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Menkes disease. A clinical case report of a rare disorder of copper metabolism caused by a mutation in the *ATP7A* gene

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The article presents the features of diagnostics and dynamic monitoring of a patient with Menkes disease, a rare disorder of copper metabolism caused by a mutation in the *ATP7A* gene. The data of scientific literature on the epidemiology, etiology, pathogenesis of this disease are analyzed, and the basic principles of therapy and the outcomes of the disease are considered. The described patient was admitted for treatment with a diagnosis of consequences of severe perinatal lesions of the central nervous system with a typical clinical picture for this group of diseases: spastic tetrapresis, pseudobulbar syndrome, structural focal epilepsy. However, during the follow-up process, uncharacteristic symptoms were noted: short blonde coarse hair, bladder diverticulosis and progressive atrophy of the cerebral cortex in dynamics according to MRI. During the diagnostic search, tests for copper concentration and serum ceruloplasmin levels were performed twice, indicating Menkes disease, and complete exome sequencing was performed, which confirmed the presence of a point mutation in the *ATP7A* gene.

Keywords: Copper, ceruloplasmin, hypsarrhythmia, Menkes disease.

Introduction: Most hereditary metabolic disorders are extremely rare, but together they represent a fairly common group of diseases. As a rule, they are incurable and often lead to early disability and death, however, for many hereditary diseases, pathogenic therapy has been developed and with timely diagnosis and early start of treatment therapy, it is possible to achieve a favorable prognosis for life. One of these is hereditary disorders of copper metabolism.

The most famous neurodegenerative disease associated with impaired copper metabolism is Wilson-Konovalov disease, caused by a mutation in the ATP7B gene, which is responsible for the synthesis of copper-transporting ATPase and is characterized by the accumulation of copper in various organs and tissues, with predominant damage to the liver and central nervous system [2. 5, 13]. However, in addition to Wilson-Konovalov disease, there is a much less well-known hereditary disorder of copper metabolism, in which there is an uneven copper deficiency in various organs. This disease is called Menkes disease or curly hair disease and is an X-linked recessive neurodegenerative disease caused by mutations in the ATP7A gene located on chromosome Xq21.1 [1, 13]. Being an X-linked disease, clinical manifestations are possible only in males, in women who are carriers of ATP7A mutations, with the exception of rare cases associated with sex chromosome aneuploidy or X-autosome translocations, the disease is asymptomatic. However, some carriers of the mutant gene have minor hair and skin abnormalities [6, 8, 14].

The ATP7A gene is responsible for the synthesis of the transport protein of the same name, the function of which is to transport copper across cell membranes; this protein is expressed in all organs except the liver. In the small intestine, the ATP7A protein is necessary for the absorption of copper from food by active transport; in the cells of other organs, it acts as a carrier of copper from the cell membrane to the Golgi apparatus, where the synthesis of proteins and enzymes takes place, for the functioning of which copper [5] is required. One of these enzymes is lysyl oxidase, which binds tropocolagen into strong fibrils of mature collagen. When the mechanism of lysol oxidase synthesis is disturbed, defective collagen is formed, the properties of which determine many of the symptoms of Menkes disease. Normally, when there is an excess of copper inside the cell, the same ATP7A protein transports it to the cell membrane and removes the excess from the cell. Mutations in the ATP7A gene lead to the synthesis of a defective protein that is incapable of normal functioning. As a result, the absorption of copper from food in the intestine is sharply reduced, the synthesis of enzymes in the Golgi apparatus is disrupted, and the transport of excess copper from cells is blocked. Ultimately, copper accumulates in the small intestine and kidneys, and in the brain and other tissues, its content becomes catastrophically low, which together contributes to the formation of a kind of clinical picture of the disease [3, 4].

Menkes disease occurs in 1: 250,000-1: 350,000 newborn boys. Manifests, as a rule, in the neonatal period. Early symptoms include hypothermia, hyperbilirubinemia, growth retardation, and multiple stigmas of dysembryogenesis. Hair in the neonatal period, as a rule, looks normal [3, 11, 13].

Upon completion of the first 2-3 months of relatively normal development, a regression of previously acquired skills occurs, followed by a gross delay in psychomotor development. These children are characterized by the appearance of various types of epileptic seizures (focal, generalized, myoclonic) [11], general weakness with further formation of spastic tetraparesis [8]. Over time, a striking distinctive feature of these children becomes obvious - trichoplidystrophy, their hair becomes matted, coarse, gray or ivory [12]. A characteristic feature of the course of the disease is multiple diverticula of the urinary tract, often leading to rupture and secondary infection. Among other signs, it is important to note gen-

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eralized osteoporosis with frequent rib fractures [3, 4].

