Received: 02.11.2020

Accepted: 15.03.2021

Published: 04.06.2021

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Aetiology of febrile seizures – a problem not fully understood

Etiologia drgawek gorączkowych – problem nie w pełni poznany

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Abstract

Febrile seizures are seizures that occur during febrile illnesses in the absence of central nervous system infection or other identifiable aetiology in children who have never had any non-febrile seizures before. Although the condition is quite common, affecting 2–5% of children between 3 months and 5 years of age, the underlying pathomechanism is not fully explained. Immaturity of the nervous system, as well as environmental, genetic and immune factors are contemplated. Viruses are the main aetiological factor of febrile infections accompanied by seizures. The risk of febrile seizures after vaccination is low and may be associated with the child's genetic predisposition. Deficiency of trace elements, including zinc and iron, may also promote seizures. The association between febrile seizures and vitamin D levels was reported in only few studies. It seems that genetic background plays an important role, at least in some cases. In recent years, particular attention has been paid to the possible involvement of immune factors, including pro- and anti-inflammatory cytokines. Previous studies on the aetiology of febrile seizures confirmed their multifactorial nature and indicated their heterogeneity within this group of patients. Further research may not only contribute to a better understanding of the mechanisms underlying the pathogenesis of febrile seizures, but also determine the direction of actions that may reduce the risk of their occurrence and/or recurrence.

Keywords: febrile seizures, cytokines, vitamin D, vaccinations, coronavirus

Streszczenie

Drgawki gorączkowe to napady drgawek występujące w trakcie chorób przebiegających z gorączką, przy braku infekcji ośrodkowego układu nerwowego lub innych dających się określić przyczyn napadu, u dzieci, które nie miały wcześniejszych napadów niezwiązanych z gorączką. Mimo że zaburzenie nie jest rzadkie i dotyczy około 2–5% dzieci w wieku od 3. miesiąca do 5. roku życia, jego patomechanizm nadal nie został w pełni wyjaśniony. Pod uwagę bierze się między innymi niedojrzałość układu nerwowego, uwarunkowania środowiskowe, genetyczne i immunologiczne. Wśród przyczyn infekcji gorączkowych, którym towarzyszą drgawki gorączkowe, dominują infekcje wirusowe, natomiast ryzyko wystąpienia drgawek gorączkowych po szczepieniu jest niewielkie i może się wiązać z predyspozycją genetyczną dziecka. Wśród przyczyn mogących je promować uwzględnia się niedobory pierwiastków śladowych, w tym cynku i żelaza. Jedynie pojedyncze badania odnosiły się do związku drgawek gorączkowych ze stężeniem witaminy D. Istotną rolę, przynajmniej w części przypadków, wydają się odgrywać uwarunkowania genetyczne. W ostatnich latach szczególną uwagę zwrócono na możliwy udział czynników immunologicznych, w tym cytokin prozapalnych i przeciwzapalnych. Dotychczasowe badania dotyczące etiologii drgawek gorączkowych potwierdzają ich wieloczynnikowy charakter i wskazują na ich heterogenność w obrębie tej grupy pacjentów. Dalsze badania mogą nie tylko przyczynić się do lepszego poznania mechanizmów związanych z patogenezą drgawek gorączkowych, ale również wskazać kierunek działań mogących wpłynąć na zmniejszenie ryzyka ich wystąpienia i/lub nawrotu.

Słowa kluczowe: drgawki gorączkowe, cytokiny, witamina D, szczepienia, koronawirus

INTRODUCTION

Descriptions of febrile seizures (FS) date back to the times of Hippocrates⁽¹⁾. This ancient physician found a relationship between seizures and fever in children, noting that the condition primarily affects children under the age of 7 years. Hippocrates also pointed out that children between 16 and 20 months of age are at the highest risk. Febrile seizures are seizures that occur during febrile illnesses, in the absence of central nervous system infection or other identifiable aetiology (e.g. electrolyte imbalance, hypoglycaemia, pharmacotherapy) in children who have never had any non-FS before. It is estimated that about 2–5% of children aged between 3 months and 5 years experience at least 1 FS episode, with peak incidence at 18 months⁽²⁾. Similar rates of FS (2.69%) have been also reported for a Polish population of children from the Łódź region⁽³⁾.

Simple FS are generalised, they last up to 15 minutes and occur once a day, while complex FS have focal symptoms, last longer than 15 minutes and/or occur more than once during one febrile episode⁽²⁾. Although FSs are not a rare disorder in paediatric practice, their pathomechanism has still not been fully explained. Immaturity of the nervous system, environmental, genetic and immune factors are contemplated.

