An overview of risk factors in children with febrile seizures

Les facteurs de risque chez les enfants atteints de convulsions fébriles

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Abstract

Introduction: Febrile seizures (FS) are the most common neurologic disorder seen in children. Caused mainly by fever without any damage to the central nervous system (CNS). The associations of several factors, which we can find in the inflammatory response and genetic predisposition, are involved in the occurrence of FS.
Aim: This review provides insight into risk factors, particularly the involvement of the inflammatory response and genetic susceptibility in the occurrence of FS.
Methods: A PubMed search was performed using the keywords « febrile seizures », « inflammatory response », « Pro-inflammatory cytokines », «And anti-inflammatory cytokines ». The search strategy included meta-analyses, prospective case-control studies, clinical trials, observational studies, and reviews.
Results: Febrile seizures with a peak incidence of 18 months usually occur between 6 months and 5 years. A variety of genetic, inflammatory, and environmental factors, including viruses and vaccines, trigger FS. A positive family history of febrile seizures increases the risk for FS occurrence with (20%) in siblings and (33%) in one parent. The involvement of inflammatory response genes, including the cytokine genes IL1B, IL1R, IL6, and IL4. According to these findings, FS is associated with the activation of a cascade of pro- and anti-inflammatory cytokines and the unbalance between these cytokines in the inflammation regulation plays a role in the development of FS.
Conclusion: Current knowledge suggests that genetic susceptibility and inflammatory response dysregulation contribute to FS's genesis.

Key words: Febrile seizures, inflammatory response, Cytokines, Genetics.

Résumé

Intoduction: Les convulsions fébriles (CF) sont le trouble neurologique le plus observé chez les enfants. Provoqués principalement par la fièvre en dehors de toute atteinte du système nerveux central (SNC), L'association de plusieurs facteurs y compris la réponse inflammatoire et la prédisposition génétique sont impliqués dans la survenue des CF.
Objectif: Cette revue donnera un aperçu sur les facteurs de risque, en particulier l'implication de la réponse inflammatoire et la prédisposition génétique dans la survenue des CF.
Méthodes: Une recherche sur PubMed a été effectuée en utilisant les termes clés suivants « Convulsions fébriles », « Réponse inflammatoire », « Cytokines pro-inflammatoires », « Cytokines anti-inflammatoires ». La stratégie de recherche comprenait des méta-analyses, des études prospectives cas témoins, des études cliniques, des études observationnelles et des revues.
Résultats: Les CF, surviennent généralement entre 6 mois et 5 ans avec une incidence maximale de 18 mois. Plusieurs facteurs génétiques, inflammatoires et environnementaux, y compris les virus et les vaccins, déclenchent les CF. Les facteurs de risque de l'apparition des CF augmente avec les antécédents familiaux de CF, avec (20 %) chez les frères et sœurs et (33 %) chez l'un des parents. L'implication des gènes de la réponse inflammatoire, notamment les gènes des cytokines IL1B, IL1R, IL6 et IL4. Selon ces résultats, les CF sont associé à l'activation d'une cascade de cytokines pro- et anti-inflammatoires et le déséquilibre entre ces cytokines dans la régulation de l'inflammation joue un rôle dans le développement des CF.
Conclusion: Les données actuelles suggèrent que la prédisposition génétique et la dérégulation de la réponse inflammatoire contribuent à la survenue des CF.

Mots clés: Convulsions fébriles, Inflammation, Cytokines, Génétique.

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Introduction

Febrile seizures (FS) are the most frequent neurological disorder, in children between 6 months and 5 years of age, caused by fever, without central nervous system (CNS) involvement. The pathophysiological mechanisms of FS are not clearly defined. Current data suggest that inflammation and genetic predisposition are involved in the occurrence of FS and its progressive modes [1]. This review discusses the different characterization issues of FS and its underlying mechanisms.

