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Clinical features of developmental and epileptic encephalopathy, caused by *KCNQ2* gene mutation

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SUMMARY

Current classification of epileptic syndromes proposed in 2022 by the International League Against Epilepsy, developmental and epileptic encephalopathy (DEE) caused by mutation in the *KCNQ2* gene is identified as an independent nosological form. Alternative names for this disease are DEE type 7 or early infantile epileptic encephalopathy type 7 (OMIM: 613720). The article presents a brief literature review on the topic as well as our personal clinical observation of this rare pathology.

KEYWORDS

KCNQ2 mutation, developmental and epileptic encephalopathy, DEE, early infantile epileptic encephalopathy type 7, EIEE7.

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Клинические особенности эволюционной и эпилептической энцефалопатии, вызванной мутацией в гене *KCNQ2*

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РЕЗЮМЕ

В современной классификации эпилептических синдромов, предложенной Международной Противоэпилептической Лигой в 2022 г., эволюционная и эпилептическая энцефалопатия (англ. developmental and epileptic encephalopathy,

DEE), вызванная мутацией в гене *KCNQ2*, выделена в качестве самостоятельной нозологической формы. Альтернативные названия этого заболевания: DEE 7-го типа или ранняя инфантильная эпилептическая энцефалопатия 7-го типа (OMIM: 613720). В статье представлен краткий обзор литературы по данной теме, а также приведено собственное клиническое наблюдение этой редкой патологии.

КЛЮЧЕВЫЕ СЛОВА

Мутация в гене *KCNQ2*, эволюционная и эпилептическая энцефалопатия, ранняя инфантильная эпилептическая энцефалопатия 7-го типа.

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INTRODUCTION / ВВЕДЕНИЕ

Developmental and epileptic encephalopathy (DEE) caused by a mutation in the *KCNQ2* gene (*KCNQ2*-DEE) is registered in OMIM (English Online Mendelian Inheritance in Man) under the code number 613720. Alternative names: DEE type 7 or early infantile epileptic encephalopathy type 7 [1].

The *KCNQ2* gene (potassium channel, voltage-gated, KQT-like subfamily, member 2) is located at locus 20q13.33 and encodes a potential-dependent potassium channel that is expressed in the brain [2]. The spectrum of diseases associated with various mutations in this gene includes, in addition to DEE type 7, benign neonatal epilepsy type 1 and/or myokymia (OMIM: 121200), which is an example of phenotypic allelic heterogeneity [1]. Both diseases are inherited according to the autosomal dominant type. *KCNQ2*-DEE is more often caused by *de novo* missense mutations.

The main clinical signs of *KCNQ2*-DEE are pharmacoresistant epileptic seizures that occur in early childhood, often in the neonatal period, as well as persistent severe neuropsychiatric disorders that persist even in remission of seizures [3]. Due to the similar clinical features of seizures and their detection on electroencephalography (EEG) in the debut of the burst-suppression pattern, the disease was often considered as a type of early infantile Ohtahara DEE [4].

In the current classification of epileptic syndromes proposed by the International League Against Epilepsy (ILAE) in 2022, the disease is identified as an independent nosological form in the subgroup of etiologically specific syndromes included in epileptic syndromes with onset in the neonatal period and infancy [5]. Mandatory criteria for *KCNQ2*-DEE diagnosis are tonic, myoclonic, and/or other focal seizures in combination with the burst-suppression pattern or multifocal discharges on the EEG that occurred before the age of 3 months, as well as an obvious delay in the development of nervous system or encephalopathy at the time of the disease onset [6]. In mild cases, heterozygous mutations in the *KCNQ2* gene are manifested by the phenotype of self-limited (familial) neonatal epilepsy (SeLNE). It is characterized by the occurrence of focal (mostly tonic) seizures at the 1st week of life with a change in the lateralization of motor phenomena both during an attack (migration) and in different attacks (alternation). In most cases, seizures stop by age of 6 weeks or, less often, by age of 6 months.

KCNQ2-DEE is characterized by a very different degree of expression of the mutant gene with phenotypic diversity, even with the same mutations. Thus, in one case study [7], a mother and son with a heterozygous *KCNQ2* mutation and neonatal onset of epilepsy had different outcomes. The mother was already in remission of seizures in infancy, and subsequently normal psychomotor development was observed. The son, despite treatment, developed epileptic encephalopathy with pharmacoresistant seizures and mental underdevelopment with hypotension and dystonia. In another case [3] out of 4 family members, the phenotype of mother and the youngest daughter corresponded to typical benign neonatal epilepsy. However, the mother's own sister had pharmacoresistant seizures before the age of 5 and moderate mental retardation in adulthood. The eldest daughter developed clusters of right-sided tonic seizures on the 8th day of life. Polymorphic, therapy-resistant seizures persisted for up to 7 years. She also had severe mental retardation with lack of speech and spastic tetraparesis, which was consistent with DEE.