ENVIRONMENTAL FACTORS

The first years of a child's life are a time of further intensive development and maturation of the nervous system, which is associated with its high plasticity, but, at the same time, sensitivity to environmental factors. Environmental risk factors for FS include intrauterine foetal hypotrophy, prematurity, prolonged hospitalisation in the neonatal period, maternal smoking and/or alcohol consumption during pregnancy, developmental disorders in the child, attending a nursery (higher risk of infection), positive family history of FS⁽²⁾.

Trace elements may also play a role in the pathogenesis of seizures. They affect synaptogenesis, ligand- and voltage-gated ion channels, peroxidation, neurotransmitter synthesis, and immune function. Higher copper levels and lower selenium, zinc and iron levels (in the acute phase of fever) were found in patients with FS compared to controls with non-convulsive fever^(4–6). Some reports also indicate lower sodium and potassium levels in the group of children diagnosed with FS compared to controls⁽⁷⁾.

THE AETIOLOGICAL FACTOR OF INFECTION

Viral respiratory and gastrointestinal infections are dominant causes of febrile infections accompanied by FS. The viruses most strongly associated with FS include human herpes virus type 6, respiratory syncytial virus, influenza and parainfluenza viruses, human coronavirus,

rotavirus, adenovirus, norovirus, and human bocavirus^(8–10). It is worth noting that children with diarrhoea without electrolyte disturbances or fever may develop benign convulsions with mild gastroenteritis (CwG)⁽¹¹⁾.

The observations and studies to date indicate neurotropic and neuroinvasive properties of coronaviruses in humans. Such human pathogens include HCoV-OC43, HCoV-229E, HCoV-HKU1 and HCoV-NL63, as well as epidemic viruses: SARS-CoV, SARS-CoV-2 and MERS-CoV. Neurological problems found in patients with coronavirus infection include FS, convulsions, change in mental status, encephalomyelitis, and encephalitis^(12,13). Neurological symptoms reported in patients infected with SARS-CoV-2 causing COVID-19 disease (coronavirus disease 2019) include headache, dizziness, impaired consciousness, acute cerebrovascular diseases, ataxia, and seizures. These disturbances may be a consequence of the direct influence of the virus, its effects on the immune system, as well as respiratory and circulatory failure and concomitant metabolic disorders and hypoxia^(12,13). This virus may also contribute to FS. There have been isolated reports on febrile status epilepticus in children with multisystem inflammatory syndrome associated with SARS-CoV-2 infection (MIS-C)^(14,15).

VACCINATIONS

The risk of developing FS after vaccination is low and may be related to the child's genetic predisposition. Vaccines associated with an increased risk of FS include measles (MMR), a whole-cell pertussis-component diphtheria-tetanus-pertussis vaccine (DTP) vaccine, some trivalent inactivated influenza vaccines (TIV), and 13-valent pneumococcal conjugate vaccine (PCV13)^(2,9). Not all influenza vaccines increase this risk. A large population study in Norway conducted during the 2009 influenza A (H1N1) epidemic showed an increased risk of FS 1–3 days after pandemic vaccination (incidence rate ratio, IRR = 2.0). It turned out, however, that the infection with the pandemic influenza virus was associated with a much stronger increase in the risk of FS than the vaccination itself (IRR = 116.70 on the day of symptom onset, IRR = 10.12 within 1–3 days of onset)⁽¹⁶⁾.

It should be remembered that vaccinations reduce the risk of febrile infection and may therefore contribute to a reduced risk of FS. Research on the rotavirus vaccine has suggested a possible protective effect of vaccination in terms of reducing the risk of FS⁽¹⁷⁾.

