# ASSESSMENT OF THE SIGNIFICANCE OF RISK FACTORS FOR THE TRANSFORMATION OF FEBRILE SEIZURES INTO EPILEPSY IN CHILDHOOD

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***Abstract.*** *Febrile seizures are an age–dependent and prognostically favorable condition that is observed in children under 6 years of age. Febrile seizures are classified as a group of conditions that do not require a mandatory diagnosis of epilepsy, and most children remain healthy. The genetic, social, exo- and endogenous factors of febrile seizures have been very well studied. Nevertheless, until now, many aspects of preventive measures for recurrent febrile seizures and their transformation into epilepsy remain controversial.*
***Keywords:*** *children; febrile seizures; epilepsy, febrile status, risk of epilepsy.*

Definitions. Febrile seizures are a common variant of paroxysmal conditions in pediatric practice. These are episodes of epileptic seizures that occur in preschool children with hyperthermia unrelated to neuroinfection [17,29]. According to the definition, febrile seizures are a benign, age-dependent, genetically determined condition in which the brain is susceptible to epileptic seizures that occur in response to high fever. Febrile seizures in most cases are transient in preschool children, but may also be part of the structure of individual epileptic syndromes [3,4]. For the first time, the term "febrile convulsions" was used to refer to convulsive paroxysms developing in childhood against the background of Hochsinge B. fever in 1904 [9]. Currently, it is preferable to use the term "febrile seizures" rather than "febrile seizures", since not only convulsive, but also non-convulsive paroxysms can be observed in the clinical picture, such as prolonged atonic, syncope-like states [3, 4, 16,23]. In the International Classification of Epilepsy and Epileptic Syndromes in 1989, AF was considered as a relatively benign disorder in childhood, and the risk of epilepsy in the future, the frequency of which is about 5% [11, 17, 29]. Later in 1993, the International Antiepileptic League (ILAE) gave the following definition: AF is seizures observed in children over the age of 1 month, associated with febrile disease not caused by CNS infection, without previous seizures in the neonatal period and unprovoked seizures, as well as not meeting the criteria of other acute symptomatic seizures [7]. According to the 2001 draft classification, AF is classified into a group of conditions that do not require a mandatory diagnosis of epilepsy [8]. Thus, AF is defined as an episode of epileptic seizures that occur in children aged 6 months to 5 years with an increase in temperature during a viral or bacterial disease unrelated to neuroinfection and metabolic disorders [1, 9, 6, 10]. True AF should be distinguished from febrile provoked seizures, which can be part of the structure of a number of forms of epilepsy, for example, Dravet syndrome, as well as from seizures with symptoms of symptomatic epilepsy in the clinical picture [4, 11].

Epidemiology. The frequency of AF among children under 5 years old, according to different authors, varies from 1 to 14% and averages 2-5% [2, 16, 23]. The frequency of febrile seizures is higher in Japan – 6-9%, in India –5-10%, in Guam – up to 14%. 90% of children have febrile seizures under the age of 3 years with a peak frequency between the ages of 18 and 24

months [1]. Such inconsistency of indicators can be explained by different approaches to the definition of "febrile seizures" due to their pathogenetic and clinical heterogeneity. There was also a predominance of AF in winter and spring, reflecting seasonal peaks of respiratory and gastrointestinal infections, respectively. Febrile seizures are somewhat more common in boys than in girls: an approximate ratio of 1.4:1 [2, 9].

