integrity in the presence of threats.<sup>1</sup>

Although there is broad disagreement in the literature concerning normal body temperature in children, normal axillary temperature is generally considered to range between 36.0°C in the morning to 37.7°C in the afternoon. Any values above this range should be regarded as abnormal.<sup>2</sup>

The correlation between fever and epileptic seizure is strong and has been well-established for years. When treating the child with fever and epileptic seizure, the clinician may actually be faced with at least four distinct patient subgroups: children with febrile seizures; patients with controlled epilepsy in whom fever triggered new seizures; patients with acute symptomatic seizure, that is, seizure as a manifestation of non-epileptic conditions, such as metabolic changes or acute illness (central nervous system infection or severe water–electrolyte imbalance secondary to diarrhea with dehydration, for instance). Finally, the fourth group comprises patients in whom onset of fever occurred post-ictally; these cases are extraordinarily difficult to distinguish from actual febrile seizure, particularly in children presenting with low-grade fever and early in the course of the episode.

Febrile seizure is one of the most common neurological conditions of childhood; 2% to 5% of children under the age of five are estimated to develop at least one epileptic seizure during a febrile illness. The only incidence study performed thus far in South America was conducted in Chile, and reported a rate of 4%.<sup>3,4</sup>

The objective of this review of the literature is to summarize current knowledge on febrile seizures and recent recommendations on management of this condition.

## Definition and overview

In the now conceptually outdated but still widely cited Consensus Development Meeting on Long-Term Management of Febrile Seizures (1980), febrile seizure was defined as follows: “an event in infancy or childhood, usually occurring between 3 months and 5 years of age, associated with fever but without evidence of intracranial infection or defined cause. Seizures with fever in children who have suffered a previous non-febrile seizure are excluded. Febrile seizures are to be distinguished from epilepsy, which is characterized by recurrent non-febrile seizures.”<sup>5</sup>

However, this definition was widely criticized over the years, particularly due to the nonspecific nature of the term “event” and to the need for recognizing a broader age range in which febrile seizures occur, as seen in clinical practice. In 1993, an International League Against Epilepsy (ILAE) committee established the current definition of febrile seizure as “an epileptic seizure [...] occurring in childhood after age 1 month, associated with a febrile illness not caused by an infection of the CNS, without previous neonatal seizures or a previous unprovoked seizure, and not meeting criteria for other acute symptomatic seizures”<sup>6</sup>.

An important aspect of febrile seizure is that it will always occur during the course of an infectious disease that does not affect the central nervous system. Viral infections are more commonly associated than bacterial ones, most likely due to the higher incidence of the former in clinical practice. The literature also describes as febrile seizures those due to fever after

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immunizations, particularly with the DTP vaccine (due to the pertussis component) and the MMR vaccine (due to the measles component).<sup>7</sup>

The etiology and pathogenesis of febrile seizures have yet to be fully elucidated, particularly at the molecular level. However, some environmental aspects are already understood and believed to be essential to development of the condition.

The underlying cause of the infectious process does not appear to be a determining factor of febrile seizures. The presence of fever is of course essential, even though its mechanism of action is unknown. Febrile seizures are also most common in the first day of fever, and correlate more with peak temperature than with speed of onset.<sup>7,8</sup>

Genetic aspects have been clearly established in the etiology and pathogenesis of febrile seizures. A history of febrile seizures in first-degree relatives is common, and concordance rates of febrile seizures are much higher in monozygotic than in dizygotic twin pairs.<sup>7,9</sup> Reports in the literature have described a connection between febrile seizures and various chromosomes, including 2q, 5q, 5, 8q, and 19, which appear to be associated with changes in neuronal sodium channel function. These studies are still incipient, however, and there is no single gene or well-defined inheritance pattern associated with febrile seizures.<sup>10</sup>

One of the most remarkable characteristics of febrile seizures is the fact that they occur only in a well-defined age range. Although the immature brain is more susceptible to epileptic seizures, febrile convulsions cannot be ascribed to this factor alone, and the reasons behind the age-dependent nature of this condition (even though it rarely occurs outside specific age ranges) remains unclear.<sup>7</sup>

### Natural history of the disease

The clinical course of febrile seizures is quite well understood. Seizures are usually generalized tonic-clonic, hypotonic, or clonic, short-lasting, and produce mild post-ictal manifestations.

Occasionally, febrile seizures are focal, prolonged, or lead to neurological signs in the post-ictal period; these are known as complex febrile seizures.<sup>7,10,11,12</sup> Table 1 shows the characteristics of simple and complex febrile seizures, which has major implications for the clinical course and prognosis of children presenting with this condition.

