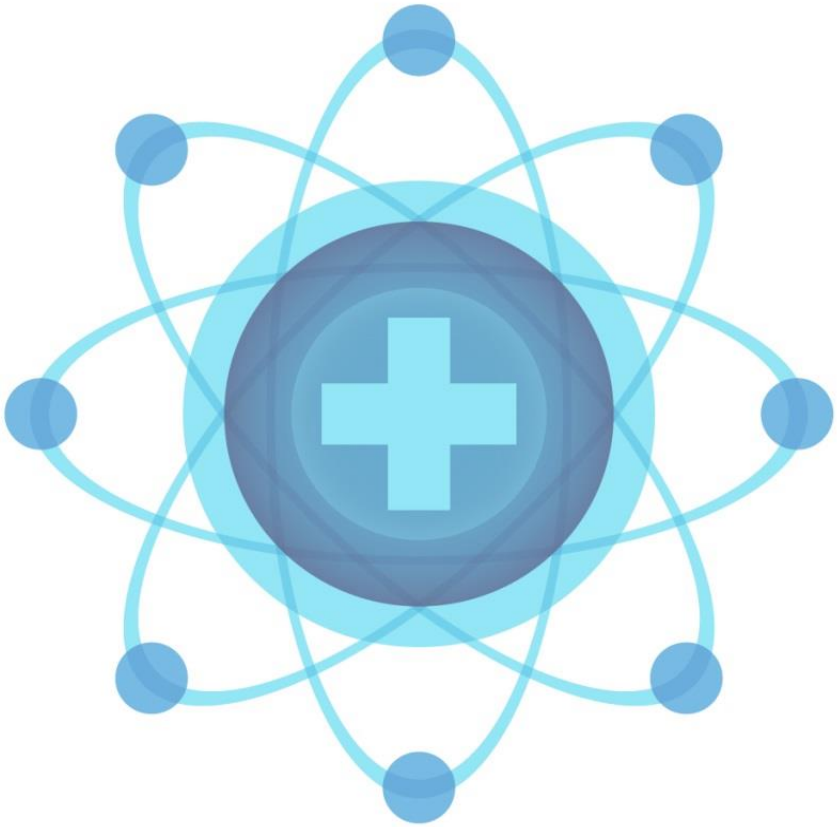

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Epileptic encephalopathy and Angelman syndrome

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Abstract: Angelman syndrome (AS) - is a chromosomal syndrome characterized by atypical autism with intellectual retardation, epilepsy, a gross impairment of speech, motor disorders, ataxia, as well as special the behavior (happy demeanor) of patients in combination with frequent laughter or smiling bursts. The disease is caused by mutation of the genes on the maternally inherited 15q11.2-13 locus or gene UBE3A- part of the ubiquitin complex. These genes regulate the functional activity of neurons in the hippocampus, olfactory bulb, the primary visual cortex, cerebellum.

Keywords: epilepsy, chromosome, Angelman syndrome, the UBE3A gene, tremor-shivering, ataxia.

Introduction. The establishment of a clinical diagnosis and etiology of the disease in the examination of patients with mental retardation is the basis of medical genetic counseling. The confirmed diagnosis allows to evaluate the course of the disease, to determine the possibilities of treatment, the prognosis of the offspring for relatives, and, if necessary, the prevention of the disease in the family. One of such syndromes, difficult for diagnosis and insufficiently studied in clinical practice, is Angelman syndrome (AS).

Angelman syndrome is a genetic disease characterized by intellectual and physical developmental delay, sleep disorders, seizures, sharp movements (especially applause), frequent causeless laugh or smile and, as a rule, patients with AS, look very happy.

AS is named after the British pediatrician, Dr. Harry Angelman, who first described the syndrome in 1965. Earlier, another alternative was used to characterize the AS, the alternative name is the happy puppet syndrome, but today, officially this term is no longer used, because it is considered disparaging. People with AS are sometimes called "angels", because of the name of the syndrome, their youth and happy appearance.

