



EDITORIAL

## Epidemiology of febrile seizures and epilepsy: a call for action<sup>☆,☆☆</sup>



## Epidemiologia das convulsões febris e epilepsia: um apelo à ação

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Seizures triggered by fever, qualified as febrile seizures, have been for decades a major issue for children in developed countries and more so in resource-limited settings. Approximately 2–5% of children are affected by this kind of seizure. Many studies aimed to describe, measure, and analyze several hypotheses, including the assessment of the physiopathological mechanisms, epidemiological indicators, care management, and their impact on their later neurological impairments, such as epilepsy, but many unknowns remain.

In this issue of *Jornal de Pediatria*, Dalbem et al.<sup>1</sup> report a population-based cross-sectional study conducted in the city of Barra do Bugres in Brazil to assess the prevalence of benign febrile seizures during childhood. The main outcome was a prevalence of 6.4/1000 habitants (95% confidence interval [CI], 3.8–10.1), which is much lower than the results reported in two studies also performed in Brazil, ranging from 13.9 to 16.0/1000,<sup>2,3</sup> but within the literature range, from 3.5/1000 in an Arab population<sup>4</sup> to 17.0/1000 in a rural north American population.<sup>5</sup> One of the strengths of

their study was that almost all the pediatric population in the study area was included. Several hypotheses were discussed to explain this lower result. The authors reported a selection bias and a lack of standardized method, which did not allow for comparisons between studies. In addition to these divergences, it is admitted that interview and/or questionnaire surveys have lower level of evidence, especially in this case. Febrile seizures with motor manifestations were the most identified, leading to a sub-selection of prevalent cases, generating an information bias. Therefore, the selection phase of the present study used a history of febrile seizure to identify cases, which could lead to a recall bias. Nevertheless, these studies are essential to increment epidemiological data. Among 12 of the main studies assessing febrile seizures worldwide, only five measured the prevalence; patient recruitment methods were widely different and there was no homogeneity regarding data recorded. These variations in results are not necessarily an irremediable result of methodological problems, but more frequently than expected it could be related to population features (age, sex-ratio, genetic factors, origins, environmental impacts, etc.), different etiologies (e.g. heterogeneity of prevalence of infectious diseases), and/or unknown factors. As an example and for matter of comparison, Yemadje et al.<sup>6</sup> have investigated the differences in prevalence of epilepsy in tropical regions. Their conclusions corroborate the abovementioned assumptions, enhanced by the stigmatization of people with epilepsy, leading to an underestimating of prevalence, even in well-conducted studies.

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A febrile seizure is a convulsion in a child triggered by a fever, often occurring in families, and most often in children between ages of 9 months and 5 years according to the National Institutes of Health (NIH).

Most febrile seizures occur in the first 24 h of an illness, and the fever has an unexpected important weight; body temperature over than 38.3 °C increases the risk factor compare to lower fever than 38.3 °C. Major upper airway infections such as ear infections, cold or viral infections represent the main triggering factors. Most often, febrile seizure has spontaneous resolution and does not require any drug treatment. In some cases, when the duration of the seizure exceeds 5 min, infusion of lorazepam or midazolam can avoid convulsions. If there is no resolution, febrile seizure should be considered as status epilepticus and the management should follow the corresponding medical protocol. In this regard, phenobarbital is proposed in several guidelines. Farwell et al.<sup>7</sup> reported in 1990 that a treatment using phenobarbital (versus placebo) can be worse in the care of febrile seizures, and iatrogenic cognitive impairments have been observed. This outcome could be explained by the fundamental pharmacological effect this drug, which is anticonvulsant with a hypnotic side effect, having any effect on the fever.

The most frequent evolution is no more seizures ever but there is a 15–70% risk of recurrence in the first two years after the initial febrile seizure. In this article, only one case (5.5%) among 18 had more than one seizure; and another one (5.5%) a third seizure. Predictors of recurrence are commonly age at onset (higher risk for child who experienced febrile seizure before 18 months), temperature (low fever is curiously more likely linked with recurrence than high fever), and a positive family history of febrile seizures.<sup>8,9</sup>

As well as unprovoked seizure and epilepsy, provoked seizures are quite common in resource-limited countries under tropical areas mainly due to high rates of central nervous system (CNS) infections such as cerebral malaria, tuberculosis, schistosomiasis, HIV, and most often neurocysticercosis (NCC). The last burden has been frequently associated with a high risk of epilepsy impairment, but arising an afebrile seizure. It is noteworthy that febrile seizure should be distinguished as seizure occurring during an intracranial infection or a severe metabolic disturbance. In fact, febrile seizure has been recognized as a distinct syndrome separated from epilepsy. The International League Against Epilepsy (ILAE) defined it as a seizure occurring in childhood after 1 month of age associated with a febrile illness not caused by a CNS infection, without previous neonatal seizures or previous unprovoked seizure, and not meeting the criteria for other acute symptomatic seizures. Nevertheless, although a divergence of origin exists, the significant link between both affections is that febrile seizure represents an important risk factor for developing epilepsy.