Terminology

There are three published definitions for febrile seizures (FS). The first definition of FS was published in 1980 by the National Institutes of Health (NIH), which defined an FS as "an event in infancy or childhood, usually occurring between three months and five years of age, associated with fever, but without evidence of intracranial infection or defined cause" [2]. The International League against Epilepsy (ILAE) published the second definition in 1993, which defined an FS as "a seizure occurring in childhood after one month of age, associated with febrile illness not caused by CNS infection, without previous neonatal seizures or previous unprovoked seizures, and not meeting the criteria of other acute symptomatic seizures" [3]. Another more recent definition in 2011 announced by the American Academy of Pediatrics (AAP), defined FS as a seizure occurring in febrile children aged 6 to 60 months who do not have an intracranial infection, metabolic disorders, or a history of afebrile seizure [4].
In all three definitions, the level of temperature is not indicated. In addition, there is a difference in the age of onset of FS, which can be 1 month, 3 months, or even 6 months. However, they all agree on the absence of a history of afebrile seizures, CNS infection, and an acute cause that could explain the occurrence of seizures [5].

Epidemiology

Febrile seizures are the most common pediatric neurological disorder. They are frequent for both boys and girls. However, some studies have concluded that there is a slight masculine predominance [6]. The incidence of FS varies between countries, the highest incidence is found in the Guam population (14%), followed by the Japanese population (7-10%). The incidence in Europe and America varies between 2 to 5% [7]. In Morocco, there is no epidemiological study reported to date.
The majority of FS cases occur during the winter months and in the evenings [8]. A Japanese study reported two peaks of incidence, from November to January and from June to August, matching the peaks of upper respiratory viral infections and gastrointestinal infections, respectively [8, 9]. Furthermore, an Italian study showed a significant increase in FS during the evening and a seasonal peak in January [9, 10].

Risk factors

Role of viruses and vaccination

Several risk factors have been incriminated in the occurrence of FS. Some viruses, notably influenza A and B (15-50%), Enterovirus (20-38.9%), Adenovirus (11-21%), and HHV6 (20%) have been strongly associated with FS in children [11, 12].
A febrile reaction following vaccination is common in infants. According to the Australian Childhood Immunization Register, FS following a recent vaccination occurs in 11% of cases, mainly with simple FS [13]. The most incriminating vaccines (88%) were measles, mumps, and rubella (MMR) on average 9 days before FS. No child was enrolled with a febrile seizure after the influenza vaccine [13].

Genetic susceptibility

Genetic factors constitute, according to the literature, an important risk factor in the occurrence of FS. This risk increases even more with a history of FS in the siblings (20%) or with one of the parents (33%). Family studies have shown an incidence of FS of about 35% to 69% in monozygotic twins and 14% to 20% in dizygotic twins [1,14].
The suspected genetic determinants have been located at the following chromosomal loci (19q, 19p13.3, 18p11.2, 8q13-21, 6q22-24, 5q14-15, and 2q23-34). However, there is no established mode of inheritance. The polygenic and autosomal dominant modes are the most commonly suggested [14]. Studies have also associated FS with several mutations for example the gene coding for the γ2 subunit of the gamma-aminobutyric acid (GABA) receptor, the gene coding for the SCN1A, SCN1B, and the SCN9A sodium canal [15,16]. Studies have also shown the involvement of inflammatory response genes in the occurrence of FS. Indeed, mutations in cytokine genes including IL1B, IL1R, IL6, and IL4, have been reported in these studies [17, 18, 19].
Nevertheless, studies in this area have not been able to characterize an exact underlying molecular cause of FS. Most of these studies use a candidate gene approach targeting a limited number of genes. The use of exome sequencing or whole genome sequencing-based approaches may be a good alternative.

Clinical manifestations

According to the clinical state presented by the patient, FS can be simple or complex. The classification of FS is based on the duration of the seizure, the recurrence of the seizure during the 24 hours of fever progression, the focal or generalized character, and the post-critical state (Table 1). Studies have shown that simple febrile seizures represent about 80 to 85% of all febrile seizures [20]. Simple febrile seizures are generally benign, but there is a risk of developing epilepsy in adulthood in some children with complex febrile seizures [1].

Table 1. classification features of simple and complex febrile seizures (FS) [21].

	Simple FS	Complex FS
Duration	< 15 min	> 15 min
Recurrence within 24 hours	1 seizure / 24h	> 1 seizure / 24h
Focalization	Generalized seizure	Partial seizure
Post critical status	Rapid recovery	May have neurological abnormalities

Etiopathology

The cause of febrile seizures is multifactorial. They seem to result from a combination of different factors that vary between individuals. Vulnerability of the developing (CNS) to fever effects, genetic susceptibility, family history of FS in parents or siblings, and inflammation constitute the predisposing factors of FS according to several studies [21].