The syndrome occurs with the same frequency in representatives of both sexes. The prevalence is 1 to 10-30 thousand newborns, but a significant number of children with this disease as a result of the lack of a correct diagnosis are observed as patients with epilepsy or suffering from behavioral disorders and delayed speech development.

Seventy percent of cases occur as a result of a mutation of 15q11.2-13 de novo, 2% of observations - disomia on the paternal line (loss of the parent locus), 2-3% - defect of the imprinting center. Most of the remaining cases are associated with a mutation of the ubiquitin UBE3A gene. To establish the form of the disease in 7-9% is currently not possible.

AS is a classic example of genomic imprinting, as it usually arises from the deletion or inactivation of genes on a copy of the 15 chromosome inherited from the mother, while the activity of the parent copy (whose sequence may be normal) does not affect the functioning of the organism.

Karyotype 46 XX or XY, 15p-. Usually, the syndrome is caused by a spontaneous chromosomal defect when there is no large adjacent region of 3-4 million base pairs of DNA in the q11-q13 region of the 15th chromosome.

The Angelman syndrome arises from the loss of normal maternal copies of genes in a specific region of the 15 chromosome. Most often this happens by deletion of the segment of this chromosome. Other causes of the onset of the disease may be uniparental paternal disomia, translocation or mutation of one gene in this area.

This gene (UBE3A), involved in the metabolism of ubiquitin, is present on both copies of the chromosomes (on the paternal and on the maternal), but its effect differs from the process of methylation (imprinting). Inactivation of the father's copy of the gene UBE3A occurs in the brain (in the hippocampus and the cerebellum), whereas the maternal allele is almost always remains active.

The UBE3A gene produces the protein UBE3A (also called E6-AP) and this protein is an important component of the pathway for ubiquitin-proteasome formation. This pathway is extremely important for all cells, especially neurons of the brain. However, it is clear that UBE3A is closely related to the synaptic function of neurons. And it was the identification of four E6-AP substrates that allowed us to understand somewhat the possible molecular mechanisms underlying the onset of Angelman syndrome.

The disease is characterized by the absence of abnormalities during the perinatal period and pronounced malformations at birth. The main characteristic symptoms of Angelman syndrome are manifested at the age of 6-12 months. The circumference of the newborn's head does not deviate from the norm. In newborns with AS, you can note sluggish sucking and muscle hypotension, which may result in regurgitation, gastroesophageal reflux, and children gain weight poorly. At this age, patients can detect an obvious delay in development in the absence of a progressive loss of acquired skills.

At half of children by the end of the first year of life the insufficient head growth (microcephaly) and hyperreflexia are noted. Strabismus may develop. As the development of motor skills becomes noticeable tremor.

At the age after a year there is a constant smile, fits of laughter. Face dysmorphism becomes prominent: a wide mouth, protruding lower jaw, large interdental spaces, brachy- and microcephaly, hypopigmentation, blond hair and eyes (compared to the family). There are stereotypes (repeated strokes of hands, torsion with brushes and frequent clapping), not characteristic of healthy children. In water, children with Angelman's syndrome feel more comfortable, increased sensitivity to heat and fluid needs (a constant sense of thirst).

The results of laboratory tests do not deviate from the norm, examination using MRI or CT does not show the presence of structural changes in the brain. Possible

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moderate cortical atrophy and manifestation of selective damage to the myelin sheath (demyelination).

At preschool and school age, a child with a AS has a kind of "hard" gait, raised to the level of the chest and bent at the elbow joints with hands. Disinhibited, laughable, tongue stuck out, salivation increased. There is no speech. 10% of children with AS do not go and are usually observed with the diagnosis of "infantile cerebral palsy". Sleep disorders (dyssomnia) are very common. Typical difficulties of falling asleep and frequent awakening. Characteristic hyperactive behavior, which is more correctly called hyperdynamic syndrome. Often there are constipation, obesity. A child with a AS is continuously engaged in something: moves from object to object, grabbing, licking and discarding toys or other objects. Speech development is grossly violated. Rarely developed phrase of two words. The volume of understood speech is usually larger than the active vocabulary. Most older children and adults communicate with non-verbal means.