S. Weckhuysen et al. [8] reported 8 unrelated patients with neonatal epileptic encephalopathy associated with *KCNQ2*. All of them had seizures at the 1st week of life, and

2 mothers retrospectively noted intrauterine fetal twitches during the last 2 months of pregnancy. At the onset, daily pharmacoresistant tonic seizures were observed, but in the period from 9 months to 4 years, the frequency of seizures decreased and most of them stopped. Seven patients had profound mental and motor disorders, most often spastic tetraparesis.

KCNQ2-DEE seizures are often well controlled by anticonvulsants, but despite this, serious permanent neuropsychiatric disorders are observed in children. A.T. Berg et al. [9] conducted a structured online survey of parents of 39 children of different ages with *KCNQ2*- DEE. The debut of seizures took place in the first days of life. During the active stage of epilepsy, 35 children experienced seizures on a daily basis. Serial occurrence of seizures (3 or more per day) was observed in 37 children, and in 19 of them they occured more than 10 times per day. The most common types of seizures were bilateral tonic-clonic or, more rarely, tonic. Most patients had severe permanent disorders in the form of communication disorders, motor function disorders, hand use disorders, feeding disorders, etc. Violations in more than two domains were observed in 72% of cases. There was no clear correlation between the duration of remission for seizures and the type or number of permanent disorders.

The largest study of patients with *KCNQ2*-DEE was conducted by A. Cossu et al. in 2023 [10]. A specially designed questionnaire was used to collect data on 80 patients of various ages (from 4 months to 43 years) from 14 countries with *KCNQ2* mutations. Interestingly, 5 patients aged from 2 to 11 years never had epilepsy. Based on clinical features, the authors divided patients older than 2 years (n=71) into three phenotypes according to severity. The average age between the groups was comparable. With the milder phenotype (42%), the children were able to walk and talk. They were less likely to have active epilepsy, but more likely to be diagnosed with autism. The severe phenotype (27%) was characterized by the ability to sit and stand independently, but not walk, spastic muscle hypertonia, and speech represented by sounds or syllables. Epilepsy is noted in almost all cases, and autism is rare. In profound phenotype (31%), there was an inability to hold the head high, a change in muscle tone with hypo- and/or hypertonia, and lack of speech. Everyone were diagnosed with epilepsy, often with daily seizures, but no one had autism. In patients with the profound phenotype, certain features of epilepsy were found: a higher frequency of seizures in the first 10 hours of life, a more frequent occurrence of epileptic spasms, and the detection of the burst-suppression pattern already on the first EEG. Of the 75 patients examined with epilepsy, 41 patients aged 5 months to 32 years had no seizures at the time of the survey. The age of the last attack ranged from 2 months to 10 years. Among older patients with active epilepsy, the frequency of seizures was lower compared to patients younger than 6 years. Changes in brain magnetic resonance imaging (MRI) were detected in 43% (32/75) of cases. The following changes were noted: hypomyelination in 37% of cases, white matter abnormalities in 12%, thinning of the *corpus callosum* in 28%, cortical atrophy in 9%, cortical malformations in 6%, and other non-specific anomalies in 50% [10].

Some studies [11] emphasize the role of KCNQ2 channels in the development of the cerebral cortex. An example is the presence of cortical malformation in a child with *KCNQ2*-DEE due to abnormal neuronal migration in the form of gray matter heterotopy.

The most characteristic type of EEG epileptiform activity in *KCNQ2*-DEE, which occurs in more than 60% of cases, is the burst-suppression pattern, which can sometimes be asymmetric [6]. In other cases, or later, multifocal abnormalities may occur, including spikes and sharp waves. There may be a diffuse slowing down of the brain's bioelectric activity or its depression in one hemisphere. Hypsarrhythmia has been described [12].

In the treatment of *KCNQ2*-DEE, sodium channel blockers (SCB) are usually used, the administration of which often leads to remission of seizures [12]. The ineffectiveness of phenobarbital, which is often prescribed for neonatal seizures, and the effectiveness of SCB such as carbamazepine and phenytoin are noted as one of the important characteristics of *KCNQ2*-DEE [6]. In a study by A. Cossu et al. [10], out of 75 patients with epilepsy, 33 people took one anticonvulsant, 30 took two or more, and 12 did not take any antiepileptic drugs. SCB was administered to 40 patients, 18 of whom were treated as monotherapy, and 10 followed a ketogenic diet throughout their lives.