Simple febrile seizures are by far the most common, and are usually isolated occurrences. Complex febrile seizures are associated with higher odds of recurrence; furthermore, the differential diagnosis of epilepsy or acute symptomatic seizure must be pursued more rigorously in these cases.<sup>7,10,11,12</sup>

Overall, febrile seizures are benign, and children who have

had them show no significant difference in intelligence, head circumference growth, or behavior when compared with children with no history of the condition.<sup>11</sup>

Several factors have been described as increasing the odds of a first febrile seizure, such as fever grade, delayed development, delayed discharge from maternity care, and stay at daycare facilities. However, the main risk factor appears to be family history of febrile seizures.<sup>13</sup>

Febrile seizures recur in approximately 30% of patients, most commonly between the ages of six months and three years. The odds of recurrence also decrease over time. According to Nelson and Ellenberg, 50% of children experience a second febrile seizure within six months of the first, 75% within a year and 90% within two years of the first episode.<sup>7,14</sup> The key factors for recurrence are early age at first seizure, family history of febrile seizures, temperature (inversely proportional to grade), and duration of febrile illness (the shorter the febrile period, the higher the odds of recurrence).<sup>15</sup>

Children who have had febrile seizures also have increased odds of developing epilepsy (2% to 7%) than the general population.<sup>7,12</sup> The presence of prior neurological abnormalities and a family history of epilepsy or complex febrile seizures are the main risk factors for epilepsy reported in the literature.<sup>4,7,16</sup>

Finally, it bears stressing that a relationship (however poorly understood) exists between febrile seizures in childhood and development of temporal lobe epilepsy in adulthood. In 1995, Maher and McLachlan studied families with febrile seizures and reported an association with mesial temporal sclerosis, a frequent cause of AED-refractory symptomatic focal epilepsy.<sup>7,10,17</sup>

### Diagnosis

The diagnosis of febrile seizure is essentially clinical. Episodes should always be classified into simple or complex febrile seizure. In children with complex seizures, other differential diagnoses (such as focal epilepsy or new-onset acute symptomatic seizure) must always be considered, despite their rarity.

Lumbar puncture is indicated in children 18 months or younger with clinical signs suggesting meningitis or in particularly severe presentations. Blood glucose measurement is essential, and any further laboratory testing should be requested as necessary according to clinical condition and diagnostic hypothesis.<sup>7,18</sup>

Electroencephalography may show changes in various cases, and is therefore of no practical use. Neuroimaging is also of little value in the diagnosis of febrile seizures.<sup>7</sup>

The main differential diagnosis is CNS infection. Other common presentations include epilepsy, acute symptomatic

**Table 1 – Classification of febrile seizures**

	Simple	Complex
Symptoms	Generalized	Focal
Duration	<15 minutes	>15 minutes
Recurrence in first 24 hours	No recurrence	May recur
Focal signs in post-ictal period	Absent	Present

seizure, febrile delirium, tremor, syncope, and anoxic seizure.

### Management

Management of febrile seizures may be divided into acute treatment, prophylaxis, and parent teaching.

Acute care of the febrile seizure should be as for any epileptic seizure. General principles of emergency care, such as assessment with the ABCs (airway, breathing, and circulation), should precede administration of any specific drugs.

Furthermore, most seizures cease spontaneously prior to arrival at the emergency department, and the clinician will often assess a child in the post-ictal state.

Benzodiazepines are the abortive treatment of choice: intravenous diazepam (0.2 to 0.3 mg/kg/dose) or, if IV access cannot be obtained, midazolam (0.2 to 0.7 mg/kg), which may be given intramuscularly, rectally, or intranasally.<sup>7</sup>

The prophylactic treatment of febrile seizures is highly controversial, and is the source of extensive discussion in the literature: is treatment actually required? When should these patients be treated? Which is the best treatment option?

Most children with febrile seizures will have a single lifetime episode; seizures will recur in the rest.<sup>3</sup> Risk of recurrence is highest in patients with age less than 18 months at first seizure, family history of febrile seizures, and onset of fever less than one hour prior to the first seizure. If the child has one or more of these risk factors, prophylaxis may be considered.<sup>15</sup>

Several authors oppose prophylactic treatment of febrile seizures, arguing that they are a benign condition, that treatment does not alter prognosis, and that adverse effects can be a significant concern even in intermittent prophylaxis.<sup>7,19</sup>

However, we find such a stance practically impossible to adopt in the Brazilian reality, mostly due to parental and psychological issues associated with epileptic seizures. Another argument in favor of prophylaxis is that the abrupt onset of seizure may lead to trauma, and that febrile seizures may sometimes progress to status epilepticus.<sup>7,19</sup>

The current consensus in the literature is that prophylaxis of simple febrile seizures carries no benefit. Conversely, prophylaxis for complex febrile seizures, is still debatable, and available data are unconvincing.<sup>19</sup>

American Academy of Pediatrics guidelines published in 2008 state that "the potential toxicities associated with [antiepileptic agents]...outweigh the relatively minor risks associated with simple febrile seizures." When febrile seizures prompt significant parental anxiety, short-term intermittent prophylaxis may be given, but continuous treatment is not recommended.<sup>20</sup>

However early and effective, antipyretic therapy does not prevent seizure recurrence. Both paracetamol and NSAIDs have been tested in double-blind randomized controlled trials and showed no benefit.<sup>21,22</sup>

Although they do not reduce risk of febrile seizures, antipyretics are often used to reduce fever and improve the patient's general condition. It bears noting that seizure prophylaxis does not preclude general pediatric care for the underlying condition, and any other relevant measures, such as antipyretics or antibiotic therapy, should be continued.

