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Leukodystrophy in children. Globoid cell leukodystrophy. Clinical case

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Annotation: Pediatric globoid cell leukodystrophy (GLD, or Crabbe's disease) is a rare hereditary degenerative disease of the central and peripheral nervous systems. It is characterized by the presence of globoid cells (multinucleated cells), the destruction of the protective myelin coating of the nerve and the destruction of brain cells. Globoid cell leukodystrophy is one of a group of genetic diseases called leukodystrophy. These disorders disrupt the growth or development of the myelin sheath and cause severe degeneration of mental and motor skills. Myelin, which gives its color to the "white matter" of the brain, is a complex substance consisting of a number of different glucoproteins and glucolipids, the most important of which is galactocerebroside. Each of the leukodystrophy affects one of these substances. Globoid cell leukodystrophy is caused by a deficiency of galactocerebroside-β-galactosidase (GALC), an important enzyme for myelin metabolism. The disease most often affects infants, with onset before the age of 6 months, but can occur in adolescence or adulthood. Symptoms include irritability, unexplained fever, limb stiffness (hypertension), seizures, difficulty feeding, vomiting, and slowing of mental and motor development. Other symptoms include muscle weakness, spasticity, deafness, and blindness.

Key words: Leukodystrophy, globoid cell leukodystrophy, Crabbe's disease, galactocerebroside-β-galactosidase(GALC), myelin, autosomal recessive

Relevance

Leukodystrophy is a genetically determined disease, and the type of inheritance depends on the specific type of leukodystrophy. Most leukodystrophy (including metachromatic and globoid cell) is inherited by autosomal recessive type, that is, the probability of a child's disease is 25% if both parents are carriers of the disease. Such diseases affect boys and girls with the same frequency. They occur more often in communities where closely related marriages are common, and may occur with different frequency in different nations.

Leukodystrophy is a group of severe hereditary metabolic diseases characterized by damage to the white matter of the brain. With leukodystrophy, the metabolism of myelin is disrupted, that is, a substance that forms the shell of nerve processes and provides effective signal transmission in the nervous system (it is myelin that gives the white matter of the brain its color).

Myelin consists of a number of different components, and therefore its functioning depends on many genes. A defect in one of these genes can disrupt the formation of myelin sheaths or their maintenance in a normal state. The transmission of nerve signals slows down dramatically, motor and intellectual disorders occur, and the perception of signals from the sensory organs worsens. With

the further destruction of myelin, these disorders intensify, leading to deep physical and mental degradation for several years and then to the death of the patient.

Leukodystrophy is a group of rare diseases that differ in their nature and frequency of occurrence. Here are some of them:

Adrenoleukodystrophy. Substances of a special type accumulate in the tissues — fatty acids with very long chains, since their cleavage in this disease is disrupted. As a result, the structure and functions of myelin are disrupted. Adrenoleukodystrophy occurs with a frequency of approximately 1 in 40 thousand newborn boys. Adrenoleukodystrophy is usually characterized by X-linked inheritance and, therefore, in most cases occurs in boys — if the mother is a carrier of the disease, the probability of the disease in her son is 50%.

Metachromatic leukodystrophy is caused by a deficiency of the enzyme aryl sulfatase A. Sulfatides accumulate in the body — substances that have a destructive effect on myelin. Metachromatic leukodystrophy has a frequency of about 1 in 50-70 thousand newborns.

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Globoid cell leukodystrophy, or Crabbe's disease, is associated with a violation of the production of the enzyme galactocerebrosidase. This leads to the accumulation of substances that have a toxic effect on the myelin sheaths. Globoid cell leukodystrophy has a frequency of about 1 per 100 thousand newborns.

With many leukodystrophy, several forms of the disease are distinguished, depending on the age at which the first symptoms occur. This is important for predicting the development of the disease (as a rule, the earlier symptoms occur, the faster the disease develops) and for planning bone marrow transplantation, if possible. So, for adrenoleukodystrophy, there is a typical childhood form with the appearance of symptoms in 4-10 years and several other forms, including adrenomyelopathy, which is characteristic of adulthood and is not so severe. For metachromatic leukodystrophy, there are late infantile (the appearance of symptoms in 1-2 years), juvenile (in 3-10 years) and adult (after 16 years) forms. For globoid cell leukodystrophy, infantile (from 3-6 months), late infantile (from 6-18 months), juvenile and adult forms are known.

At birth, children with leukodystrophy usually look healthy and develop according to age for some time. However, then gradually there are symptoms of damage to the central nervous system. These symptoms vary somewhat depending on the specific disease and its form, but still have common features.