The pubertal in patients with AS does not differ from the norm, the fertility is preserved. The main problems: scoliosis and gastroesophageal reflux. Adult patients with AS are not capable of self-care, they need constant supervision. Life expectancy - as in the general population.

Epilepsy is noted in the vast majority of patients with AS (80-90% of cases). Epileptic seizures debut at the age of 3 months to 20 years, but more often in young children (up to 2 years), often - with febrile seizures. In 50% of cases, epileptic seizures continue to be febrile - provoked. In older children, even with a small subfebrile condition, there is a greater frequency of seizures; often marked by the transition of seizures to serial and the development of epileptic status. Atypical absences and epileptic myoclonus are the main types of epileptic seizures in AS, which in most cases are detected for the first time during video-electric-phalographic (video-EEG) monitoring and are much less frequent complaints of the parents of patients. Atypical absences are manifested by a decrease in the level of consciousness, motor activity is suspended, there is a general inhibition. Minimal atonic (nodding, lowering of the shoulders, torso of the trunk) and myoclonic (twitching of limbs and facial musculature) are possible. Salivation may increase during seizures. Consciousness often fluctuates. Absences can occur so often that a clinical picture of the epileptic status develops (peak-wave stupor), especially this is characteristic in the morning, after awakening. Anxiety epileptic status is noted in more than half of patients with AS and can last for days, weeks and even months.

Myoclonic seizures may occur in isolation (usually in the limbs and facial muscles) or as a myoclonic component in the structure of atypical absences. Epileptic myoclonus in the structure of arbitrary movements is difficult to differentiate from tremor. In a dream of myoclonic seizures, as a rule, no. The status of myoclonic seizures can develop in isolation or in combination with the status of atypical absence. Generalized convulsive seizures and focal epileptic seizures, from the cortex of the occipital lobe, are also characteristic.

In some patients with the AS phenotype, mutations in the MECP2 genes (Rett's syndrome), CDKL5 (X-linked early epileptic encephalopathy) and X-linked mental

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retardation are revealed. In most cases, the diagnosis is made to the patient at a more adult age, about 3-7 years. By this moment, the signs of a defect are, as a rule, pronounced. The speed with which the disease progresses will depend on the nature of the damage to the 15 chromosomes. For this reason, some patients will be able to lead an independent life, while others will not be able to even speak normally. Doctors in Europe have drawn attention that children with this disease have much in common with patients suffering from autism. They are united by impulsiveness, problems in communication, obsessive movements, and also a tendency to use things that are not suitable for children of their age.

One of the most notable features of the Angelman syndrome is its pathognomonic neurophysiological characteristics. For patients with AS, three different EEG results are common: very low amplitude rhythms, whose frequency is 2 -3 Hz, the greatest deviations are observed in the prefrontal zone; symmetrical high-amplitude rhythm with a frequency of 4-6 Hz; the presence of close-connected acute sharp waves in the occipital areas at a frequency of 3-6 Hz.

Due to the rarity of such descriptions in the domestic literature, we give a description of the clinical case.

Clinical case.

Girl K. 4 years. Complaints: delay in psycho-speech development, restless sleep, cramps, tremor.