When conducting MRI studies, progressive atrophy of the cerebral cortex is detected. On angiograms, the vessels look twisted, elongated, with multiple stenoses, dilatations and aneurysms, which further leads to vascular complications - subdural hemorrhages, rupture of arteries and thrombosis, which, as a rule, become the cause of death

Pathogenetic treatment includes the use of copper histidinate 0.2-0.45 mg / day intravenously, which is able to restore normal levels of copper in plasma, cerebrospinal fluid and liver, however, the drug is ineffective for the treatment of neurological symptoms [3, 7, 13].

Life expectancy usually does not exceed 3 years.

Materials and methods:

- analysis of literary sources in the databases MEDLINE, Embase, US National Library of Medi-cine's PubMed database, ISI Web of Knowledge, Google Scholar, uMEDp and e-library, etc.

- analysis of the medical history of copper metabolism disorders caused by a mutation in the ATP7A gene.

Results and discussion. Patient M., 2 years old, was admitted to the palliative department of the regional clinical children's hospital No. 2 in Vladivostok on 17.03.20 with a diagnosis of West syndrome, in order to correct anticonvulsant therapy. He was hospitalized immediately after suffering acute community-acquired pneumonia, during which he was transferred to invasive mechanical ventilation (ALV). On admission, the following complaints were noted: frequent, up to several dozen per day, polymorphic convulsive seizures (adversive, myoclonic), severe retardation of psychomotor development, lack of independent urination, inhibition of swallowing with the possibility of feeding only through a nasogastric tube, as well as respiratory failure 2-3 degrees.

From the anamnesis of life, it is known that the child is from the first pregnancy, which proceeded physiologically. First birth, at thirty-eight weeks by emergency caesarean section. In childbirth, pronounced intrauterine fetal hypoxia was diagnosed, an Apgar score of 1/3 point, resuscitation measures were carried out. Birth weight 2500 g, height 48 cm. Breastfed up to 2.5 months, then transferred to an adapted formula. From birth he grew and developed with a delay in neuropsychic development. Was observed by a neurologist with a diagnosis of severe perinatal lesion of the central nervous system, received symptomatic treatment.

At the age of three months, convulsive syndrome first appeared, and the emergency medical team admitted the child to the neurological department of the regional clinical hospital No. 1 in Vladivostok. During the initial examination on the electroencephalogram (EEG) of 10/22/2018, acute - slow wave complexes were found in the left frontal regions, on the magnetic resonance imaging (MRI) of the brain from 10/23/2018, signs of linear periventricular zones of gliosis in the region of the seven-oval centers, foci of gliosis in the caudate nuclei, signs of replacement hydrocephalus, asymmetry of the lateral ventricles. A consultation with a neurosurgeon was carried out, the conclusion: PPTSNS, episyndrome, delayed psycho-motor development. The following treatment tactics were used: intravenous dexamethasone at the rate of 2 mg per kg of body weight per day, with a gradual decrease in dosage, a general course of 2 months and a solution of valproic acid (depakin) at a dosage of 30 mg per kg of body weight for a long period. At discharge, outpatient supervision of a neurologist, epileptologist and continuous administration of valproic acid are recommended. Against the background of the ongoing treatment, the condition in the future without positive dynamics. The results of dynamic observation and additional research methods:

- 6 months (01/14/19): computer EEG - specific epileptiform activity was revealed in the form of bilateral synchronous high-wave activity with a focus in the frontotemporal leads up to 200 μV, “shark teeth”.

- At the age of nine months, the correction of anticonvulsant therapy was carried out - a prolonged form of valproic acid (depakin chronosphere) at the rate of 40 mg / kg per day, topiramate tablets at the rate of 2 mg / kg per day for 2 doses and phenobarbital tablets at the rate of 8 mg / kg per day for 2 receptions.

- 11 months EEG (05/28/2019) - pronounced changes in cortical rhythm by the type of gypsum rhythm. The diagnosis was revised to West syndrome. In addition to the treatment, a solution of levetiracetam (keppra) was added at the rate of 30 mg / kg per day.

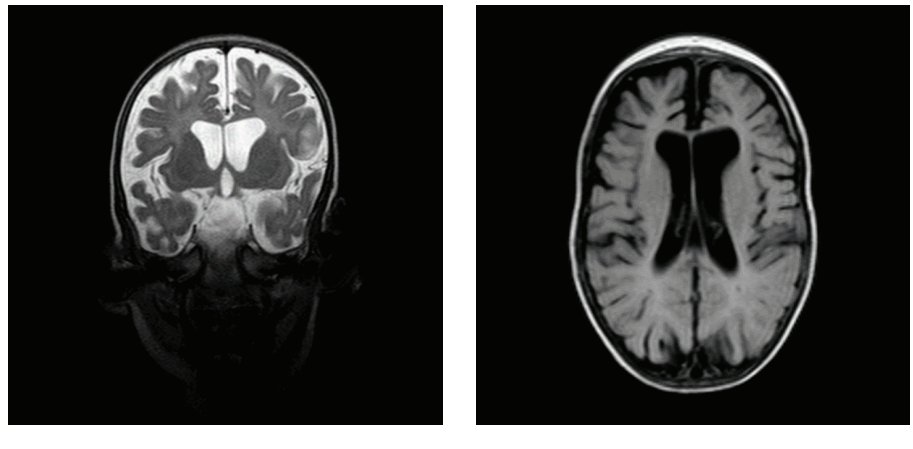
- 1 year 2 months EEG (08/21/19) - a pronounced slowdown of cortical rhythmics, registration of epileptiform activity in the form of diffuse discharges of deformed broadened "acute-slow wave" complexes with predominant localization in the central regions.

