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New Aspects of Diagnosis and Treatment of Leukodystrophy

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Abstract:

Leukodystrophies- a group of severe hereditary metabolic diseases characterized by damage to the white matter of the brain. In leukodystrophies, the metabolism of myelin is disrupted, that is, the substance that forms the sheath of nerve processes and ensures effective signal transmission in the nervous system (it is myelin that gives the white matter of the brain its color).

Keywords: Leukodystrophies, adrenoleukodystrophy, degeneratsiya, Sulfatides accumulate, transplantation, Metachromatic.

Introduction

Myelin is made up of a number of different components and therefore depends on many genes to function. A defect in one of these genes can interfere with the formation or maintenance of myelin sheaths. The transmission of nerve signals slows down sharply, motor and intellectual disorders occur, and the perception of signals from the senses deteriorates. With further destruction of myelin, these disorders intensify, over several years leading to deep physical and mental degradation and then to the death of the patient.Allogeneic bone marrow transplantationis so far the only method to stop or slow down the development of the disease.[1,2]

Leukodystrophies are a group of rare diseases that vary in nature and frequency of occurrence. Here are some of them:

Adrenoleukodystrophy. A special type of substance accumulates in the tissues - fatty acids with very long chains, since their breakdown is impaired in this disease. As a result, the structure and function of myelin are disrupted[3].

Metachromatic leukodystrophycaused by a deficiency of the enzyme arylsulfatase A. Sulfatides accumulate in the body - substances that have a destructive effect on myelin.

Globoid cell leukodystrophy, or Krabbe disease, is associated with a disruption in the production of the enzyme galactocerebrosidase. This leads to the accumulation of substances that have a toxic effect on the myelin sheaths[4,5].

There are also several other very rare leukodystrophies. For many leukodystrophies, several forms of the disease are distinguished depending on the age at which the first symptoms appear. This is important for predicting the progression of the disease (generally, the earlier symptoms appear, the faster the disease progresses) and for planning bone marrow transplantation, if possible. Thus, for adrenoleukodystrophy, there is a typical childhood form with the onset of symptoms at 4-10 years of age and several other forms, including adrenomyelopathy, which is characteristic of adulthood and is not so severe. For metachromatic leukodystrophy, late infantile (onset of symptoms at 1-2 years), juvenile (3-10 years) and adult (after 16 years) forms are distinguished. For globoid cell leukodystrophy, infantile (from 3-6 months), late infantile (from 6-18 months), juvenile and adult forms are known. Leukodystrophies are rare diseases. Thus, adrenoleukodystrophy occurs with a frequency of approximately 1 in 40 thousand newborn boys. Metachromatic leukodystrophy has a frequency of about 1 in 50-70 thousand newborns, globoid cell leukodystrophy - about 1 in 100 thousand. Some types of leukodystrophies are so rare that only a few hundred cases have been described worldwide[5,9].

Leukodystrophies are genetically determined diseases, and the type of inheritance depends on the specific type of leukodystrophy. Most leukodystrophies (including metachromatic and globoid cell) are inherited byautosomal recessive type, that is, the probability of a child becoming ill is 25% if both parents are carriers of the disease. Such diseases affect boys and girls with equal frequency. They occur more often in communities where consanguineous marriages are common, and may occur with varying frequencies among different nations[6,10].

Adrenoleukodystrophy is usually characterized byX-linked inheritanceand 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%.

For families who have already had children with any type of leukodystrophy, consultation with a geneticist is recommended before the birth of all subsequent children.

At birth, children with leukodystrophy usually appear healthy and take some time to develop according to their age. However, then symptoms of damage to the central nervous system gradually appear. These symptoms vary somewhat depending on the specific disease and its form, but still have common features[8,11].

Movement disorders are common. In children, coordination of movements worsens, problems with balance are noted, and it becomes difficult to walk and run. Possible muscle weakness, abnormally increased or decreased muscle tone, muscle twitching. Convulsive attacks appear. Changes in behavior occur. Memory and intelligence gradually decline. 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, and the inability to swallow food normally occur. As a rule, the earlier in age signs of the disease appear, the faster it progresses[12].

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

Damage to the white matter of the brain, characteristic of leukodystrophies, is detected throughmagnetic resonance imaging(MRI). Typically, MRI abnormalities associated with myelin destruction are visible long before the onset of clinical symptoms, and subsequently the degree of these abnormalities corresponds to the severity of the patient's condition. With many leukodystrophies inliquorhigh levels of protein are detected.

To clarify the type of leukodystrophy, biochemical tests can be used - measuring the levels of enzymes whose synthesis or transport is impaired in a particular disease, or detecting those substances that accumulate in this disease. Other studies are possible, includingmolecular genetic[5,6].

Prenatal diagnostic methods have been developed for some types of leukodystrophy (including metachromatic, globoid cell and adrenoleukodystrophy).

In fact, the only effective treatment for leukodystrophies at present isallogeneic bone marrow transplantation(orcord blood) from a healthy donor. If successful, it can lead to normalization of the level of missing protein, and therefore to an increase in the duration and quality of life. Thus, there are known cases of using transplantations for the treatment of adrenoleukodystrophy, metachromatic leukodystrophy and globoid cell leukodystrophy[4,11].

At the same time, the use of transplantations for leukodystrophies is associated with certain limitations. It is very important to perform transplantation as early as possible, before significant neurological impairment develops. Indeed, transplantation does not allow to “correct” existing lesions of the central nervous system, but only stops or slows down their further progression. But it is also necessary to take into account the rate of development of neurological lesions[10].

Thus, with the most rapidly developing forms of leukodystrophies, it is often impossible to avoid death or severe disability of the patient even after transplantation. This is due to the fact that after transplantation some time still passes (for example, in some leukodystrophies we can talk about 12 or even 24 months) until the work of the donor cells leads to normal functioning of myelin. And all this time the development of the disease will continue. Therefore, in forms with a very early onset of the disease, hopes are associated mainly with those transplantations that were performed before the appearance of clinical symptoms (for example, if the eldest child in the family had already been diagnosed with leukodystrophy and therefore the younger child was diagnosed early). With a slower progression of the disease, the chances of success increase[12].

As with any allogeneic bone marrow transplantation, serious risk factors for the patient's life are: graft versus host disease, the possibility of infectious and other complications, as well asgraft rejection.

If bone marrow transplantation is not possible or recommended, thenpalliative careaimed at alleviating the symptoms of the disease. New treatment approaches are constantly being developed, but for now they remain experimental[11].

There is an opinion that it is possible to slightly slow down the development of adrenoleukodystrophy (including while awaiting transplantation) with the help of a special diet. Sometimes Lorenzo's oil is also used, a remedy developed by the parents of a boy with adrenoleukodystrophy. However, it is still unclear how effective this remedy is.

The prognosis for leukodystrophies is very serious, especially in forms of the disease with early onset and rapid increase in symptoms. However, a number of patients can benefitallogeneic bone marrow transplantationorcord blood. If successful, it stops or slows down the progression of the

disease and allows one to largely preserve motor and intellectual functions. In this case, the most important condition is timely transplantation

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