From the anamnesis of life, it is known that the child was born from the first pregnancy, which was taking place with mild toxemia. Childbirth on the 38th week, immediately screamed. The score for Apgar is 6/7 balls, weight-3450 kg, height 50 cm. The neonatal period proceeded smoothly. Not a kindred marriage. Heredity for neurological diseases is burdened by the father of the girl. After discharge from the maternity home, parents noted the increased excitability of the child. From the age of two months were observed in the neurologist about anxiety, frequent flinch. From the words of the mother until the year the girl developed according to age: crawling, sitting alone, playing toys. The first epileptic seizures appeared against the background of apparent well-being, from 1 year 2 months in the form of head bendings with lifting of the shoulders and dilution of elbows to the sides. Attacks with a duration of no more than 5 seconds, without disturbance of consciousness, during waking period, 2-4 times a day. The mother began to notice the tremor first in the distal parts of the limbs, most of all the torso. We started taking Convulex 50 mg / ml at 20 mg / kg per day. As the attacks increased, the child began to experience delayed psychomotor development and muscle hypotension. In the further because of frequent paroxysms, Convulex was calculated from the calculation at a daily dose of 40 mg / kg. Paroxysms were absent for 6 months, but there were no positive changes in psychomotor development.

After the acute respiratory viral infection, the paroxysms resumed. Paroxysms of atonic character (a drop of a head on a breast, a torso of a trunk), on 10-20 times a day were observed. Then the therapy scheme was used - Convulex + Lamictal in the maximum tolerated therapeutic doses. Paroxysms partially decreased, insomnia

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joined and tremor increased, in connection with which hormonal therapy was prescribed (prednisone in a daily dose of 1 mg per 1 kg of weight with a gradual decrease in a month). The effectiveness of the drugs was partial - the number of paroxysms decreased (5-6 times a month). In general, the duration of the relatively "quiet" period was about two months.

On the video EEG monitoring (daytime): background EEG slow-wave activity originating from the central-parietal divisions at a frequency of 3 Hz. These epileptiform patterns are present in all stages of non-REM with different amplitudes from 50 to 150 μV, mainly in the anterolateral parts of the brain on the right. After awakening with active wakefulness in the frontal areas slow slow wave complexes and rhythmic slow wave activity of the delta range are recorded (Figure 1).

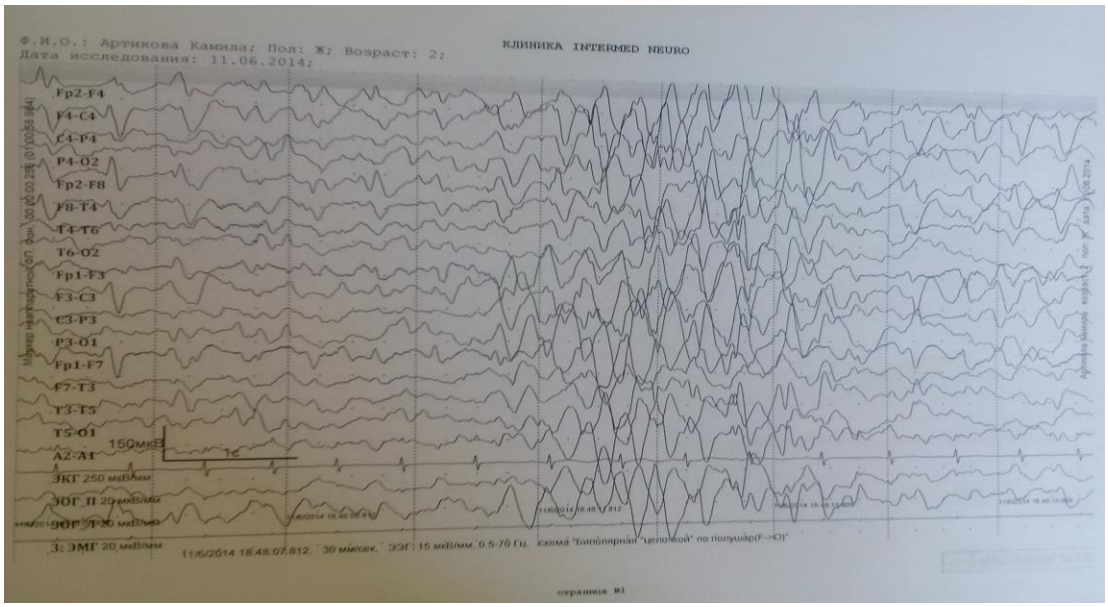

Fig.1

Based on the above data, a diagnosis was made: Epileptic encephalopathy. The Lennox-Gastaut syndrome.