Infectious epilepsy is one of the main etiologies described in several studies. Bhalla et al.<sup>10</sup> described in 2011 with genetic, brain tumors, and head trauma cases, that cerebral infections have a significant weight in the world burden of epilepsy. As mentioned above, NCC is highly associated with epilepsy (30% to 50% of all epilepsy in endemic zones) and South America is deeply impacted by this public health issue, as well as Asia and Africa. Mac et al.<sup>11</sup> conducted a literature review of epidemiology, etiology, and

clinical management of epilepsy in Asia, which was published in 2007. They reported that main causes were dominated by head injury, birth trauma, and intracranial infections, such as NCC or meningoencephalitis. Furthermore, their article highlighted the lack of methodological and powerful studies undertaken in those countries, which would strengthen the body of evidence. The same issues were raised in a sub-Saharan Africa conducted by Preux and Druet-Cabanac, published in 2005,<sup>12</sup> as well as in a review and update by Ba-Diop et al. in 2014.<sup>13</sup> The main risk factors for epilepsy in that area of the world were family history of seizures, previous febrile seizures, perinatal trauma, head injury, and CNS infections, such as NCC. They confirmed that febrile seizures were commonly associated with epileptic seizures among the pediatric population (6–38% of patients with epilepsy had a history of febrile seizures). In malaria-endemic areas, most acute seizures are caused by malaria, but whether they are febrile seizures or acute symptomatic seizures is unclear. Some studies have assessed the link between epilepsy and cerebral malaria (CM) as a consequence mostly in sub-Saharan Africa. In Gabon, a case-control study observed an adjusted odds ratio of 3.9 [95% CI, 1.7–89.0],  $p=0.001$ ) to develop epilepsy after CM. An additional risk factor was febrile convulsions (aOR=9.2, [95% CI, 4.0–21.1],  $p<0.0001$ ).<sup>14</sup> An exposed-non exposed study carried out in Mali reported a relative risk of 14.3 [95% CI, 1.6–132.0],  $p=0.01$ ) adjusted on age and duration of follow-up to develop epilepsy after a CM.<sup>15</sup> In the same way, seizures triggered by malaria infections could result from fever only (and then febrile seizures), but convulsions could also occur without fever in malaria.<sup>16</sup> The authors assumed that interleukins involved in inflammatory reaction could be involved in the association between seizures with CM and sequelar epilepsy, the same interleukins that are involved in the generation of febrile seizures and epileptogenesis.

Assessing the epidemiology of illness is a duty to further medicine knowledge; however, every disease can have variations in expression and etiology due to many known and unknown factors. This postulate emphasizes the importance of performing studies in various countries, areas (rural, urban), and populations to collect as much useful and relevant data as possible. As example of NCC, which is endemic in many regions where pigs are raised including Latin America, Africa, and Asia, but more often a public health issue in resources-limited settings has been quite assess. For now, aside from the epidemiological data that have been measured, new research approaches have been pointed out, such as human NCC, which offers opportunity to understand basic mechanisms of seizures.<sup>17</sup> To focus on Latin America, Brazil does not have the same health concerns than low and middle-income countries (LMICs). However, neurological affections such as epilepsy are not insignificant. In a cross-sectional evaluation of neurological diseases in a rural region of Brazil, the most common groups of diseases were headache (32.2%) and epilepsy (16.3%).<sup>18</sup> But in contrast of tropical and sub-tropical areas, tropical diseases (including malaria) were observed in a lower proportion than expected in this study, even though Brazil is a country that present most of the main tropical diseases according to WHO. Each of these elements highlights the difficulties and the danger to generalize a result in all situations, mainly due to randomness and unpredictable events. Performing a well-conducted

study requires several features that are not easily reachable under all circumstances. Bharucha et al.<sup>19</sup> raised methodological difficulties in the conduction of epidemiological studies in LMICs. To specify, LMICs face regulatory issues and lack of infrastructure (lack of census data, lack of a well-developed healthcare system, etc.), with a wide variety of different key features (perception of the disease, language, migratory patterns, etc.) depending of regional conditions and environmental factors. Medical tools frequently used in primary studies, such as the questionnaire to identify cases in the Dalbem study, must be adapted to local conditions and validated in order to give relevant and meaningful data. Only with uniform and comparable methodology, primary studies can provide usable data for systematic reviews and meta-analyses. These recommendations are even more important for public health issues, as epilepsy remains one of the major neglected diseases. Indeed, approximately 70 million people worldwide may have epilepsy, and nearly 80% of them live in resource-limited countries. In 2011, Thurman et al.<sup>20</sup> have defined standards (operational definitions, methods, useful analysis, etc.) for these studies, taking into account the variability of country resources and different study purposes. Each study, as that by Dalbem et al. in Brazil, should be supported and encouraged to provide essential information needed for extend the understanding of the disease, to promote prevention and effective healthcare, and to contribute for the development of operational support programs.

### Conflicts of interest

The authors declare no conflicts of interest.

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