Inflammation is considered the most important factor in the pathogenesis of FS. Several studies have shown the involvement of immune response components in the occurrence of FS, particularly the activation of the inflammatory cytokine network [17, 18, 19, 21].

Role of fever in FS

Fever occurs during an inflammatory reaction triggered by an infection. A pathogen in the body causes cytokines release including IL-1β, IL-6, TNF-α an,d INF- γ. These proinflammatory cytokines, produced by different cell types, increase the reference value of the hypothalamic thermostat via prostaglandin E2 (PGE2) [16, 22]. However, the use of antipyretics that inhibit PGE2 production does not decrease the risk of FS occurrence [23, 24].

It has been shown that peripheral inflammation provokes a "mirror" inflammatory response in the CNS, characterized by excessive cytokine production and excessive action in the brain.[23,25]. These cytokines act on the brain and disrupt the blood-brain barrier (BBB) despite its protective role, altering its functional characteristics and causing its leakage. Several studies have revealed a modification in BBB permeability after the administration of IL-1, IL-6, TNFα, and INF-γ [25, 26, 16, 22].

This leakage of the BBB leads to the activation of microglia responsible for cytokine production in the CNS, such as IL-1β and IL-1ra which are simultaneously released and compete for the same binding site the IL-1 type 1 receptor (IL-1RI) [27,28,29]. The binding promotes IL-1β over IL1ra leading to an imbalance between IL-1β and IL-1ra [27, 28, 29, 30]. IL-1β acts on both excitatory (glutamatergic) and inhibitory (GABAergic) circuits in the brain, causing the dysregulation of these circuits and leading to seizures [29, 30, 22, 31]. In addition, it has been shown that an increased brain level of IL-1β increases neuronal excitability promoting the occurrence of seizures (Figure 2) [28, 32, 33]. It is also suggested that increased brain temperature affects many neuronal functions, including several temperature-sensitive ion channels, which increases the likelihood of synchronized neuronal activity leading to seizure induction [29,32].

Febrile seizures usually disappear by age 6, suggesting a likely link between seizure onset and stages of brain development in children. There is a difference in seizure susceptibility between immature and adult brains. Most evidence supports the age-specificity of brain sensibility to fever [33]. However, the exact mechanism of this enhanced sensibility is not clear. Heightened neuronal excitability during normal brain maturation has been suggested in animal models [33, 34].

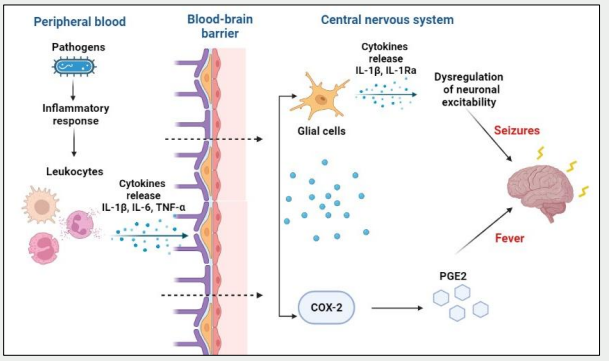

Figure 2. Diagram illustrating the pathogenesis of febrile seizures.

Following infection, an inflammatory response is triggered by a pathogen, which is followed by cytokine release by leukocytes such as IL-1β, IL-6, TNF-α, and INF-γ, which leads to changes in BBB permeability altering its functional properties and causing it to leak. This increased BBB permeability leads to excessive cytokine penetration into the brain highly sterile, which activates microglia and cyclooxygenase-2 (COX-2). COX-2 catalyzes the production of prostaglandin-E2 (PGE2) which induces fever in the hypothalamus. Additionally, activation of microglia releases pro- and anti-inflammatory cytokines such as IL-1β and IL-1Ra causing dysregulation of excitatory (glutamatergic) and inhibitory (GABAergic) brain circuits leading to seizures.

Role of the immune-inflammatory response

It is currently known that there is a link between inflammation and the occurrence of FS. Following infection, pro-inflammatory cytokines, produced by the organism during infections, have pro-convulsant effects [35, 36]. Experimental data suggest that IL-1β production is increased immediately during the first hours after seizures [37]. Well-known for its pro-convulsant and neurotoxic effects on neurons, IL-1β is inhibited by its natural antagonist IL1-ra, which has neuroprotective and anticonvulsant effects. [37, 38]. Anti-inflammatory cytokines, such as IL1-ra and IL-10, have a negative feedback effect on pro-inflammatory cytokine release and have anticonvulsant activity [38, 39].

