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Clinical and Encephalographic Features of Epilepsy in Patients with Angelman Syndrome in Crimea

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ABSTRACT

Over the past decade, the number of patients with Angelman syndrome and epilepsy has increased. It is important to diagnose this disease at an early age and promptly begin treatment and rehabilitation measures that will improve the quality of life and social adaptation of patients. The article discusses the clinical characteristics, results of additional research methods and therapeutic approaches in children with Angelman syndrome and epilepsy. Special attention is paid to the clinical and electroencephalographic characteristics of epilepsy in patients with Angelman syndrome using the example of clinical cases of Angelman syndrome and epilepsy in Crimea.

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Introduction

Angelman syndrome (AS; OMIM: 105830) is a genetic disease based on morphological or functional disorders of the locus q11-q13 copies of maternal chromosome 15, accompanied by loss of expression of the UBE3A gene in brain neurons. Angelma syndrome is clinically manifested by intellectual deficits, delayed speech development, disorders of the nervous system, seizures, and a specific behavioral profile. The prevalence of AS varies between 1:10,000 and 1:20,000 of the population [1]. It is important to note there are 4 genetic variants of AS: 1) de novo deletion at locus 15q11-q13; 2) paternal dysomy on chromosome 15; 3) defect of the imprinting center; 4) mutation of the maternal copy of the ubiquitinlase gene UBE3A. Scientists have proven that only the third and fourth variants of Angelman syndrome occur with epilepsy, which requires combined therapy with antiepileptic drugs [2].

Seizures are one of the most common symptoms of AS. The first paroxysms of seizures can be initiated at various age periods-from three months to 20 years of age. In 60 % of cases, the first seizure attack It is marked up to the age of three. Seizures occur in almost 70-80% of patients during the first three years of life, in the first year of life-only in 25% of patients [3]. The most characteristic manifestations of epileptic syndrome in young children are myoclonic seizures (30%), atonic seizures (25%), generalized tonic-and clonic seizures (20%) and atypical absences (15%). In the first year of life, such manifestations are possible, such as atypical absences and epileptic myoclonus. It is quite common in patients with AS epileptic status (about 30%), which can last for several days, weeks, and possibly months [4].

The most typical EEG changes are AS, described in most studies on Angelman syndrome: runs of generalized high- amplitude plasma (often more than 300 Mv) delta activity, usually with an amplitude predominance in the frontal regions, often in combination with epileptiform activity; high-amplitude theta-range activity (200 Mv or more) with a frequency of 4-6 Hz, localized in the posterior regions or diffusely; changes in the posterior regions - rhythmic high-amplitude epileptiform activity with a frequency of 3-4 Hz in the form of spikes, sharp-slow wave complexes localized mainly in the occipital regions. These changes are triggered by closing the eyes and can be asymmetrical [5]. Due to the rarity of the disease, this article will present the clinical cases of patients with Angelman syndrome and epilepsy. The parents of the patients have given written consent to the use of their children's data in this article.

Clinical Case: 1

The boy's parents (Patient 1, 5 years old) contacted the Center of Pediatric Neurology in Crimea when the child was 3.5 years old with symptoms of epileptic seizures with fever, behavioral disorders (hyperactivity, unmotivated laughter, inappropriate reactions, uncontrollability), delayed mental and speech development (lack of speech, lack of understanding converted speech). The onset of seizures at the age of 1 year. Typical febrile seizures were observed against a background of high fever - 38.0 C: generalized tonic-clonic seizures lasting up to 1 min. After 1.5 years, febrile seizures recurred twice more with an interval of 3 months. After another 1.5 years, a short generalized clonic attack was observed in acute bronchitis against a background of high fever - 39.0 C. The parents began to notice that the child began to lag behind in mental development. It is known from the medical history that the child from the first pregnancy, which proceeded physiologically, from an urgent birth at the 39th week, screamed immediately, birth weight 3200 g, was discharged from the hospital on the 5th day. Early development with a delay: started holding head at 4 months, sitting-in 1 year 2 months, walking with a handshake, out of the question. The inheritance for epilepsy and neurological diseases is not burdened; the mother is 32 years old,

the father is 31 years old. The neurological status shows a delay in mental, motor and speech development. He does not walk independently, there is no speech, understands simple speech with difficulty, and follows simple instructions. No specific symptoms were detected. Moderate diffuse muscular hypotension. Behavioral features attract attention: hyperactivity, stereotypies in the form of waving arms, frequent and unmotivated laughter.

