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GENETIC ASPECTS OF THE PATHOGENESIS OF EPILEPTIC ENCEPHALOPATHY IN CHILDREN

Vafoeva G.R.
Tashkent Pediatric Medical Institute

Saidkhodzhaeva S.N.
Tashkent Pediatric Medical Institute

Annotation
Epileptic encephalopathy is a condition when a pathological altered brain electrogenesis is the cause of impaired brain function [5,6]. The epileptic process leads to progressive impairment of brain functions. According to the literature, these disorders depend on the form of 5 to 40% of behavioral, mental and neuropsychological disorders [2,4,8,9]. Currently, some researchers consider interictal epileptic psychoses as a manifestation of epileptic encephalopathy. Epileptic encephalopathy is a condition where pathologically altered brain electrogenesis is the cause of brain dysfunctions. In which the epileptic process as such leads to progressive dysfunctions of the brain.

Keywords: epileptic encephalopathy, epilepsy, West syndrome, Lennox-Gastaut syndrome, Otahara syndrome.

ГЕНЕТИЧЕСКИЕ АСПЕКТЫ ПАТОГЕНЕЗА ЭПИЛЕПТИЧЕСКОЙ ЭНЦЕФАЛОПАТИИ У ДЕТЕЙ

Вафоева Г.Р., Саидходжаева С.Н.
Ташкентский Педиатрический Медицинский Институт

Аннотация
Эпилептическая энцефалопатия – это состояние, при котором патологический измененный электрогенез головного мозга является причиной нарушений функций головного мозга [5,6]. Эпилептический процесс ведет к прогрессирующим нарушениям функций мозга. Эти расстройства составляют по данным литературы в зависимости от формы от 5 до 40% поведенческих, психических и нейропсихологических расстройств [2,4,8,9]. В настоящее время некоторые исследователи рассматривают интериктальные эпилептические психозы в качестве проявления эпилептических энцефалопатий. Эпилептическая энцефалопатия - это

состояние, где патологический измененный электрогенез головного мозга является причиной нарушений функций головного мозга. При которой эпилептический процесс как таковой ведет к прогрессирующим нарушениям функций мозга.

Ключевые слова: эпилептическая энцефалопатия, эпилепсия, синдром Веста, синдром Ленноксо-Гасто, синдром Отахара.

БОЛАЛАРДА ЭПИЛЕПТИК ЭНЦЕФАЛОПАТИЯ ПАТОГЕНЕЗИНИНГ ГЕНЕТИК АСПЕКТЛАРИ

Вафоева Г.Р., Саидходжаева С.Н.
Тошкент Педиатрия Тиббиёт Институти

Аннотация
Эпилептик энцефалопатия – бош мия функцияларининг бузилиш ҳолати бўлиб, унинг асосий сабаби бош миянинг патологик ўзгарган электрогенези ҳисобланади [5,6]. Бунда эпилептик жараён мия функциялари бузилишининг зўрайишига олиб келади. Адабиётлардан олинган маълумотлар бўйича, шаклига кўра бу бузилишлар юриш – туриш, рухий ва невропсихологик бузилишларнинг 5% дан 40% гачасини ташкил қилади [2,4,8,9]. Кўпчилик тадқиқотчилар ушбу касалликни интериктал эпилептик психозни бир кўриниши деб ҳисоблашади. Шу сабабли ушбу касалликни кечишининг ўзига хослигини аниқлаш ушбу жараёнга эрта ташхис қўйиш ва бошқа касалликлардан дифференциал диагноз қилишга ёрдам беради.

Калит сузлар: эпилептик энцефалопатия, тутқаноқ, Веста синдроми, Ленноксо-Гасто синдроми, Отахара синдроми.

Introduction

Epileptic encephalopathy in children is one of the most common neurological pathologies, especially in childhood. The incidence ranges from 15 to 113 cases per 100 thousand of the population, with a maximum among children of the 1st year of life. The prevalence of epilepsy in the population is high and ranges from 5 to 8 cases (in some regions - 10 cases) per 1000 children under the age of 15 years [1].