In Table 2, we summarize the various case-control studies that have measured cytokines in FS patients over the past 10 years. This table shows conflicting results between

studies, particularly for IL-1β levels in the blood and CSF of FS patients have been reported (Table 2). Jieun Choi and al., Mei-Hua Hu and al., and Ahmad Talebian and al. have reported a high blood level of IL-1β in FS [37, 40, 41]. Kai A. Lehtimäki and al. and Abolfazl Mahyar and al. [42, 43] revealed low blood and CSF levels of this interleukin in patients with FS. In the remaining studies, no significant difference was reported between febrile children with seizures and their controls in both blood and CSF. [45,45,46]. These conflicting findings between studies could be explained by the fact that IL-1β is generally difficult to detect due to its binding to large proteins such as α-2 macroglobulin and complement, and by a compensatory suppression mechanism due to its natural antagonist IL1-ra, especially when the seizure is prolonged [42]. For pro-inflammatory cytokines, such as IL-6, TNF-α, INF- γ, IL-8, and IL-17. High blood levels have been reported by some authors [37, 40, 43, 45, 47, 48], while others have reported low blood levels of IL-6 and TNF-α, in patients with FS [43, 48].

Table 2. Findings of prospective studies from 2010 to 2020 on cytokines and FS.

Study (year of publication)	Number of FS patients	Nature of the sample	Dosage technique	Level of cytokines studied												References
				Pro-inflammatory								Anti-inflammatory				
				IL-1β	Il-6	TNF-α	IFN-γ	Il-2	Il-8	Il-12	Il-17	Il-10	Il-1ra	Il-4	Il-22	
Kai A. Lehtimäki (2010)	N= 24	CSF	Elisa	-	*NM*							*NM*	+	*NM*		43
Jieun Choi (2011)	N= 41	Serum	Elisa	+	+	*NS*	*NS*	*NM*				+	*NM*			40
Fatemeh Behmanesh (2012)	N=30	Serum	Elisa	*NS*	*NM*											45
Mei-Hua Hu (2013)	N= 9	Serum	Flow cytometry	+	+	*NS*	+	*NS*	NM	*NS*	+	+	*NM*	*NS*	*NS*	41
Abolfazl Mahyar (2014)	N=46	Serum	Elisa	-	*NM*	-	*NM*					*NM*				44
Kyungmin Kim (2017)	N= 50	Serum	Luminex	*NS*	+	*NM*	+	*NS*	+	*NM*		+	+	*NM*		46
Jongseok Ha (2018)	N= 50	Serum	Elisa	*NM*		+	*NM*					*NM*		+	*NM*	48
Surbhi Gupta (2018)	N= 80	Serum	Elisa	*NM*	-	*NM*						*NM*				49
Sevim Şahin (2019)	N= 76	CSF	Elisa	*NS*	*NM*					*NS*	*NM*	-	*NM*			47
Ahmad Talebian (2020)	N=60	Serum	Elisa	+	NM							*NM*			*NS*	42

(-): Low level / (+): High level / (NS): No significant difference / (NM): not measured.

Regarding anti-inflammatory cytokines, increased levels of these cytokines in blood and CSF of patients with FS have been reported in several studies [37, 42, 40, 45, 47]. The authors explain these high levels of anti-inflammatory cytokines by their neuroprotective and anticonvulsant actions to counterbalance the convulsive effect of inflammatory cytokines. However, in another study, the authors reported low levels of IL-10 in the CSF of children with FS. The size of the study population is the main limitation of this study [46].

The findings from various studies show that FS is associated with the activation of a cascade of pro- and anti-inflammatory cytokines and that the unbalance between these cytokines in the inflammation regulation plays a role in the occurrence of FS. [38, 42].

Conclusion

Febrile seizures are common and generally benign, among children aged 6 months to 5 years.

The occurrence of FS seems to be the result of the interaction of several factors including common viral infections in childhood, genetics, and inflammation. Despite the various studies conducted, the physiopathological mechanisms of FS remain poorly explained. However, it is currently admitted that there is a genetic susceptibility and that the unbalance between pro-inflammatory and anti-inflammatory cytokines plays an important role in the occurrence of FS in some febrile children.

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