Variants of targeted therapy are considered depending on the type of mutation, which can be either with gain-of-function (GOF) or with loss of function (LOF), which requires different therapeutic approaches [13]. According to F. Miceli et al. [14], the absence of neonatal seizures in the presence of seizures in childhood is a reliable and important clinical sign in favor of GOF-variants of *KCNQ2* gene mutations. For mutations with enhanced function, such as *KCNQ2* R144, the authors suggest the effectiveness of amitriptyline, which blocks channels containing the R144Q subunits Kv7.2 and Kv7.3. For mutations that cause the effect of loss of function of neuronal potassium (K+) channels Kv7.2, clinical-EEG improvement is noted when the Kv7 activator gabapentin is prescribed [15]. Retigabine, which selectively opens the potassium channels KV7.2 and KV7.3, is also used as a precision therapy for patients with *KCNQ2*-DEE [16].

Due to the rare occurrence of the disease and the fact that we have not found any descriptions of *KCNQ2*-DEE clinical cases in the domestic publications, we present our own observation.

CASE REPORT / КЛИНИЧЕСКИЙ СЛУЧАЙ

Patient X. was first admitted to the neurological department at the age of 1.5 months with complaints of daily attacks in the form of tonic head rotation more often to the right with limb strain lasting up to 1 min.

Ethical aspects / Этические аспекты

All medical care was provided in full compliance with the standards, procedures and clinical guidelines, as well as the principles of the Helsinki Declaration of the World Medical

Association (Fortaleza, Brazil, 2013). The patient's parents gave informed consent for publication. Anonymity of the patient is ensured by the absence of personal information, including the image, name, initials of the child and medical document numbers.

History of disease / Анамнез

From the anamnesis, it is known that the child is from the first pregnancy, which took place against the background of anemia, chronic pyelonephritis and acute respiratory viral infection at 27 weeks in the mother, urgent delivery. Delivery was operative due to pelvic presentation. Apgar score was 8/9 points, but no special features. Body weight at birth was 3490 g, height 53 cm. Heredity for epilepsy was not burdened.

According to mother, she noticed seizures from the 2nd–3rd day of life. However, among the doctors "no one believed her", and she "stopped complaining". The child was first examined by a neurologist at the age of 1 month. In connection with the suspicion of "epileptiform paroxysms", it was recommended to conduct EEG on an outpatient basis. The patient was sent for inpatient examination only after 2 weeks.

Seizure description / Описание приступов

The department recorded serial tonic focal motor seizures in the form of turning the head to the right and/or left with simultaneous tension of the limbs, sometimes with the formation of a pose of an asymmetric cervical tonic reflex. The change in lateralization of head rotation could occur both during one attack (migration) and during different seizures (alternation). Regurgitation may occur at the beginning of the attack, bilateral myoclonia, mainly in the handles, and nystagmus may occur during the attack, and automatism in the form of tongue movements or/and swallowing may occur at the end. At the end, and sometimes during the seizure, the child cried violently, which indicated that he was still conscious. The duration of attacks was usually several minutes, but often they were grouped into clusters of up to half an hour, which could be repeated several times a day. Taking into account the serial course of seizures, valproates in the form of depakine syrup were prescribed from the first day with a gradual titration of the dose from 10 to 40 mg/kg/day. Already at the beginning of therapy, seizures began to flow more easily, but complete remission was achieved only at the maximum dose.

Objective neurological examination revealed diffuse hypotension with uncertain support. Head circumference 39 cm, large fontanel 2×2 cm. The patient was consulted by a pediatrician. The diagnosis was established: chronic eating disorder of the 2nd degree postnatal hypotrophy type (body weight 4.2 kg). After ultrasound examination of the pyloric part of the stomach, the patient was consulted by a surgeon. The diagnosis was established: pylorospasm. In connection with a suspected hereditary metabolic disease, a consultation with a geneticist was conducted, blood was taken for tandem mass spectrometry for amino acids and acylcarnitines spectrum, the result of which, obtained later, turned out to be without features. The blood lactate level was 2.7 mmol/l (normally 0.5–2.2 mmol/l).

