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Febrile seizure and related syndromes

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ABSTRACT

Febrile seizures (FS) are the result of particular sensitivity to fever in the developing brain, have a major genetic predisposition, and nearly always have a benign outcome. Febrile seizures are the most common for of seizures in childhood. They have been observed in 2–6% of children before the age of 5 years, but in some populations this figure increase to 15%. Febrile seizures could be the first manifestations of epilepsy. About 13% of epileptic patients have a history of febrile seizures, and 30% have had recurrent febrile seizures Their phenotypic characteristics allow, in the majority of cases, a classification of the seizure, an elaboration of a prognosis and to assume a specific therapeutic attitude. It is possible to describe a spectrum according to their severity, from the benign simple seizure to the more complex, febrile seizure plus (GEFS+), Dravet syndrome, Epilepsy syndrome related infection febrile FIRES and Idiopatic Hemiconvulsion Hemiplegia and Epilepsy syndrome (IHHE). FS has a multifactorial inheritance, suggesting that both genetic and environmental factors are causative. Five areas of the genome have shown to be linked to FS in some ways. Two of them, FEB1 and FEB2 found on chromosomes 8 and 19p, are only involved in FS. During the past decade, molecular genetic studies have contributed to identification of genetic factors involved in febrile seizure and related disorders marking the necessary of careful follow up of the patients in order to detect risk factor earlier. We have reviewed the medical literature to update current knowledge of febrile seizures, their prognosis and their relation to new epileptic syndromes.

1. Introduction

Febrile seizures are the most common paroxysmal episode during childhood, affecting up to one to de 10 children. Febrile seizures (FS) are among the most common reasons that patients present with to pediatric emergencies.

FS has been recognized as a separate disease entity from other type of seizures since the early mid-nineteenth century. These seizures are classically associated with high fever in children during their lives (Hirtz et al., 2003). Their etiology and pathophysiological pathways are being understood better over time; however, there is still more to learn. Genetic predisposition is thought to be a major contributor leading to an increased susceptibility to seizure (Lennox, 1949).

Febrile seizures have been historically classified as benign; however, many emerging febrile seizure syndrome behave differently.

Lennox was the first clinician to study the background and risk factors for FS and the risk of progression to epilepsy (Lennox, 1949).

The American Academy of Pediatricś (AAP) committee of quality improvement published the first evidence-based practice parameters for FS (Baumann & Duffer, 2000). The International League Against Epilepsy (ILAE) then developed a clearer consensus regarding the recognition and treatment of children with FS (Capovilla, Mastrangelo, Romero, & Vigevano, 2009). More recently, the American Academy Pediatrics (AAP) has announced a standard definition of febrile seizures as any seizure associated with fever of > 38 °C (rectal or tympanic), but without central nervous infection (CNS), metabolic disturbance or history of afebrile seizures, in child aged 6 months to 5 years (American Academy of Pediatrics, 2008).They are the result of a particular sensitive to fever in the developing brain, have a mayor genetic predisposition, and nearly always have a being outcome.

2. Physiopatology

2.1. Epidemiology, risk factors

The life-time prevalence of one or more febrile seizures is about

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3–4% of all children in North America and western Europe, but has been reported to be somewhat higher in Finland, Japan and Guam (Annegers, Hauser, Shirts, & Kurland, 1987; Camfiel & Camfield, 2015). The peak age is 18 months with about 80% of incident febrile seizures occurring between 1 and 3 years of age (Annegers et al., 1987; Camfiel & Camfield, 2015). Several studies have explored the profile of children with a first febrile seizure (Bethune, Gordon, Dooley, Camfield, & Camfield, 1993). Factors statically associated with a febrile seizure are family history of febrile seizures, any suggestion of neurological dysfunction or developmental disability, delayed neonatal discharge, and attendance at day care (Huang et al., 1999).

Based on many studies, it becomes clear that febrile seizures have a major genetic predisposition (Camfiel & Camfield, 2015).

It has been demonstrated that there is an increased risk of febrile seizures shortly after many childhood vaccinations, including acellular pertussis (Chung, 2014; Hirtz, Nelson, & Ellenberg, 1983). It is now understood that this association is simply based on vaccine-induced fever in a susceptible child (Brown, Berkovic, & Scheffer, 2007).

Vaccine administration represents the second most common medical event associated with FS, after viral infection (Kohl et al., 2004; Principi & Esposito, 2013). Immunization has been associated with FS and an event occurring within 72 h of immunization is commonly accepted as being associated with vaccine (Kohl et al., 2004).

Exceptions are represented by the live-attenuated vaccines for which febrile seizure may be delayed until 7–14 days after vaccination. Estimates of relative risk of seizure are dependent on vaccine type and components (Brown et al., 2007). Seizure is more likely to occur after administration of certain vaccines, particularly live-attenuated vaccines such as the measles, mumps, and rubella (MMR) vaccine and toxin-2 containing or whole cell preparations such as diphtheria-tetanus-cellular pertussis (DTaP) (Blumberg et al., 1993; Braun, Montrey, Salive, Chen, & Ellenberg, 2000; Chung, 2014).