During video EEG monitoring, a slowdown in the main activity of background recording is noted. Rhythmic delta activity with a frequency of 2.5-3.0 Hz and an amplitude of up to 250 Mv is periodically recorded in the frontal lobes. FIRDA during wakefulness, epileptiform activity is recorded in the posterior regions, mainly in the right temporal and parieto-posterior temporal regions, less often in the left occipital region, represented by spike-slow wave complexes, often occurring in the delta-deceleration structure, with an amplitude of up to 300 Mv (on average 100-250 MV). At the same time, there is often a tendency to group peak-wave complexes into duplets, triplets and longer groups, as well as bilateral distribution. Periodically, regional epileptiform activity in the left and right occipital regions coincides in time, creating a pattern of bioccipital discharges with a low degree of synchronization. Rhythmic discharges of peak- and polypik-wave complexes with a high degree of synchronization and a frequency of 2.5 are also recorded in the posterior regions, with an amplitude predominance in the occipital regions. 3 Hz, with an amplitude of up to 450 Mv. This activity often appears when the eyes are closed and is blocked when the eyes are opened. Polypik-wave complexes with a high degree of synchronization, which corresponds to the EEG patterns of focal epileptic seizures originating from the occipital regions. In sleep, epileptiform activity is mainly represented by regional acute waves and complex acute is a slow wave with an amplitude up to 350 MV, with a predominance in the right temporal -posterior temporal-parietal region; less often-in the left occipital-parietal region. Periodically, the discharges in the left and right posterior sections coincide in time with the formation of a pattern of bioccipital discharges with a low degree of synchronization. The index of epileptiform activity during sleep at certain periods of the recording approaches 70-80%, decreasing with deepening sleep, averaging 30% for the entire sleep.

An MRI scan of the brain revealed a moderate atrophic process with mild secondary ventriculomegaly.

Regarding the delay in mental development, the patient underwent karyotyping and a special FISH study. Karyotype 46, XY, deletion at locus 15q11–q13 was revealed. Thus, during the genetic examination the Angelman syndrome was verified.

The patient received basic antiepileptic drugs in various combinations and doses. Carbamazepine, levetiracetam, topiramate are benzodiazepines were used. Currently, he receives Valproic acid retard at a dose of 750 mg/day, Ethosuximide 500 mg /day and Oxcarbazepine 450 mg/day. On the background of antiepileptic therapy, there is a positive trend in the form of relief of seizures with fever for 1 year or less the index of epileptiform activity on the EEG. The use of polytherapy was due to the maintenance of a high level of epileptiform activity with the formation of frequent EEG patterns of seizures. The addition of Ethosuximide to the therapeutic regimen significantly reduced the frequency of occurrence of EEG patterns of seizures originating from the occipital leads. This clinical example vividly illustrates typical electroclinical specific features of Angelman syndrome in combination with epilepsy.

Clinical Case: 2

Boy E. (Patient 2) was born from the fourth pregnancy. The first pregnancy ended with a medical abortion, and the second and third with a spontaneous miscarriage. This pregnancy, independent, proceeded against the background of the threat of termination at 16 weeks. The birth weight is 2500 g, the body length of the boy is 43 cm. The APGAR score is 6-7 points. Child started holding his head from the age of 6 months, sitting-from the age of 10 months, getting up-from the age of 1.5 years, walking with support for 2 hands-from the age of 2, and independent walking appeared only after 3 years. He walks on his own, often falls down. Muscle tone is moderately elevated, symmetrical, tendon reflexes are revived, D = S. Gait is atactic, with legs wide apart, there is a constant tremor of the hands and head, which increases when you don't get enough sleep. Myoclonia in the hands and face were noted. The elements of humming appeared in the second half of life and were poorly expressed, inactive, babbling speech appeared after a year, vocabulary in the form of single simplified words-from the age of 2. Boy E. understands spoken speech at the everyday level, performs simple requests, pronounces about 10 words, many syllables, self-service skills are not formed, by the age of 9 years. He eats on his own, uses a fork and spoon, and drinks from a mug. Since the age of 4, the boy E. has been experiencing disturbances in the form of shallow restless sleep with frequent restlessness, tremor of the head and hands, which increases with lack of sleep, as well as with emotional arousal, and an atactic gait has become clearly noticeable. At the age of 1.5 years, the boy E. first developed a seizure with a sudden fall, spreading his arms to the side, turning his head to the right, throwing his head back, and leaning in his limbs without loss of consciousness, since the child's reaction to the environment during the attack was saved. He has been taking valproic acid in combination with levetiracetam also showed a decrease in seizures and relief from the age of 5.5 years. Against the background of drug-induced remission of epileptic seizures, there is a slight improvement in night sleep, a decrease in the severity of hand and head tremors. During video EEG monitoring: rhythmic discharges of peak- and polypik-wave complexes with a high degree of synchronization and a frequency of 3.5 are also recorded in the frontal regions, with an amplitude predominance in the parietal regions. Saved atactic gait, episodes of unmotivated laughter, stereotypes in the hands. The MRI of the brain of a boy E. at the age of 2 years: signs of focal posthypoxic changes in the white matter of the frontal and parietal lobes, signs of moderate expansion of the subarachnoid convexital spaces of the frontal and parietal regions, signs of microcysts of the pineal gland, lateroventriculoasymmetry (S > D), incomplete fusion of the leaves of the transparent septum with the formation of the Verge cavity. At the time of the description of this clinical case at the age of 10 years, children still have a severe delay in mental and speech development.