The study of the etiology and pathogenesis of epilepsy, the development of new approaches to the diagnosis and treatment of this disease are topical issues of modern neurology. This is evidenced by a large number of publications in domestic and

foreign periodicals, the development of new classification approaches [2,4,6,8], the active introduction of modern surgical methods of treatment and the regular appearance of new antiepileptic drugs on the pharmaceutical market [5]. Meanwhile, modern ideas about epilepsy have undergone an impressive evolution from the empirical views of Hippocrates on the painful formation of mucus in the head as the cause of seizures [5,10], to the well-developed concepts of epileptic systems [2] and the concept of functional areas of the cerebral cortex today [3] . An important stage in the development of the doctrine of epilepsy is the period of the second half of the 19th century, marked by active experimental searches for the causes and conditions for the development of "epilepsy" disease, as well as the improvement of methods for its treatment.

In epilepsy, there are different types of inheritance: monogenic, or Mendelian, inheritance; multifactorial inheritance; mitochondrial type of inheritance (maternal, or cytoplasmic); imprinting; transmission of chromosomal abnormalities to offspring. So far, significant progress has been made in studying the genetics of monogenic epilepsy. In the near future, due to the improvement of the laboratory base of large institutions involved in the diagnosis and treatment of epilepsy, an increase in the number of genetic studies in this area is expected. Therefore, it is important to understand what the genetic testing algorithm for epilepsy in children is. In our opinion, it provides for several clinical situations:

1. Based on the results of the examination, we can assume the presence of a certain monogenic genetic epilepsy in a child. To date, a lot of monogenic epilepsies and sometimes mutations of different genes have been described in one epileptic syndrome. When we clearly understand what kind of genetic epilepsy we are faced with, we can confirm its presence by searching for the most characteristic and frequent mutations for it. Let us dwell on the genetic diagnosis of Dravet's syndrome (severe myoclonic epilepsy of infancy). In this syndrome, epileptic seizures begin in a healthy child around 6 months of age, often with febrile status (focal or generalized). Hemiclonia may be alternating. Then other types of seizures appear - myoclonus, partial, atonic and absences. Often attacks are provoked by fever. Psychoverbal development in the 1st year of life is normal, but then the rate of development of the child slows down and regression of psychoverbal development can be observed. In the neurological status, pyramidal symptoms and ataxia may occur over time. Despite frequent seizures, an electroencephalogram (EEG) in a child under 2 years of age may be normal, then generalized epileptiform discharges appear. Magnetic resonance imaging (MRI) of the brain also does not reveal abnormalities or nonspecific atrophy. Dravet's syndrome can serve as an example of the successful application of genetic

methods to understand the etiology and pathogenesis of the disease and deepen knowledge about its phenotype. The monogenic nature of the disease has recently been proven: the most frequent mutation of the α1-subunit of sodium channels, SCNA1, has been identified. It is important to note that the 10% of patients who do not have the most common mutations characteristic of Dravet syndrome on examination have copy number variations, including exon deletion or duplication of an exon, several exons, and the whole gene. Genetic diagnostics led to the clarification of the phenotype of the disease. It is known that this is a severe epileptic encephalopathy resistant to most anticonvulsants. In addition, it is known that mutations in the α1 subunit of sodium channels in 95% of cases are de novo mutations, which facilitates the prognosis of childbearing.

2. Sometimes it becomes not clear what kind of genetic epilepsy we are dealing with, and then it is necessary to exclude several genetic epilepsies with a similar phenotype at once. Particularly relevant is the search for a genetic etiology in a child with epileptic encephalopathy, in which seizures and/or epileptiform activity cause developmental regression. Genetic encephalopathies include such a catastrophic epileptic syndrome as Otahara syndrome, 35% of which are caused by a mutation in the SNXBP1 gene, infantile spasms with an early onset (STK9 / CDKL5 mutations are detected in 10–17% of patients), X-linked infantile spasms (with a mutation ARX gene - in 5% of patients) and many others. All these syndromes are severe and insensitive to AED; they are quite similar clinically and electroencephalographically. Therefore, today special diagnostic panels are used in the world to determine the most common mutations that cause these diseases [7]. It is known that this syndrome is a partially reversible age-related epileptic encephalopathy, which is characterized by a triad of symptoms: continued spike wave activity during sleep (electrical status epilepticus during non-REM sleep), seizures, and neuropsychological disorders. In about a third of cases, it is impossible to establish the etiology of this serious disease, in addition, even with an established etiology, it is not clear why epileptiform activity is activated in children at a certain age and the electrical status epilepticus of sleep develops.