GENETIC FACTORS

About 30% of children with FS have a positive family history of febrile convulsions. Studies in twins and family studies helped identify familial genes responsible for FS, while possible differences in phenotypes within a given family suggest incomplete gene penetration and a multifactorial

Location	Phenotype	Inheritance	Gene
2q24.3	Generalized epilepsy with febrile seizures plus, type 2	AD	SCN1A (GEFSP2, SMEI, FEB3A, EIEE6, FHM3)
2q24.3	Febrile seizures, familial, 3A	AD	SCN1A (GEFSP2, SMEI, FEB3A, EIEE6, FHM3)
2q24.3	Generalized epilepsy with febrile seizures plus, type 7	AD	SCN9A (NENA, PN1, FEB3B, GEFSP7, SFNP, HSN2D)
2q24.3	Familial febrile seizures, 3B	AD	SCN9A (NENA, PN1, FEB3B, GEFSP7, SFNP, HSN2D)
3p24.2–p23	Familial febrile seizures, 9	AD	FEB9
3q26.2–q26.33	Familial febrile seizures, 10		FEB10
5q14.3	Familial febrile seizures, 4	AD	ADGRV1 (GPR98, MASS1, VLGR1, KIAA0686, FEB4, USH2C)
5q34	Familial febrile seizures, 8	AD	GABRG2 (EIEE74, FEB8, ECA2, GEFSP3)
5q34	Generalized epilepsy with febrile seizures plus, type 3	AD	GABRG2 (EIEE74, FEB8, ECA2, GEFSP3)
6q22–q24	Familial febrile seizures, 5	AD	FEB5
8q13–q21	Familial febrile seizures, 1	AD	FEB1
8q13.2	Familial febrile seizures, 11	AR	CPA6 (CPAH, ETL5, FEB11)
18p11.2	Familial febrile seizures, 6	AD	FEB6
19p13.3	Familial febrile seizures, 2	AD	FEB2
21q22	Familial febrile seizures, 7		FEB7

AD – autosomal dominant; **AR** – autosomal recessive.

Tab. 1. Familial febrile seizures phenotypes (based on: <https://www.omim.org/phenotypicSeries/PS121210>)

Location	Phenotype	Inheritance	Gene
1p36.33	Generalised epilepsy with febrile seizures plus, type 5	AD	GABRD (GEFSP5, EIG10, EJM7)
1p36.33	Idiopathic generalised epilepsy, 10	AD	GABRD (GEFSP5, EIG10, EJM7)
1p36.33	Juvenile myoclonic epilepsy	AD	GABRD (GEFSP5, EIG10, EJM7)
2p24	Generalised epilepsy with febrile seizures plus, type 4	AD	GEFSP4
2q24.3	Familial febrile seizures, 3A	AD	SCN1A (GEFSP2, SMEI, FEB3A, DEE6, DRVT, FHM3)
2q24.3	Generalised epilepsy with febrile seizures plus, type 2	AD	SCN1A (GEFSP2, SMEI, FEB3A, DEE6, DRVT, FHM3)
2q24.3	Familial febrile seizures, 3B	AD	SCN9A (NENA, PN1, FEB3B, GEFSP7, SFNP, HSN2D)
2q24.3	Generalised epilepsy with febrile seizures plus, type 7	AD	SCN9A (NENA, PN1, FEB3B, GEFSP7, SFNP, HSN2D)
5p12	Generalised epilepsy with febrile seizures plus, type 10	AD	HCN1 (BCNG1, DEE24, GEFSP10)
5q34	Generalised epilepsy with febrile seizures plus, type 3	AD	GABRG2 (EIEE74, FEB8, ECA2, GEFSP3)
5q34	Familial febrile seizures, 8	AD	GABRG2 (EIEE74, FEB8, ECA2, GEFSP3)
6q16.3–q22.31	Generalised epilepsy with febrile seizures plus, type 8		GEFSP8
8p23–p21	Generalised epilepsy with febrile seizures plus, type 6		GEFSP6
16p11.2	Generalised epilepsy with febrile seizures plus, type 9	AD	STX1B (GEFSP9)
19q13.11	Generalised epilepsy with febrile seizures plus, type 1	AD	SCN1B (GEFSP1, BRGDA5, ATFB13, EIEE52)

AD – autosomal dominant.

Tab. 2. Generalised epilepsy with febrile seizures plus (based on: <https://www.omim.org/phenotypicSeries/PS604233>)

nature of the disorder. Febrile seizures can also be the first manifestation of epilepsy, including Dravet syndrome or genetic epilepsy with febrile seizures plus, GEFS+) ^(2,18,19) (Tabs. 1, 2).

IMMUNE FACTORS – CYTOKINES

Pro-inflammatory cytokines seem to play an important role in the mechanism modulating the seizure response during an infection ⁽³⁾. However, their role has not been clearly explained. The differences between individual studies may result from the time of sample collection, the type of infection or fever severity and duration ⁽²⁰⁾.