Clinical Case: 3

The girl's parents (Patient 3) contacted the Center of Pediatric Neurology in Crimea when the child was 5 years old. She understands spoken language at the household level, is more sociable, follows simple instructions, participates in children's games, eats by herself from the age of 8, tries to discuss herself, she dresses with the help of adults, tries to dress herself. At the same time, active speech is completely absent. The girl had walking ataxia from the age of 5, and at the age of 6.5, stereotypies in the form of hand clapping, difficulty falling asleep, and hyperkinesis in the form of tremors of the hands and head joined the clinic. She had her first seizure at the age of 2.5 years while awake. Muscle tone is moderately elevated, symmetrical, tendon reflexes are revived, D = S. Gait attacks tic, with legs wide apart, is marked tremor of the

hands with anxiety, increases with lack of sleep, myoclonia is not noted. The MRI of the girl brain was: signs of focal posthypoxic changes in the white matter of the frontal and parietal lobes, signs of moderate expansion of the subarachnoid convexital spaces of the frontal and parietal regions. The video EEG monitoring of girl demonstrated: intermittent long discharges more than 5 seconds of delta wave activity with low -amplitude spikes in the occipital regions spread diffusely. Based on characteristic phenotypic signs (microbrachycephaly, wide interdental spaces, macrostomy, progenia, divergent strabismus, protruding pointed chin) in combination with severe mental and speech retardation, developmental delay in the formation of verticalization and independent walking, epileptic seizures, behavioral and movement disorders (stereotypies, unreasonable laughter, ataxia, tremor) and the detection of a mutation in the ubiquitin ligase gene UBE3A (in exon 7). At the age of 2.5 years, when using Valproic acid in combination with Ethosucamide, followed by the formation of drug remission from the age of 6 years. In addition, the child received rehabilitation courses with a speech pathologist and speech therapist with a frequency of 2-3 times a year.

Conclusion

The main directions of AS therapy are the organization of a regimen, syndrome- by-syndrome drug therapy for epileptic seizures and sleep disorders in combination with the provision of psychological, pedagogical, orthopedic care, and measures aimed at social adaptation of patients. In the first year of life, it is necessary to select an individual feeding regime with the preferred preservation of breastfeeding. If there are pronounced difficulties in breastfeeding, they switch to breastfeeding through a pacifier with an individual selection of special pacifiers, taking into account the flow rate of the jet from it and the rate of sucking of the baby. From the moment of verticalization of the child, it is necessary to organize a safe space for movement in order to avoid injuries in such patients, taking into account coordination disorders and peculiarities of motor activity. It can be a special configuration and shape of furniture without sharp corners, its rational arrangement and good stability. Be sure to observe sleep hygiene: the formation of a proper regime sleep, creating a bedtime ritual. Speech therapy and pedagogical correction of speech disorders is aimed at the formation of non-verbal communication of such children with others. Drug-based therapies for AS include the control of epileptic seizures, correction of sleep disorders and hyperactivity. Valproic acid combinations are effective acids with levetiracetam or ethosuximide, or the use of levetiracetam with ethosuximide. Monotherapy with these drugs is also possible in some cases. It is known that there is no etiological therapy for AS, however, the combination of anticonvulsant therapy with behavioral therapy methods is effective in patients with Angelman syndrome and epilepsy. The patients described in the article were continued to be monitored to assess the long-term results of therapy and rehabilitation.

Conflicts of Interest: The Authors of the Article Have No Conflicts of Interest

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