Administration of acetaminophen at the time of primary immunization with an inactive–component vaccine (DtwP-Polio) has been shown to significantly reduce or prevent the appearance of fever and found wide acceptance (Ipp et al., 1987; Lewis et al., 1988). Ibuprofen and acetaminophen have been equally recommended for administration at the time DTaP immunization, both prior to vaccination, and every 4 h for 24 h thereafter for children with a history of FS, to reduce the possibility of post-vaccination fever (Baumann & Duffer, 2000).The administration of acetaminophen and ibuprofen do not prevent febrile seizures caused by another cause. None of standard vaccinations is currently contraindicated for children with FS (Chung, 2014; Sugai, 2010).

2.2. Etiology

Febrile seizures have a familial tendency in some cases and are sporadic in others, suggesting that both genetic and environmental elements contribute to their generation (Chung, 2014). Family history also has a role in determining whether children have FS recurrences and subsequently develop afebrile seizures (Berg, Shinnar, Levy, & Testa, 1999). Twenty –five to 40% of patients showed a positive family history for FS; the incidence of FS being 20.7% among sibling, 10.9% among parents, and 14% among first degree relatives of probands (Greenberg & Holmes, 2000). Five areas of the genome have shown to be linked to FS in some way. Two of them FEB1 and FEB2, found on chromosomes 8q and 19p, are only involved in FS (Greenberg & Holmes, 2000).

A new FS susceptibility locus, FEB4 (chromosome 5q14) was suggested in nuclear FS families, indicating that FEB4 may be the most common linkage locus in FS families (Iwasaki, Nakayama, Hamano, Matsui, & Arinami, 2002). Although the mechanism of FS remains unclear, animal model are informative (Dube & Brewster Al Baram, 2009).First elevated brain temperature alters many neuronal functions, including several temperature-sensitive ion channels. Second, the fever promoting pyrogen interleukin – 1B contributes to fever generation and conversely, fever leads to the synthesis of this cytokine in the hippocampus (Shibasaki, Suzuki, Mizumo, & Tominga, 2007). In addition, intereukin – 1B has been shown to increase neuronal excitability, acting via both glutamate and GABA. These actions of interleukin 1B enhance the actions of seizure provoking agents.

Third, hyperthermia-induced hyperventilation and alkalosis have been proposed as a pivotal element of FS generation in that alkalosis of the brain provokes neuronal excitability and contributes to seizure pathophysiology (Aram & Lodge, 1987). Recently, clinicians have begun to re-classifying, febrile seizure (FS) as either simple or complex (American Academy of Pediatrics, 2008) The concept is that simple febrile seizure are associated with a very low risk of long term squeal, while complex febrile seizures carry a much greater risk (Sugai, 2010).

A simple febrile seizure last lees than < 10 min, is generalized, and does not repeat in 24 h the same illness. Subjects with simple febrile seizures have a risk of subsequent epilepsy of 2–3%, which is greater than in the general population (Camfiel & Camfield, 2015)

A complex febrile seizure may be long (> 15–20 min) is focal, or reacted in > 24 h in the same illness. Complex febrile seizures are followed by epilepsy in 4–15% (Annegers et al., 1987). One study showed a 13% incidence of epilepsy caused by the presence of at least two of the following risk factors. The risk factors for developing subsequent epilepsy after FS are summarized in Table 1.

3. Febrile status convulsive

This condition describes prolonged FS lasting more than 30 min in duration. Most of our current knowledge about this condition comes from the famous FEBSTAT study (Lewis et al., 2014). The peak age is between 12 and 24 months, and this condition is very unusual after 5 years. Two –thirds of seizures are generalized, and one-third is of focal semiology. There is no clear reason why some children tend to have prolonged FS and other does not. The Wolf-Hirschhorn syndrome (SWH) or Syndrome 4p- is a developmental disorder characterized by typical craniofacial features, delayed pre-and postnatal growth, mental retardation, severe psychomotor retardation, seizure and hypotonia. Status epilepticus occurs in half of the patients. More than 30% of children develop atypical absences from 1 to 6 years old. SWH is caused by delection in the short arm of chromosome 4 (4p16.3 region) including at least one of the genes LETM1 and WHSC1 (Motoi et al., 2016). Magnetic resonance imaging (MRI) studies show hippocampal swelling in half of patients from the third day of seizure. Whether this is the start of the process evolving into temporal lobe epilepsy has been debated for over 50 years.

4. Indications for lumbar puncture, electroencephalography, and neuroimaging studies

Recommendations by the AAP (2008) for lumbar puncture (LP) in children with first simple FS were summarized as follows: 1) in infant younger than 12 months, performance of a LP is strongly revised,

Table 1
Risk factors for developing subsequent epilepsy after FS.

Definite risk factor
Neurodevelopment abnormality
Complex FS
Family history of epilepsy
Duration of fever
Possible risk factor
> 1 complex feature
Not a risk factor
Family history of FS
Age at first FS
Peak temperature
Sex and ethnicity