Etiology and risk factors. Febrile seizures are considered a multifactorial condition, in the development of which both genetic and environmental factors are involved. A significant proportion of patients (from 25 to 40%) have a history of febrile seizures [5, 9, 27]. Currently, the genetic, social, exo and endogenous factors of febrile seizures have been studied. According to most scientists, genetic factors play a leading role in the development of AF [4, 14, 15, 16, 17]. For example, in some families, the presence of frequent recurrent AF may indicate the autosomal dominant nature of the disease, whereas with polygenic inheritance, rare episodes of AF are mainly noted [25]. In general, the risk of developing febrile seizures is 1:5 in the presence of those in sibs, 1:3 – if both parents had febrile seizures in childhood. In family cases, the exact type of inheritance has not been established, it is probably polygenic. In some families, the type of inheritance is described as autosomal dominant with low penetrance [1, 5, 22, 28]. Several genes have been found whose mutations predispose to the development of febrile seizures, but in clinical practice it is not accepted to identify these mutations due to their favorable prognosis. Febrile seizures can be observed within the framework of individual genetic epilepsies, but this issue is not subject to discussion in this article. Currently, the OMIM international database provides information on at least 10 types of AF with different gene loci [20]. Thus, in the predisposition of children to AF, the importance of loci is given: 8q13-q21 and 19p13.3, 2q23-24, as well as 5q [5, 16]. And the presence of a gene defect localized on chromosome 19p is a consequence of mutation of the gene p-1 subunit of the SCN1B sodium channel [14]. In the presence of a mutation of the γ2S subunit of GABA receptors, an acceleration of endocytosis in hyperthermia is noted, which may explain the cause of AF in children with a mutation of the γ2S subunit in the absence of a mutation in the α1 (A322D) subunit [21].

Of the environmental factors, fever is of the greatest importance. An increase in body temperature can be caused by any infectious diseases of the ear, nose and pharynx, respiratory and gastrointestinal infections. The most common cause of febrile seizures is considered to be otitis media. Despite the lack of specificity of infections, with prolonged seizures and febrile status, a high frequency (up to 30%) of detection of herpes virus type 6-B has been described and the development of acute viremia is expected [34]. Other risk factors for the development of febrile seizures also include the early age of the child (up to 12 months of life), a rapid rate of temperature rise, high temperature figures, vaccination (especially against whooping cough and diphtheria, as well as against measles–mumps–rubella), prematurity and prenatal hypotrophy [14].

Examination of patients with febrile seizures. When examining a child by a pediatrician, it is necessary to determine the cause of fever and the need for antibacterial therapy. To make a decision on the tactics of further examination, it is necessary to know the family history of febrile seizures and epilepsy, as well as the type of febrile attack [12,19,33]. When examining a child, it is important to pay attention to assessing the level of consciousness (sometimes it is necessary to examine the child several times, since post-onset deafness and sleep are possible) and meningeal symptoms.

Lumbar puncture is usually not performed in all patients with febrile seizures. It is shown to be performed in cases where there are meningeal symptoms. In the recommendations of the Japanese authors, prolonged (more than 30 minutes) disturbance of consciousness and bulging of the large fontanel are rightly added to meningeal symptoms [10]. In the USA, indications for lumbar puncture also include the absence of vaccinations in a child and treatment with antibiotics before hospitalization, which can lead to the erasure of the clinical symptoms of neuroinfection [11]. The detection of pleocytosis (an increase in the number of cellular elements) in the cerebrospinal fluid, even despite normal protein and sugar levels, is more likely to indicate neuroinfection than the consequences of prolonged febrile seizures or febrile status [23].

Blood and urine tests (clinical and biochemical) help to identify the source of infection, but are uninformative for understanding the diagnosis, differential diagnosis and prognosis of febrile seizures. Nevertheless, these studies are necessary if the child's somatic condition requires it.

Neuroimaging is not indicated for patients with simple and complex seizures. Previous studies (including magnetic resonance imaging of the brain, MRI) demonstrate a low percentage of detection of changes. Prolonged and focal seizures (especially repeated ones) can cause swelling of the hippocampus and the development of its sclerosis in the future, but in such cases, afebrile seizures (i.e. epilepsy) develop [4].

Electroencephalography (EEG) is not indicated for children with simple febrile seizures [1, 5, 9, 10]. Despite the probability of detecting epileptiform (intercept) activity, the EEG has no reliable prognostic value (it does not determine either the risk of recurrence of febrile seizures or the possibility of developing epilepsy). The percentage of detection of epileptiform discharges in febrile seizures is still not precisely known: according to various authors, from 2 to 80%, depending on the age of the examined children and the time elapsed after the attack [4]. It is known that the slowdown in bioelectric activity on the EEG can persist up to 7 days after a febrile attack. It can be assumed that in complex seizures, the prognostic value of the EEG is higher, but so far there are no clear recommendations regarding the need for its implementation [11]. D. Nordli et al. (2012) believe that the changes noted on the EEG within 72 hours after the febrile status may become a biomarker of the manifestation of epilepsy in the future [25]. The inability to prevent the development of epilepsy in general minimizes the clinical significance of EEG in febrile seizures.

