RISK FACTORS FOR CONVERSION OF FEBRILE SEIZURES TO EPILEPSY

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Abstract*. "Febrile convulsions" is a term used to describe the occurrence of convulsions in children with an increase in body temperature to 38° C and above. This can occur in the age group from six months to 5 years, most often from one to one and a half years. In most cases, infections are responsible for the development of this symptom, less often it is observed as a post-vaccination reaction (after the introduction of vaccines). In general, febrile seizures are not dangerous. But it is important to show the child to the doctor to make sure that the symptom is caused by fever, and not by other diseases.*
Keywords*: children, febrile seizures, epilepsy, febrile status, risk of epilepsy.*

Introductions. Febrile seizures (seizures, FS) are a common variant of paroxysmal states in pediatric practice. These are episodes of epileptic seizures that occur in preschool children with hyperthermia that is not associated with neuroinfection. PS is a benign, age -dependent, genetically determined condition in which the brain is susceptible to epileptic seizures that occur in response to high fever. In preschool children, FS is mostly transient, but it can also be part of the structure of individual epileptic syndromes. The question of the relationship with subsequent non -febrile seizures and epilepsy remains debatable. According to epidemiological data, FS is the most common manifestation of a predisposition to epilepsy in childhood; in patients with epilepsy, FS in the anamnesis occurs in 15-25% of cases. In children with a history of FS, the rate of transformation of FS into epilepsy does not exceed 2-10% [1,2,28]. Identification of risk factors for the transformation of FS into epilepsy determines the management tactics of patients with FS (duration of follow-up, volume and frequency of studies).

For the first time, the term "febrile convulsions" was used to refer to convulsive paroxysms that develop in childhood against the background Hochsinge B. fever in 1904 [9,31,32]. Currently, it is preferable to use the term "febrile seizures" rather than" febrile convulsions", since the clinical picture may include not only convulsive, but also non-convulsive paroxysms, such as prolonged atonic, syncope-like states [3,4,16,23,30]. In the International Classification of Epilepsy and Epileptic Syndromes of 1989, AF was considered as a relatively benign disorder in childhood, and the riskом of developing epilepsy in the future, the frequency of which is about 5% [11,17,29]. Later in 1993, the International Antiepileptic League (ILAE) defined AF as seizures that occur in children over 1 month of age, are associated with a febrile disease that is not caused by CNS infection, without previous neonatal seizures and unprovoked seizures, and do not correspond to the criteria of other acute symptomatic seizures [7,19]. According to the 2001 draft classification, AF is classified as 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 when the temperature rises during a viral or bacterial disease that is not associated with neuroinfection and metabolic disorders [1,9,6,10]. True AF should be distinguished from febrile-induced seizures, which may be part of a number of forms of epilepsy, such as Dravet syndrome, as well as from seizures that have symptoms of symptomatic epilepsy in the clinical picture [4,11].

Epidemiology. According to various authors, the frequency of AF among children under 5 years of age 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%), and in Guam (up to 14%). 90% of children have febrile seizures before the age of 3 years with a peak frequency between the ages of 18 доand 24 months. [1]. This inconsistency of indicators can be explained by different approaches to the definition of "febrile seizures" due to their pathogenetic and clinical heterogeneity. There is also a predominance of AF in the winter and spring periods, which reflects seasonal peaks of respiratory and gastrointestinal infections, respectively. Febrile seizures are slightly more common in boys than in girls: an approximate ratio of 1.4:1 [2, 9].

Etiology and risk factors. Febrile seizures are considered to be a multi-factorial condition, in the development of which both genetic factors and environmental factors take part. 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 an autosomal dominant nature of the disease, whereas in 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 is not established; it is probably polygonal. In some families, the type of inheritances described as autosomal dominantнwith low penentrance [1,5,22,28]. Several genes have been identified with mutations that predispose to the development of febrile seizures, but in clinical practice, these mutations are not usually detected due to their favorable prognosis. Febrile seizures can be observed within the framework of individual genetic epilepsies, but this issue is not discussed in this article.

Currently, the OMIM international database contains information on at least 10 types of AF with different gene loci [20]. Thus, loci 8q13-q21 and 19p13.3, 2q23-24, as well as 5q are considered important in children's predisposition to AF [5,16,32].

The presence of a gene defect localized on chromosome 19p is a consequence of a mutation of the p-1 subunit of the sodium channel SCN1B [14].

In the presence of a mutation of the gamma-2S GABA receptor subunit, an acceleration of endocytosis in hyperthermia is noted, which may explain the cause

the occurrence of AF in children with a mutation of the γ2S subunit in the absence of a mutation in the α1 (A322D) subunit [21,30].

Из факторOf the environmental factors, fever is the most significant. An increase in body temperature can be caused by any infectious diseases of the ear, nose and pharynx, respiratory and gastrointestinal infections. The most frequent cause of febrile seizures is considered to be otitis media. Despite the lack of specificity of infections, м a high frequency (up to 30%) of herpes virus type 6-B detection is described in patients with prolonged convulsions and febrile status, and acute viremia is expected to develop time [32].