In our practice, we use metamizole (dipirone), 10 to 25 mg/kg/dose in up to four daily doses (100 mg/kg/day); paracetamol,

10 to 15 mg/kg/dose, also in up to four daily doses (up to 2.6 g/day); and, in children over the age of six months, ibuprofen, 5 to 10 mg/kg/dose in three or four divided doses (up to 40 mg/kg/day in children weighing less than 30 kg and 1200 mg/day otherwise)<sup>2</sup>.

Side effects are rare, and include hepatotoxicity (in paracetamol overdose), metabolic acidosis, renal failure and coma (in ibuprofen overdose) and agranulocytosis (with metamizole)<sup>2</sup>

Regarding best choice of prophylactic regimen, continuous prophylaxis with phenobarbital (3 to 5 mg/kg/day in one or two divided doses) or valproic acid (15 to 60 mg/kg/day in two or three divided doses) has been used for many years, and provide a proven reduction in seizure recurrence<sup>7,19</sup>. Other drugs have also been tested, but either failed to prevent recurrent episodes (phenytoin) or were no more effective than phenobarbital (carbamazepine)<sup>19</sup>.

However, continuous prophylaxis is now exceedingly rare, due to the unfavorable side effect profile of both phenobarbital (drowsiness, hyperactivity, learning difficulties) and valproic acid (weight gain, nausea, hair loss, liver injury)<sup>7,19</sup>.

We choose to begin continuous prophylaxis only in cases in which onset of fever was so rapid as to prevent the mother or caregiver from noticing it, and high temperature was only detected after the seizure. Other indications supported by the literature include failure of intermittent prophylaxis and any case in which the initial febrile seizure progressed to status epilepticus. Such cases are fortunately rare, and use of continuous prophylaxis is increasingly rare.<sup>7,19,23</sup>

Currently, the most widely accepted regimen when the choice for prophylactic treatment is made is intermittent therapy with benzodiazepines. This class of drugs is inexpensive, associated with good compliance, and provide excellent outcomes in terms of seizure prevention.

Brazilian studies have assessed the efficacy of oral clobazam 1 mg/kg/day BID, with excellent results. The following weight-based dosages can be prescribed: 5 mg/day in children 5 kg or under; 10 mg/day in children 5 to 10 kg; 15 mg/day in children 11 to 15 kg; and 20 mg/day in children weighing 15 kg or more.<sup>24</sup>

Oral diazepam 0.5 to 1 mg/kg/day in two divided doses has also been assessed in Brazilian studies. Although the international literature often cites rectal administration of diazepam, oral diazepam is effective for preventing recurrence of febrile seizures, well-tolerated, and easy to administer.<sup>19,23,25,26</sup>

Parent teaching should focus on the benign nature of the condition, mentioning the possibility of recurrence and the slight increase in risk of developing epilepsy, but always stressing the importance of letting the child lead a normal life.

Parents should also receive guidance on responding to a seizure. Measures that should be taught include protecting the child from physical trauma during the seizure, not allowing the insertion of any objects into the child's mouth, preventing aspiration in the post-ictal period, and monitoring seizure duration.

Finally, parents should be informed of the association between immunization and febrile seizures, but encouraged to vaccinate their children nonetheless. Clinical observation for 48 hours after DTP vaccination and seven to ten days after measles vaccination is recommended.<sup>7,27</sup>

## CONCLUSION

Febrile seizures are a common neurological event in childhood, but carry low morbidity and rarely recur. Although a great deal is known about the natural history and prognosis of these events, the need for prophylaxis and the best choice of prophylaxis are still the subject of much discussion.

In most cases, febrile seizures are benign and pose a low risk of progression to epilepsy, and there is no compelling evidence that the prevention of recurrent seizures would have any risk-modifying effect. Nonetheless, these episodes are a source of substantial suffering for patients, their families and caregivers.

Secondary prophylaxis after simple febrile seizures is unsupported by the current literature, but intermittent prophylaxis may be considered after complex seizures, especially in the event of protracted episodes or focal seizures.

This guidance provided by the literature must of course be analyzed carefully and presented to the patient's family in an appropriate manner. The choice of whether to institute prophylaxis, and of the optimal regimen for prophylaxis when it is indeed chosen, will require not only a knowledge of the evidence but also an understanding of individual aspects of the patient, of his or her family, and of the social structure of which the child is a part.

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