3. In cases where monogenic mutations are not found, copy number variations are determined - a type of genetic polymorphism, which includes differences in individual genomes in the number of chromosome segments ranging in size from 1 thousand to several million base pairs. So, in the study by S. Lund et al. in Lennox-Gastaut syndrome, 38% of patients had rare copy number variations, which apparently influenced their phenotype, and in 19% of children, copy number variations were the cause of the disease; 3 patients had known chromosomal syndromes (22q13.3; 2q23.1; MECP2) [3]. The world is searching for variations in the number of copies in a variety

of neurological and mental diseases, including epilepsy, their registration and comparison of clinical and genetic data, which will ultimately allow us to describe a new class of diseases.

4. In some cases, it is not possible to confirm the genetic nature of the disease, then whole genome sequencing is performed. An example of how important genetic research is in epilepsy in children, especially in children with epileptic encephalopathies, is West syndrome. The syndrome is polyetiological and is observed in more than 200 different diseases. When establishing a diagnosis, it is quite easy to single out children with an acquired (non-genetic) etiology of the disease from the general group. These are the consequences of both intrauterine and acquired infections (meningitis, encephalitis) and hypoxic-ischemic encephalopathy. The rest of the reasons are mostly genetic. A large group - malformations of the brain. Of course, some of them are not genetic in nature. The appearance of tubers, subependymal nodes and other changes in the brain in West syndrome caused by tuberous sclerosis is genetically determined. With some genetically determined metabolic defects that cause West syndrome (in particular, metabolic disorders of amino acids and organic acids, mitochondrial encephalomyopathies), molecular genetic confirmation of the diagnosis is possible. There are chromosomal rearrangements that lead to the development of West syndrome (Down and Miller-Dieker syndromes), etc. Thus, the etiological diagnosis of West syndrome is difficult and often impossible without molecular genetic testing. The diagnosis of monogenic epilepsy was discussed above, and it is obvious that so far this is a rather complicated process. But the biggest challenge in epilepsy genetic research is to clarify the genetics of idiopathic (genetic) generalized epilepsies. Their main characteristics: high population frequency (>1 per 1000 population), higher prevalence among relatives than in the general population, inconsistency with Mendelian inheritance, dependence of the risk of developing the disease on the degree of relationship - confirm multifactorial (complex) inheritance. It is possible that their development requires the participation of several genes along with environmental factors (what exactly is not determined). The number of genes that cause such conditions is also unknown. However, an increase in copy number variation in patients with idiopathic generalized epilepsy indicates that certain structural changes in the genome may be associated with a significant risk of developing epilepsy. In general, sophisticated molecular studies show that most common epilepsies are polygenic (with the exception of a few monogenic conditions) and there is no evidence yet that any particular gene determines a significant or moderate risk of developing epilepsy.

When establishing a diagnosis, it is quite easy to single out children with an acquired (non-genetic) etiology of the disease from the general group [7,9].

In general, sophisticated molecular studies show that most common epilepsies are polygenic (with the exception of a few monogenic conditions) and there is no evidence yet that any gene determines a significant or moderate risk of developing epilepsy. In the future, clarification of the genes that determine or increase the risk of developing epilepsy will be of great practical and scientific importance. From a practical point of view, the discovery of a mutation that caused the development of epilepsy makes it possible to avoid further expensive diagnostic procedures, sometimes more accurately predict the course of the disease and optimize therapy, and in some cases helps predict further childbearing. From a scientific point of view, the study of the consequences of already known mutations (and their influence on the development of the brain of a child) allows us to clarify the main processes of epileptogenesis.

Thus, epilepsy in childhood and adolescence is one of the most important social and medical problems of our time. The disease is an extensive group of pathological conditions, very diverse in their etiology, pathogenesis and clinical manifestations. Epilepsy in children is the main "source" of epilepsy in adults, and therefore the prevention of this disease begins in childhood, from the perinatal period. Of great importance are the study of morbidity, prevalence, mortality in different age groups, analysis of the structure of disability in patients with epilepsy and the factors that affect them. Epilepsy in children and adolescents is one of the complex problems that neurologists, pediatricians, psychologists, psychiatrists deal with in collaboration with teachers, jointly implementing a variety of medical, pedagogical and medical and social measures for the rehabilitation of patients.

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