Other risk factors for the development of febrile seizures include the early age of the child(up to 12 months of life), the rapid rate of temperature increase, high temperature figures, vaccination (especially against whooping cough and diphtheria, as well as against measles–mumps–rubella), prematurity and prenatal hypotrophy [14,30,31].

Examination of patients with febrile seizures. When a child is examined by a pediatrician, the cause of fever and the need for antibacterial therapy should be determined. 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 [12,19,32]. When examining a child, it is important to pay attention to assessing the level of consciousness (sometimes you need to examine the child several times, so how post-onset deafness and sleep are possible) and meningeal symptoms.

Lumbar puncture is usually not performed in all patients with febrile seizures. Its use is indicated in cases where there are meningeal symptoms. In the recommendations of Japanese physicians, long-term (more than 30 min) disturbance of consciousness and bulging of the large fontanel are justly added to meningeal symptoms [10]. In the United States, indications for lumbar пункции отpuncture also include the absence of vaccinations in the child and treatment with antibiotics before hospitalization, which can lead to the erasure of the clinical symptoms of neuroinfection [1,11,24]. 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 identify the source of infection, but are noninformative understanding the diagnosis, differential diagnosis, and prognosis of febrile seizures. However, these studies are necessary if the child's physical condition requires them.

Neuroimaging is not показанаrecommended for patients with simple and complex seizures. Previous studies (including magneticрезонансная resonance imaging of the brain, MRI) show a low percentage of changes detected. Prolonged and focal seizures (especially repeated ones) can cause hippocampal edema and the development of its sclerosis in the future, but in such cases febrile seizures (i.e., epilepsy) develop [4].

Electroencephalography (EEG) is not recommended for children with simple febrile seizures [1,5,9,10]. Despite the probability of detecting epileptiform (intercostal) activity, the EEG does not have a reliable prognostic value (it does not determine the risk of relapse of febrile seizures, nor the possibility of developing epilepsy). Until now пор точно не и, the percentage of detection of epileptiform discharges in febrile seizures is not exactly 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 a slowdown in bioelectric activity on the EEG can persist for up to 7 days after a febrile attack. It can be assumed that in complex convulsions, the prognostic value of EEG is higher, but so far there are no clear recommendations regarding the need for it [11]. D. Nordli et al. (2012) believe that changes recorded on the EEG within 72 hours after febrile status can become a biomarker of the manifestation of epilepsy in the future [25]. The inability to prevent the development of epilepsy in the central nervous system minimizes the clinical significance of EEG in febrile seizures.

Evaluation of the transformation of AF into epilepsy. A topical issue for parents of children with febrileseizuresis the outcome of febrile seizures. This is why many authors ' works 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 a seizure, and the presence of disorders in neuropsychic development from an early age are factorsи 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, with a history of febrile seizures occurring in 15-25% of patients with epilepsy [8,9]. However, convulsions on 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.

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

A number of studies [22, 23] indicate that the risk of PS and its subsequent transformation into epilepsy may increase in the presence of initial structural disorders of the brain. The association 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 ammonium horn sclerosis, or mesial temporal sclerosis [26,32].

As indicated by the results of a study conducted A. F. Dolinina etal. (2015) structural changes on MRI of the brain were statistically significantly more common in children with an outcome of AF in 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 revealed structural changes in the form of periventricular leukomalacia, extensive porencephalic cyst, diffuse cortical-subcortical atrophy of the brain, and mesial temporal sclerosis in 16.7% of cases. In the comparison group, one patient was found to have a transparent septal cyst, which is a variant of the structure and is not related to the development of epilepsy, but a small number of patients studied cannot provide accurate data [1, 2, 26, 30].

Thus, the results obtained indicate a high degree of probability and reliability of the impact on the transformation of FS into epilepsy of the following factors: hereditary burden of epilepsy, the focal nature of a febrile attack, and disorders in the neurological status. The obtained statistically significant differences between the groups based on 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 burdened heredity for FS, are markers of an increased probability of epilepsy in children with FS. According too 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 EEG epileptiform activity. At, the same time, the presence of the focal nature of seizures on temperature, burdened by heredity for epilepsy and epileptiform актanxiety on the EEG allows us to predict that the patient has epilepsy, and not atypical febrile seizures.

Conclusions:

1. Febrile seizures in children are an age -dependent and favorable prognosis condition.

2. Simple febrile seizures do not harm the child's neuropsychiatric development, 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 is less than 18 months of age.

4. There is an older group of children with long-term febrile seizures and / or febrile statuses, the presence of risk factors for the transition of febrile seizures to epilepsy. This group needs a neurologist's supervision and follow-up. Children in this WHO group can be prescribed long-term anticonvulsant therapy.

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