EEG and MRI (age 1.5 months) / ЭЭГ и МРТ (возраст 1,5 мес)

Multiregional epileptiform activity (EA) in the form of acute-slow wave (ASW) complexes with a clear focus in the left frontal region was recorded on the EEG in daytime sleep (**Fig. 1**). On the repeated EEG recorded in daytime sleep after 10 days at a 30 mg/kg/day dose of depakin, a positive trend was noted in the form of a decrease in the amplitude and representation of EA.

Brain MRI did not reveal data for any focal and diffuse changes in the brain substance. The patient was discharged under the supervision of a neurologist with a diagnosis of cryptogenic focal epilepsy. Continuous intake of valproic acid at a dose of 40 mg/kg/day and laboratory genetic examination to clarify the diagnosis were recommended.

Neurological status and EEG (age 8 months) / Неврологический статус и ЭЭГ (возраст 8 мес)

The patient was re-admitted for inpatient examination at the age of 8 months with complaints of delayed psychomotor development: did not turn, did not crawl, did not sit. The seizures did not recur. Objective examination revealed a small head circumference (42 cm), the large fontanelle was closed (postnatal microcephaly).

In neurological status: did not follow objects, unstable alternating divergent strabismus, did not tighten by the handles during traction, muscle tone was increased by spastic type mainly in the handles, Babinski symptom on both sides. The ophthalmologist first noted partial atrophy of the optic nerve discs on both sides.

Single ASW complexes were detected on the EEG, but in two regions: in the left temporal and right fronto-parietal leads. Chromosomal microarray analysis revealed no pathology.

Genetic analysis / Генетический анализ

After discharge from the department, the results of DNA sequencing were obtained by the "Hereditary metabolic diseases" panel (Genomed laboratory, Russia), for which blood had been taken at the age of 5 months. A "probably pathogenic mutation that is a possible cause of the disease" was detected. A previously undescribed heterozygous mutation in exon 17 of the *KCNQ2* gene (chr20:62038349C>CCGTA) was found out, leading to a shift in the reading frame starting from codon 756 (p.Gly756fs, NM_172107.2), which interferes with full-length protein synthesis. A heterozygous "mutation with unknown clinical significance, possibly related to the phenotype" in the *DHCR7* gene was also identified. Homozygous mutations in this gene lead to the development of an autosomal recessive disease: Smith–Lemli–Opitz syndrome.

Although the conclusion stated that heterozygous mutations in the *KCNQ2* gene had been described in patients with early infantile epileptic encephalopathy type 7 (OMIM: 613720), and the patient's clinical picture fully corresponded to the previously described manifestations of the autosomal dominant *KCNQ2*-DEE disease, the geneticist decided that exome or genome sequencing was necessary.

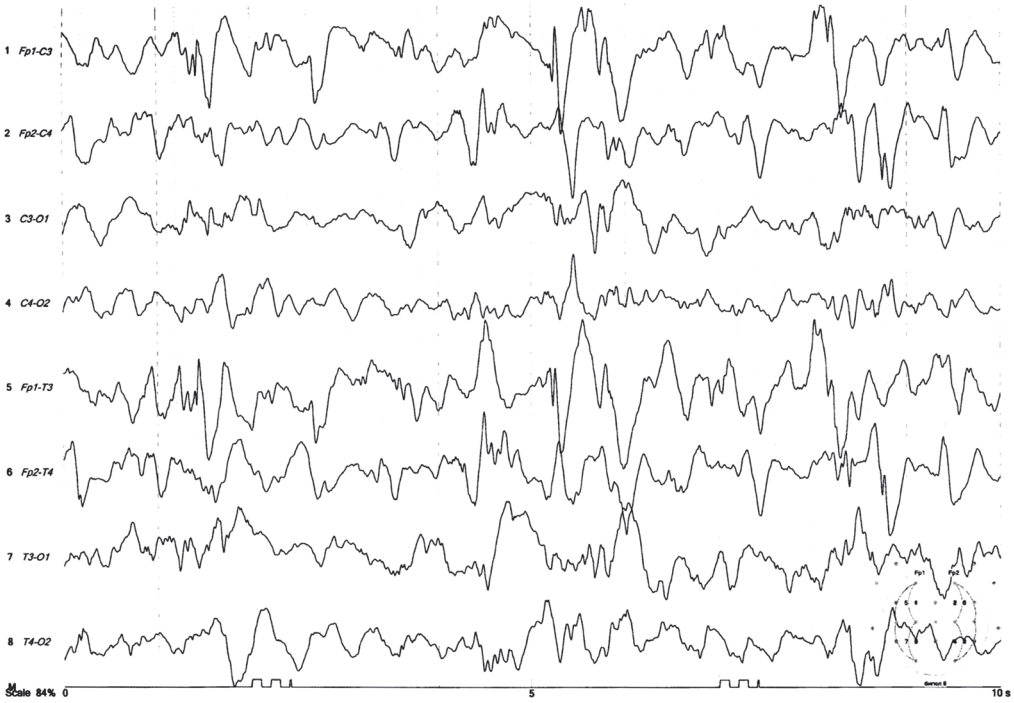

Figure 1. Patient X. (aged 1.5 months). Electroencephalogram-specific multiregional epileptiform activity highlighting the left frontal region