Assessment of the transformation of AF into epilepsy. An urgent issue for parents of children with febrile seizures is the outcome of febrile seizures. Therefore, the works of many authors are devoted to this problem [5, 8, 13, 17, 28]. A number of researchers believe that a family history of epilepsy, the complex nature of the seizure and the presence of disorders in neuropsychiatric development from an early age are factors that obviously increase the risk of developing epilepsy after FS [6, 13, 31]. At the same time, the question of whether some temperature seizures are a manifestation of epilepsy remains debatable.

According to epidemiological studies conducted by Camfieldetal., (2018) and Bergetal., (2019), febrile seizures are the most common manifestation of a predisposition to epilepsy in childhood, febrile seizures occur in 15-25% of patients with epilepsy [8, 9]. However, seizures with fever can be a manifestation of epilepsy, and temperature is only a provocative factor. Early diagnosis of epilepsy masked by fever is very difficult due to the fact that the clinical picture and duration of febrile seizures are not completely reliable diagnostic criteria.

The identification of risk factors for the transformation of FS into epilepsy determines the tactics of managing patients with FS (duration of follow-up, volume and frequency of studies).

A number of studies [22, 23] indicate that the risk of FS and their subsequent transformation into epilepsy may increase in the presence of initial structural disorders of the brain. The relationship of FS with the development of mesial temporal sclerosis is intensively discussed [24, 29]. One of the most common causes of paleocortical temporal lobe epilepsy is ammonic horn sclerosis, or mesial temporal sclerosis [26, 32].

As indicated by the results of the research conducted by Dolinina A.F. et al. (2015) structural changes on MRI of the brain were statistically significantly more common in children with the outcome of AF to epilepsy (16.7%) than in children with a favorable outcome of the disease (0.7%; $p<0.001$) [1]. In children with epilepsy, MRI of the brain in 16.7% of cases showed structural changes in the form of periventricular leukomalacia, extensive porencephalic cyst, diffuse cortical-subcortical atrophy of the brain, mesial temporal sclerosis. In the comparison group, one patient was found to have a cyst of a transparent septum, which is a variant of the structure and is not related to the development of epilepsy, however, a small number of studied patients cannot give accurate data [1, 2, 26, 30].

Thus, the results obtained indicate a high degree of probability and reliability of the effect on the transformation of FS into epilepsy of the following factors: hereditary burden of epilepsy, the focal nature of a febrile attack, disorders in the neurological status. The statistically significant differences between the groups according to the results of EEG and MRI of the brain cannot be considered as direct risk factors for the transition of FS to epilepsy. Most likely, these factors, as well as aggravated heredity for FS, are markers of an increased likelihood of epilepsy in children with FS. According to calculations, it is possible to predict the development of epilepsy based on data on hereditary burden of epilepsy and EEG results. The most important diagnostic indicator of the development of epilepsy is the epileptiform activity on the EEG. At the same time, the presence of the focal nature of seizures on temperature, burdened heredity for epilepsy and epileptiform activity on the EEG suggests that the patient has epilepsy, and not atypical febrile seizures.

Conclusions:

1. Febrile seizures in children – the age of the dependent is favorable according to the prognosis.

2. Simple febrile seizures do not harm the neuropsychiatric development of the child, do not transform into epilepsy and do not require chronic anticonvulsant therapy.

3. Hospitalization is indicated for all patients with the first episode of seizures, if the child's age is 18 months or less.

4. There is a small group of children with prolonged febrile seizures and/or febrile statuses, the presence of risk factors for the transition of febrile seizures to epilepsy. This group needs the supervision of a neurologist and additional examination. Long-term anticonvulsant therapy may be prescribed to children of this group.

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