Interleukin 1 β (IL-1 β) has strong pro-inflammatory and pyrogenic properties as well as promotes convulsions. Its possible involvement in the epileptogenesis has also

been postulated. The interleukin 1 receptor antagonist (IL-1RA), controlling the IL-1, is an anti-inflammatory protein. Studies indicate a relationship between the overexpression of IL-1 β and an imbalance between IL-1 β and IL-1RA and FS ^(20–22). Increased IL-1 and tumour necrosis factor (TNF) levels in response to exogenous pyrogens stimulate an increase in the levels of interleukin 6 (IL-6). Some studies have shown its potential relationship with FS ^(20,22). IL-6 may have both pro- and anti-convulsant effects. Furthermore, it may play a neuro-protective role in the case of prolonged convulsions, protecting nerve cells against ischaemic damage ⁽³⁾. Interleukin 10 (IL-10) inhibits the production of pro-inflammatory cytokines, including TNF- α , IL-1, IL-6 and IL-8, and its increased levels observed in experimental studies after the onset of a seizure may indicate

its protective and anticonvulsant role^(20,23). Literature data on the relationship between IL-10 and other cytokines (including IL-2, IL-4, IL-8, TNF- α) and FS are inconclusive^(3,20).

Advances in molecular biology allow for better understanding of the mechanisms underlying the disturbances in the immune response. Therefore, attention was paid to the role of genes involved in cytokine synthesis in the context of FS pathogenesis. Among these, single nucleotide polymorphism (SNP) at the –511 position of the IL-1 β gene promoter, *IL-1B* rs16944, *IL-6* (–174, –572 and –597), *TGF- β* at codon 10 (rs1982037), *IL-4* (–590 and –33), *TNF- α* (–238), *IL-2* at position –330 and polymorphism of the homozygous interleukin 1 receptor antagonist gene *IL1RN*2* and its allele 2 variable number of tandem repeats (VNTR) show an association with FS^(21,23–28).

VITAMIN D

A large body of data about vitamin D, including its role in immunomodulation and anti-inflammatory processes, has been collected in recent years. Vitamin D shows autocrine and paracrine effects, and controls the expression of over 200 different genes when combined with its receptor (VDR). Its active form stimulates (through macrophages) the innate responses, influences the chemotactic and phagocytic properties and the production of antibacterial peptides. It also influences the acquired immune response. It inhibits the maturation and differentiation of dendritic cells and inhibits, both through dendritic cells and directly, the differentiation of Th1 and Th17 cells. It also increases the population of Th2 suppressor cells. Vitamin D has also been suggested to influence the activity of regulatory T cells (Treg), including the CD4⁺FoxP3⁺ T cells, which release significant amounts of IL-10. Through its immunomodulatory effects, vitamin D inhibits the release of pro-inflammatory cytokines [interferon γ (IFN- γ), TNF- α , IL-2, IL-1 β , IL-6, IL-8 and IL-12] and stimulates the release of anti-inflammatory factors [IL-4, IL-5, IL-10 and transforming growth factor β (TGF- β)]⁽²⁹⁾.

Despite the great interest in the involvement of vitamin D in many clinical entities, there is little research on its potential role in FS. The prevalence of vitamin D deficiency in children diagnosed with FS may reach 75%. Furthermore, studies have shown that lower 25-hydroxy-vitamin D levels may be correlated with an increased risk of recurrent FS⁽³⁰⁾. Heydarian et al. found, on the other hand, that although serum vitamin D levels were lower in FS patients than in those with fever without accompanying seizures (41.92 ± 22.42 vs. 48.41 ± 15.25 $\mu\text{g/dL}$), this difference was not statistically significant⁽⁷⁾. The data collected so far indicate the need for further studies in this field. Our unpublished preliminary research indicates lower-than-normal vitamin D levels in 27.3% of children diagnosed with FS. It is worth noting that vitamin D deficiency

is lower in Polish children ≤ 2 years of age compared to older children due to supplementation of vitamin D, with its deficiency, defined as < 20 ng/mL, affecting 20% of infants 12 months of age and up to 85% of children aged 12–19 years⁽³¹⁾.

CONCLUSIONS

Previous studies on the aetiology of FS confirmed their multifactorial nature and indicated their heterogeneity within this group of patients. Further research may not only contribute to a better understanding of the mechanisms underlying the pathogenesis of FS, but also determine the direction of actions that may reduce the risk of FS occurrence and/or recurrence.

Conflict of interest

The authors do not report any financial or personal connections with other persons or organisations, which might negatively affect the contents of this publication and/or claim authorship rights to this publication.

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