Then, against the background of respiratory infectious disease at the age of 2.5 years, paroxysms resumed and paroxysms joined in the form of tonic torso and limb stresses, head and eye movements, nocturnal flinches. After the deterioration of the child's condition, another therapy scheme was used - Convulex + Levetiracetam. But this combination of the drug worsened the condition, seizures became more frequent, generalized clonic convulsions joined the paroxysms. In the future the scheme of therapy of Convulex + Topiramate was used.

At the last hospitalization at the age of 3 years 11 months the state of the child on the disease is severe. Paroxysms have become more frequent on the background of respiratory infectious disease in the form of tonic seizures of atypical absences with atonic component, frequent flinching's with a frequency of 2-3 times a day.

In objective status, physical development by age, stigma of dysembryogenesis is absent, a head of normal size, a flattened back of the head. Skin, hair and eyes of light color. Signs of the pathology of the respiratory and cardiovascular system are

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absent. Frequent constipation, increased salivation. On the lower extremities in the region of the shin there is a spot of blue color, which (according to the mother) increases with increasing temperature.

In neurological status: cranial innervation - movement of eyeballs in full volume, nystagmus, there is no strabismus. The face is symmetrical, the function of the chewing and facial muscles is not violated. The tongue along the middle line, the soft palate with phonation is symmetrically movable, the voice is loud. In the motor sphere: muscle tone is hypotonic. Tendon reflexes are called symmetrically. Pathological bone, carpal reflexes are not revealed. Severe tremor of the trunk and extremities. Expressed motor delay: does not walk alone, stands with support, takes objects with hands. Active speech is absent, hardly understands the converted speech. The mood is increased, a constant smile on the face, periodically laughs. Frequent stereotypes in the hands.

Video EEG monitoring (full-time): on the background recording, polymorphic activity with the predominance of theta waves of the diapason. The slow forms of activity are recorded widely, diffusely, often dominate the background, are mainly represented by fluctuations in theta of the range of 4-5 Hz with an amplitude of up to 150 μV, less often in the delta range with an emphasis in the fronto-central and parieto-occipital hemispheres. Against this background, on a regular basis, during wakefulness and during sleep, slow slow-wave complexes with a frequency of 1.5-3 Hz and an amplitude of 150 μV are recorded in a generalized manner. Sleep does not differentiate in phases and stages. The physiological patterns of sleep are mostly mixed in epileptiform activity. (Figure 2 and 3)