Motor disorders are common. Coordination of movements worsens in children, problems with balance are noted, it becomes difficult to walk and run. Muscle weakness, abnormally increased or decreased muscle tone, muscle twitching are possible. Convulsive seizures appear. There are changes in behavior. Memory and intelligence are gradually decreasing. Vision and hearing deteriorate. The child gradually "rolls back" in his development, losing previously acquired motor and intellectual skills. In the later stages of the disease, blindness, deafness, paralysis, inability to swallow food normally occur. As a rule, the earlier the signs of the disease appear, the faster it progresses.

There are also symptoms characteristic of specific types of leukodystrophy. So, with adrenoleukodystrophy, in addition to disorders of the central nervous system, signs of damage to the adrenal glands are also revealed.

The lesion of the white matter of the brain, characteristic of leukodystrophy, is detected by magnetic resonance imaging (MRI). As a rule, abnormalities on MRI associated with the destruction

of myelin are visible long before the appearance of clinical symptoms, and subsequently the degree of these anomalies corresponds to the severity of the patient's condition. With many leukodystrophy, a high level of protein is detected in the cerebrospinal fluid.

To clarify the type of leukodystrophy, biochemical tests can be used — measuring the levels of enzymes whose synthesis or transport is disrupted in a particular disease, or detecting those substances that accumulate in this disease. Other studies, including molecular genetic ones, are also possible. Prenatal diagnostic methods have been developed for some types of leukodystrophy (including metachromatic, globoid-cell and adrenoleukodystrophy).

Goals and objectives of the work:

The goals and objective of our work is the clinical observation of a patient with pediatric globoid cell leukodystrophy.

Pediatric globoid cell leukodystrophy (GLD, or Crabbe's disease) is a rare hereditary degenerative disease of the central and peripheral nervous systems. It is characterized by the presence of globoid cells (multinucleated cells), the destruction of the protective myelin coating of the nerve and the destruction of brain cells. Globoid cell leukodystrophy is one of a group of genetic diseases called leukodystrophy. These disorders disrupt the growth or development of the myelin sheath and cause severe degeneration of mental and motor skills. Myelin, which gives its color to the "white matter" of the brain, is a complex substance consisting of a number of different glucoproteins and glucolipids, the most important of which is galactocerebroside. Each of the leukodystrophy affects one of these substances. Globoid cell leukodystrophy is caused by a deficiency of galactocerebroside-β-galactosidase (GALC), an important enzyme for myelin metabolism. The disease most often affects infants, with onset before the age of 6 months, but can occur in adolescence or adulthood. Symptoms include irritability, unexplained fever, limb stiffness (hypertension), seizures, difficulty feeding, vomiting, and slowing of mental and motor development. Other symptoms include muscle weakness, spasticity, deafness, and blindness.

Krabbe's disease is characterized by polymorphism of clinical variants of the course. Depending on the age of the debut , 4 forms of the disease are differentiated:

• infantile (infant) – the classical form, which accounts for up to 90% of all cases. Develops at the age of 3-6 months.

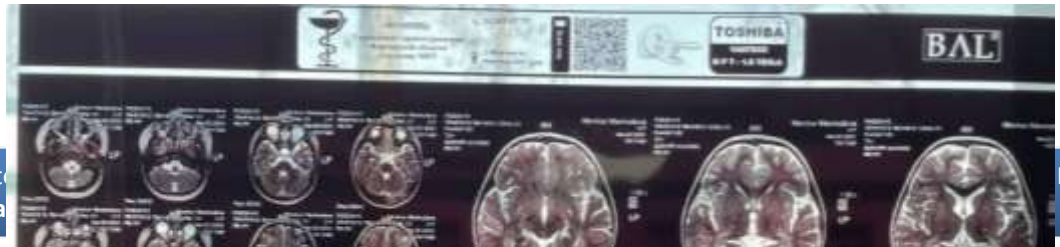
late infantile (late infantile) – the onset of the disease occurs in the age period from 6 months to 3 years.

• juvenile (juvenile) – signs of Crabbe's disease appear from 3 to 12 years old. adult – clinical manifestation begins in the post-puberty period.

Here is a clinical observation.Child M. 3 years old. Anamnesis of life: proband from unrelated marriage, occupational hazards are excluded, hereditary history of neurological pathology is not burdened. A child from 1 pregnancy, 1 birth. The course of pregnancy (probandom) against the background of anemia, toxicosis, ARVI. The course of labor: independent. Delivery: on time. Presentation of the head. All at birth 2,700g. Amniotic fluid is clean. Scream right away. Feeding immediately. There was no jaundice.

