

Case report

Clinical case of rare mitochondrial disease in a child

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Abstract: We describe a clinical case of Alpers-Huttenlocher syndrome in a child with polyneuropathy, myopathy and epileptic seizures, the development of toxic hepatitis with a fatal outcome after the use of valproic acid as an antiepileptic drug. The need for early differential diagnosis of Alpers syndrome and molecular genetic testing in cases of damage to the nervous system with various symptoms in order to select optimal therapy is shown.

Keywords: Alpers-Huttenlocher syndrome, epilepsy, valproic acid drugs, fatal toxic hepatitis, molecular genetic test.

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Introduction

Mitochondrial diseases present a group of disorders caused by mitochondrial dysfunction. Mitochondrial disorders may be caused by mutations (acquired or hereditary) in mitochondrial DNA (mtDNA) or nuclear genes. Mitochondrial diseases are characterized by clinical, biochemical and genetic diversity and can manifest in both children and adults [1, 2]. Epilepsy is one of the most common manifestations of mitochondrial diseases resulting from pathogenic POLG1 gene [1-3].

Alpers-Huttenlocher syndrome (OMIM 203700) is a mitochondrial disease associated with a mutation in the nuclear POLG1 gene. It is an autosomal recessive genetic syndrome characterized by progressive psychomotor retardation, refractory seizures and hepatopathy with liver failure [1, 2]. The POLG1 gene is located on chromosome 15q25. The frequency is about 1:100,000 live births. The distinctive clinical features of Alpers-Huttenlocher syndrome are drug-resistant seizures, developmental regression, and fatal liver dysfunction caused by valproic acid use [3].

We present a clinical case of Alpers-Huttenlocher syndrome in a boy with polyneuropathy, myopathy, epilepsy and fatal liver dysfunction caused by valproic acid. The need for early differential diagnosis of Alpers syndrome and molecular genetic studies for lesions of the nervous system, manifested by a variety of symptoms and requiring optimally selected therapy, is discussed [1-4].

Case report

The patient (boy) was born in 2010 from the first pregnancy of his mother against the background of anemia. This was the first emergency birth without complications. The marriage was consanguineous, the parents were cousins. The first years of development were normal. At the age of 5 years, the mother noticed unsteady walking of her child, difficulty climbing stairs and

getting up from the floor, weakness of the upper limbs, and also delayed speech and mental development. The boy was examined by a neurologist and electroneuromyography (ENMG) was performed. The results showed evidence of demyelinating polyneuropathy. The patient underwent panel sequencing for *hereditary neuropathy* and *frequent mutations in mtDNA*, but no pathogenic gene variants were revealed. Lysosomal diseases (Niemann-Pick disease type C), 5q spinal muscular atrophy and peroxisomal diseases were excluded. At the age of 9 years, the patient stopped gaining weight, independent movement became impossible due to severe muscle weakness and the development of tetraparesis, and convulsions with loss of consciousness appeared. Electroencephalography (EEG) showed signs of pathological epileptic activity. The administration of valproic acid increased the frequency and severity of attacks. Consequently, the drug was discontinued and replaced with levetiracetam. As a result, the frequency of attacks decreased. At the age of 9 years and 10 months, the patient was admitted to the intensive care unit due to a sharp deterioration in his condition manifested in the development of bulbar syndrome (dysarthria, dysphagia), appearance of mental confusion, and signs of respiratory failure. The symptoms were caused by protein-energy malnutrition. Physical development was below average and disharmonious due to a large weight deficit (more than 40%) with a body mass index (BMI) of 9.65 kg/m². The neurological status of the patient showed peripheral tetraparesis with a severely decreased function and bulbar syndrome. A complete blood count revealed hypochromic anemia, and crystals with a predominance of phosphates were found in the urine. Biochemical analysis revealed a moderate increase in ALT, AST, LDH, along with hypoproteinemia, hypoalbuminemia, decreased sodium levels and hypoglycemia. The coagulation test showed a decrease in markers of the blood coagulation system. Magnetic resonance imaging (MRI) of the brain revealed structural changes in the white matter

of the parietal lobes and the development of zones of paraventricular gliosis. Ultrasound imaging of the abdominal organs and kidneys exhibited diffuse structural changes in the liver, diffuse changes in the renal parenchyma, and right pelvicalyceal dilatation and suspension in the lumen of the renal pelvis. The EEG results did not indicate pathological epileptic activity. A blood test was performed for whole-exome sequencing using NGS technology. Death occurred at the age of 9 years and 11 months due to toxic hepatitis and multiple organ failure. The parents refused the autopsy for religious reasons. Clinical exome sequencing (the result was obtained after the death of the child) identified a nucleotide change in a homozygous position in the 3rd exon of the POLG1 gene (chr15-89873487-C-T; NM_002693.2:c.680G>A; p.Arg227Gln). The coverage depth was x271. This substitution is described as pathogenic in the international Human Gene Mutation Database, HGMD (CM1815564), and the POLG database.

Based on clinical, instrumental and molecular genetic changes, a diagnosis was formulated as degenerative disease of the central nervous system. Alpers-Huttenlocher syndrome (OMIM 203700): mitochondrial encephalopathy, polyneuropathy, myopathy, epilepsy, distal tetraparesis.

Complications: Bulbar syndrome. Toxic hepatitis. Respiratory failure. Protein-energy malnutrition of mixed origin with grade III body weight deficiency and stunted growth.

Genetic diagnosis: Alpers-Huttenlocher syndrome chr15-89873487-C-T; NM_002693.2:c.680G>A; p.Arg227Gln (OMIM 203700).

Discussion

The described clinical case is represented by a child born from a consanguineous marriage with the development of mitochondrial disease, which manifested itself at the age of 5 years with delayed speech and mental functions, damage to the nervous and muscular system in the form of polyneuropathy and muscle hypotonia. Subsequently, the disease progressed, and after four years from the onset, the first signs of tetraparesis and seizures appeared. The administration of valproic acid as an antiepileptic drug led to the rapid development of toxic hepatitis and other complications. Anamnesis, typical clinical features, deterioration after the use of valproic acid and the results of molecular genetic testing were useful in verifying Alpers-Huttenlocher syndrome from the mitochondrial group of diseases. According to numerous studies, the use of valproic acid in patients with POLG-associated diseases leads to the development of toxic hepatitis, liver failure, and the development and progression of encephalopathy [5-10]. Alpers syndrome is a disease with an autosomal recessive mode of inheritance [7, 8]. The POLG1 gene mutation in the patient was detected in a homozygous position, apparently inherited from cousins. Close marriages increase the likelihood of the birth of a child with hereditary diseases. Therefore, it is necessary to schedule explanatory conversations and preventive measures with future parents.

Conclusion

In children with symptoms of speech and mental development delays, in addition to polyneuropathy, myopathy, and seizures, whole-exome analysis or genome sequencing should be performed to rule out mitochondrial diseases. Diagnostic testing for

polyneuropathy and myopathy in children with developmental regression and ongoing epilepsy should include screening for gene mutations associated with POLG, since a positive result will prevent the use of valproic acid in the treatment of these patients, thereby averting the occurrence of fatal liver failure. Timely diagnosis helps ensuring appropriate counseling and family planning for future pregnancies, especially in communities with high rates of consanguineous marriages.

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