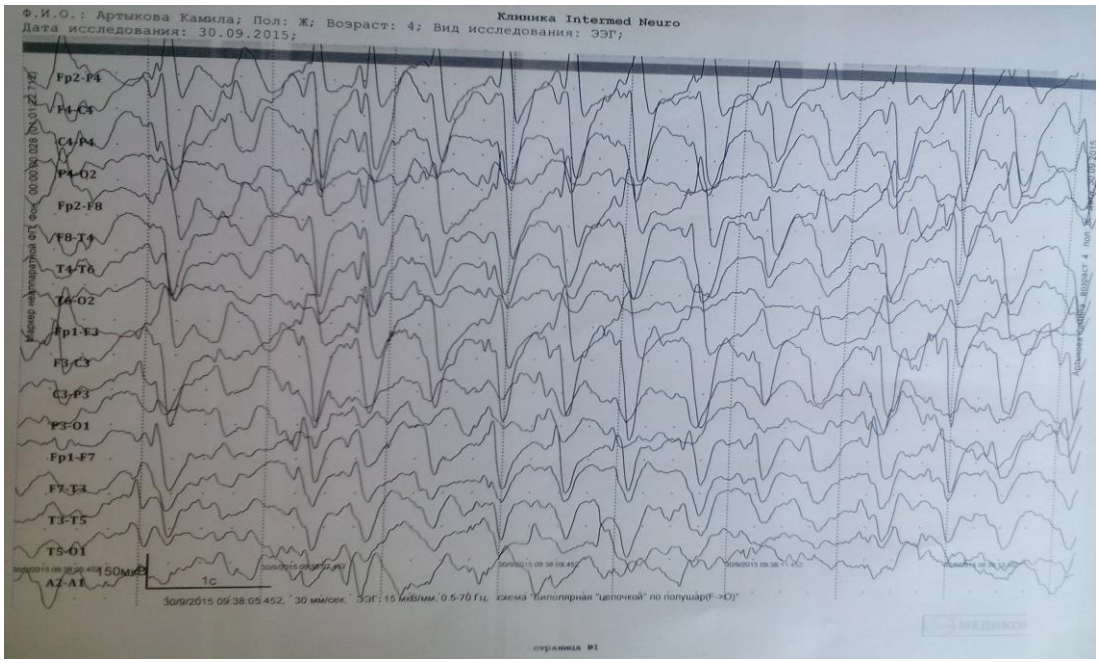

Fig.2

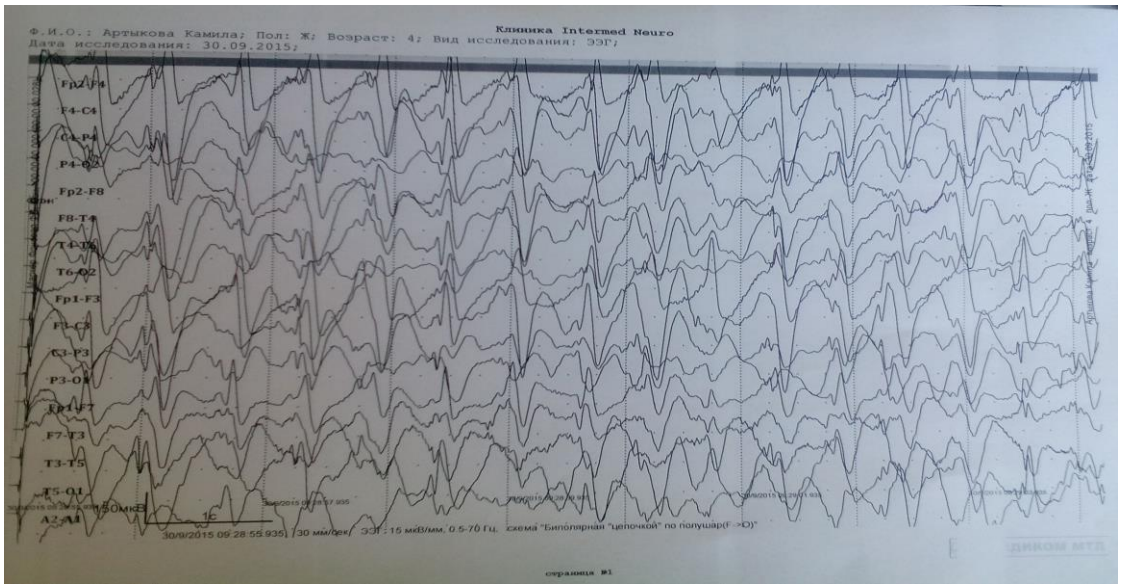

Fig.3

MRI of the brain - signs of moderate hypoxic - ischemic encephalopathy, delayed myelination (Figure 4).