Anamnesis of the disease: according to the mother, since February 7 of this year, the child has been limping on his left leg, they turned to a neurologist, electrophoresis was prescribed, after which the child gradually began to lose the acquired skills. Sent in order to clarify the diagnosis.

Phenotype: hypertonia is more on the right, a sharp delay in psycho-motor development, dysarthria, dysphonia. At the time of the examination, he does not walk, does not speak.



Magnetic resonance imaging of a 24-year-old female M. Explanation is in the text

A survey was conducted: MRI of the brain: in the supraventricular and paraventricular parts of the frontal, parietal and temporal lobes, knee and cushion of the corpus callosum, extensive drainage foci are detected, hyperintensive in T2 and FLAIR modes, reduced intensity according to T1 without signs of perifocal edema, "mass effect". Against the background of the described changes, there are areas of diffusion restriction, areas with an increased diffusion coefficient index due to degenerative changes. According to MR spectroscopy, there are signs of leukodystrophy. (see figure).

The patient was diagnosed with a preliminary diagnosis of "ecodystrophy". To clarify the diagnosis, exome sequencing was performed: The laboratory study was carried out under optimal conditions recommended in the kit, and the initial data obtained were prepared for analysis using a number of processes. The current versions of various databases (human genome hg19/GRCh37, RefSeq (realese 61), dbSNP (v 147), Phase 3 1000 genomes, gnomAD, ExAC03) were used to interpret the variants during the analyses. Mutations with a minor allele frequency of more than 5% (in 1000 genomes, ExAC and gnomAD databases) were not evaluated.

The detected variants were classified according to the ACR (American College of Medical Genetics and Genomics) criteria published in 2015. (PMID: 25741868) As a result of the analyses, pathogenic, possibly pathogenic and clinically unknown variants associated with the patient's clinic were identified. In addition, even if it is not related to the patient's clinic, pathogenic and possibly pathogenetic variants found in the genes that the ACMG recommended reporting were added to the report. (PMID: 34012068). In addition, the report did not report variants associated with other autosomal recessive diseases. The patient's eczema data is stored in our laboratory, and the patient can apply for analysis if the status of a carrier of recessive diseases is detected before marriage or when new indications appear.

GENE	Version	Location	Zygosity	Disease	Inherit	Classificati

(decryption)					ance	on
GALC (NM_000153)	c.956A>G (p.Tyr319Cys) rs183105855	Exon 9 Chr14:87965582	heterozygous	**Krabbe's disease**	AR**	**Likely Pathogenic** (PM2, PP2, PP3, PP5, PM1)
	c.1890T>A (p.Tyr630Ter) rs1057516453	Exon 16 Chr14:87939926	heterozygous			**Pathogenic** (PVS1, PM2, PP5)

* Classified according to the guidelines of the ACMG (American College of Medical Genetics) (Richards et al., 2015, Tayoun et al., 2018). It should be taken into account that the classification may vary depending on the current data.

* AR is Autosomal recessive

The child receives neurometabolic therapy, cognitive training.

Conclusions:

The continuation of the study of this problem, descriptions of clinical cases, reviews of literature data on the topic of GLD are relevant, since currently the features of the clinical course and therapeutic approaches related to GLD are insufficiently studied. Thus, the patient is recommended allogeneic hematopoietic stem cell transplantation – one of the few available methods of treatment of GLD. It is believed that with early diagnosis, late forms (juvenile and adult) GLD can be treated with allogeneic hematopoietic stem cell transplantation, which can stop further demyelination and reduce the white matter changes visible on MRI. However, due to the small number of clinical cases, it has not been sufficiently studied whether changes in the clinical picture are a feature of the course of the disease or the result of allogeneic hematopoietic stem cell transplantation.

It is necessary to systematize data on all clinical cases in order to create recommendations for the effective treatment of such patients, since at present the disease, even after the correct diagnosis of GLD in children, continues to progress steadily, motor and cognitive deficits increase, patients lose their ability to work, their social maladaptation occurs.

Experimental developments are underway in the direction of gene therapy, the search for drugs that can activate the GALC gene. However, to date, there are no scientific reports on the success of such experimental therapy yet.

Families where there have already been cases of the birth of children with any type of leukodystrophy, before the birth of all subsequent children, it is recommended to consult a geneticist. Prevention of Crabbe disease consists in carrying out genetic diagnostics at the preimplantation stage or before delivery.

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