- 1 year 6 months EEG (01/16/2020) - an increase in the paroxysmal activity index, deformed, broadened “acute - slow wave” complexes of various localization, forming a pattern like hypsarrhythmia. MRI of the brain and cervical spine - a picture of diffuse cerebral atrophy with the formation of cerebrospinal fluid cysts of the temporal lobes (photo 1).

Photo 1. MRI of the brain with diffuse cerebral atrophy, formation of cerebrospinal fluid cysts of the temporal lobes.

On January 17, 2020, he was urgently hospitalized in the urology department of the regional clinical hospital No. 1 in Vladivostok with a referral diagnosis: acute urinary disturbance. While in the urology department, the child was diagnosed with congenital malformation of the genitourinary system: urinary bladder devirticulosis, secondary pyelonephritis, active stage, bilateral cryptorchidism.

On admission to the palliative care unit, the condition is consistently severe. During examination, the contact is not available, consciousness is not determined, the reaction to examination is negative. Breathing through the ventilator. The range of movements is significantly reduced, the movements carried out are chaotic, uncoordinated. Periodic myoclonic seizures. When as-



Patient M. MRI of the brain with diffuse cerebral atrophy, formation of cerebrospinal cysts of the temporal lobes

sessing neuropsychic development - a gross delay along all lines, unable to hold his head and turn over. The skin is pale, pronounced acrocyanosis. Hair that is light, fine and coarse to the touch, has a tendency to "caking". A pronounced decrease in the subcutaneous fat layer, to the level of protein-energy malnutrition of the II-III degree. Muscle tone is diffusely reduced. Tetraparesis of central genesis. Joint movements are limited by spasticity, and there are no joint contractures. Examination of the cranial nerves: visual concentration is undetectable, the pupils are round. The reaction of the pupils to light is direct, friendly, lively. Signs of oral automatism, pseudobulbar syndrome. On auscultation of the lungs, there are many moist rales. The bladder is enlarged on palpation, tense. Urination is only possible through a urethral catheter.

The severity of the condition and the progression of neurological symptoms, combined with a detailed analysis of the course of the disease, as well as the presence of characteristic phenotypic signs (features of hair), made it possible to suspect the presence of a hereditary metabolic disease with brain damage in the child. The presumptive diagnosis was a copper metabolism disorder caused by a mutation in the ATP7A gene - Menkes's disease.

On March 24, 2020, a blood sample was taken to study the levels of ceruloplasmin and copper (in the child's analyzes, ceruloplasmin was reduced to 65.65 at a rate of 200-600 mg / l), serum copper was reduced to 4.3 mkM / l (at a rate of 13 -24 mkM / l). In March 2021, full exome sequencing was performed on the Illumina NovaSeq 6000 at the Genetico Center for Genetics and Reproductive Medicine. The rs797045338 G> C mutation in intron 7 (out of 22) of the ATP7A gene in the hemizygous state was revealed, which made it possible to confirm the presumptive diagnosis of Menkes disease.

By the age of two, the palliative service achieved a phased cancellation of artificial ventilation, and now the child is breathing independently through a tracheostomy tube. Feeding is carried out through the nazagastric tube (grated food, Nutridrink nutritional therapy). A satisfactory anticonvulsant effect was achieved with phenobarbital monotherapy at a rate of 10 mg / kg per day. Periodically, courses of levocarnitine, B vitamins are carried out, as well as repeated courses of massage and physiotherapy. The child does not receive pathogenetic therapy that can prolong life span, since the drug for intravenous life-long administration of copper histidinate is not registered in the Russian Federation.

At the moment (05/23/2021) the child is three years old, the state is without clear dynamics. Neurological symptoms are relatively stable, there are rare myoclonic seizures up to 5-7 per day, lasting no more than 1 minute. Tolerance to phenobarbital is satisfactory, from undesirable effects - hypersalivation and the need for frequent sanitation of the respiratory tract. The prognosis for life is not favorable.

Conclusion. The key feature of this clinical case is the complexity of differential diagnosis of perinatal hypoxic-ischemic brain lesions with hereditary neurodegenerative diseases. A timely diagnosis will help parents consciously plan the birth of healthy children under the supervision of a geneticist. A description of the clinical case of Menkes's disease, as well as the peculiarities of diagnosis and the experience of managing a child with this disease can be useful for specialists, including those of a palliative profile.

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