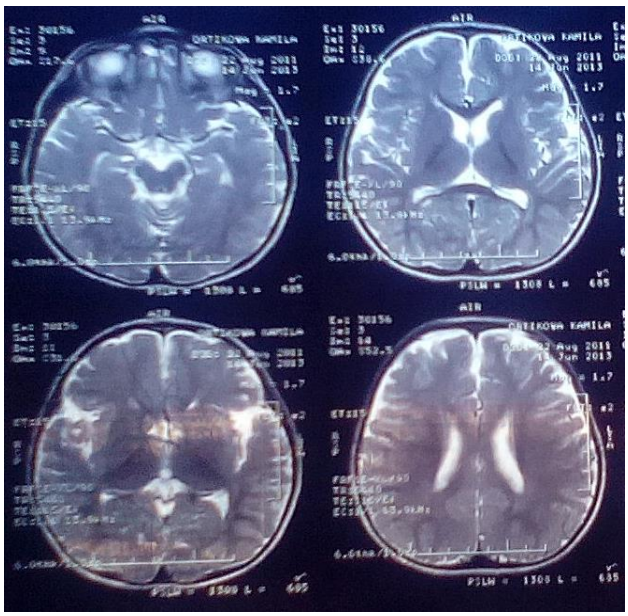

Fig.4

Ultrasound examination of internal organs: reactive changes in the liver, spleen and pancreas without pathology.

Blood chemistry: Calcium- 1.95mmol/L (N 2.02-2.60); Magnesium- 0.8mmol/L (N 0.7-1.0); Iron- 31.4mmol/L (N 8.9-21.0); Ammonia- 197mmol/L (N 9-33); Cholesterol- 4.1mmol/L (N 3.7-5.2); Triglycerides- 1.24mmol/L (N 0.1-1.1); Urea- 6,5mmol/L (N 1,8-6,4); Glucose- 3.35mmol/L (N 2.5-4.7); Lactate- 2.5mmol/L (N 0.7-2.1).

The concentration of valproate acid in the blood: 152.5 μG/ML (N 50-100).

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Immunogram: Imbalance of immunoregulatory T-lymphocytes. Presence of an allergic component in the body. Activation of apoptosis of lymphocytes. The presence of an inflammatory process on the mucous membranes (LgA increased).

Tandem mass spectrometry (MS) - pathological abnormalities are not revealed.

Genetic research: Results of karyotyping - 46, XX.

Conclusion of the Exome sequencing (WES): on chromosome-15 was detected a chromosomal microdeletion, that included a total of 282 exon genes: MKRN3, MAGEL2, NDN, PWRN1, NPAP1, SNRPN, SNORD116-1, SNORD114, SNORD116-10, SNORD116-22, IPW, SNORD115-1, UBE3A , ATP10A, GABRB3, GABRA5, GABRG3, OCA2, HERC2. The deletion is identified as probably pathogenic. It should be noted that the UBE3A gene is entered the deletion region (OMIM 105830 Angelman syndrome), heterozygous mutations in this gene leads to the clinical manifestations of AS.

Clinical diagnosis: Epileptic encephalopathy. Angelman syndrome.Based on laboratory data (elevated blood ammonia level, reactive hepatitis), the anticonvulsant therapy regimen was changed. Despite the attacks, the dose of Convulex was reduced to 25 mg/kg per day, Lamotrigine was added at a rate of 5 mg/kg per day, Topiramate was canceled. Hepatoprotectors were added to the treatment. After a month, the condition of the girl improved, the attacks decreased, ammonia in the blood normalized to 40.6 mmol/L. Currently, seizures 2-3 times a month, tremor and ataxia persists, night sleep restless.

This clinical case seems interesting with a few poses. The clinical picture of the disease itself is of interest - the impossibility of a clear syndromological diagnosis of this syndrome and unclassified form of epilepsy. By the type of seizures and according to EEG data, we can not attribute this case to classical encephalopathies of early childhood. In all cases of early epileptic encephalopathy, we can not explain a certain etiology (hypoxic-ischemic encephalopathy, developmental defects of the brain), the child needs to carry out a genetic examination, in particular comparative genomic hybridization and full genome sequencing. The most important aspect of this clinical observation is the mutation of the UBE3A gene, which in some patients can be detected with a mutation in the MECP2 genes (Rett syndrome), CDKL5 (X-linked early epileptic encephalopathy). But it is possible that such cases are much more common than they are. The development and accessibility of modern methods of genetic research, such as comparative genomic hybridization and full genome sequencing, will soon make it possible to clarify the genesis of a number of genetic and epileptic syndromes, and possibly help in the development of new ways of treating childhood epilepsy.

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