Рисунок 1. Мультирегиональная эпилептиформная активность с акцентом в левой лобной области на электроэнцефалограмме пациента Х. (возраст 1,5 мес)

The results of full-exome sequencing of the child's DNA confirmed the mutations in both genes. Sanger sequencing of these genes in the parents revealed the heterozygous mutation in the *DHCR7* gene in the mother. Thus, the mutation in the *KCNQ2* gene occurred in the child *de novo*.

EEG and MRI (age 2 years, 3 years, 5 years) / ЭЭГ и МРТ (возраст 2 года, 3 года, 5 лет)

At the age of 2, the child began to follow bright objects, hold (but not take) objects with his hands, but could not sit or stand. Although seizures did not recur due to regular antiepileptic therapy (valproic acid at a dose of 30 mg/kg/day) and only "elements" of EA were detected on the EEG, permanent disorders were significant. Mental underdevelopment with total lack of speech was revealed, and pronounced central tetraparesis was formed.

At the age of 3 years, lying on his stomach, the boy began to raise himself on his elbows, sometimes crawl on his bellies, turning over, but there was no speech. Brain MRI for the first time showed signs of mild replacement hydrocephalus as a manifestation of cortical atrophy.

At the last hospitalization at the age of 5 years, there was no positive dynamics in the neurological status, and sitting and standing skills were not formed. However, seizures did not recur during the previous dose of valproate, and EA was not recorded on the EEG.

DISCUSSION / ОБСУЖДЕНИЕ

Analyzing our clinical observation in comparison with the literature data, we can note the following features. The onset of the disease was registered in the first days of life, which is typical for *KCNQ2*-DEE [3]. A series of seizures in the form of turning the head with limb strain and changes in the lateralization of motor phenomena with migration and alternation phenomena is more typical for SeLNE [6]. Multiregional epileptiform activity on the EEG was observed, although the burst-suppression pattern is considered more typical for *KCNQ2*-DEE [6]. The rapid and persistent effect of valproic acid, which blocks both calcium and sodium potential-dependent channels, and the effectiveness of SCB is one of the important features of *KCNQ2*-DEE in contrast to other DEEs [6, 12]. The absence of changes on brain MRI at the beginning of the disease with the appearance of signs of cortical atrophy only at the age of 3 years is often found in *KCNQ2*-DEE [10]. Pronounced permanent neuropsychiatric disorders persisted even at the age of 5 years, which corresponds to the profound phenotype that was observed in almost a third of the patients examined by A. Cossu et al. [10].

In recent years, a genotype-phenotype correlation has been established for *KCNQ2*-associated epilepsies [16]. Heterozygous variants with loss of function (read-frame shift variants, nonsense variants, splicing variants, and some missense variants) cause SeLNE. Missense variants with a dominant negative effect cause *KCNQ2*-DEE, reducing potassium currents in neurons by more than 50%. An interesting phenomenon is the possibility of forming *KCNQ2*-DEE or SeLNE phenotypes in different members of the same family [3, 7], i.e. with identical mutations of the *KCNQ2* gene.

There is no doubt that the elucidation of the causes of various degrees of mutant gene expressiveness will contribute to the further development of methods for *KCNQ2*-DEE precision therapy, which has been actively occurring in recent years in monogenic epileptic syndromes [17].

CONCLUSION / ЗАКЛЮЧЕНИЕ

Thus, a special feature of this observation is the combination of signs of *KCNQ2*-DEE and SeLNE, which is also more often caused by mutations in the *KCNQ2* gene.

The onset of serial tonic focal seizures in combination with regional interictal EA on the EEG from the first days of life, and their reduction with the appointment of anticonvulsants blocking sodium channels are possible in both diseases. Changes in the lateralization of motor phenomena both during an attack (migration) and in different attacks (alternation) are more typical for SeLNE. However, the presence of persistent neuropsychiatric disorders, which persist despite the remission of seizures and normalization of EEG, is observed only in *KCNQ2*-DEE.

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