Impact Factor: 9.9 ISSN-L: 2544-980X

Clinical and Morphological Characteristics and Treatment of Gaucher Disease

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Abstract: Gaucher disease is a rare genetic pathology with a frequency of 1/50 000 cases. Types II and III of the disease, manifested in children and adolescents, with severe course, disability and high mortality, require special attention. The aim of the study was to evaluate the clinical and morphological data of a patient with Gaucher disease type 1, a rare disease, in one center.

Methods. The data of a patient with Gaucher disease type 1 who was treated in the surgical department of the Republican Specialized Scientific and Practical Medical Center of Oncology and Radiology of the Ferghana branch of the Republic of Uzbekistan in 2020 were analyzed.

Conclusion. Gaucher disease is a rare lysosomal disease affecting many body systems. It leads to irreversible consequences in patients whose diagnosis is delayed. The main treatment method was enzyme replacement therapy. Since this is a rare and multisystem disease with many complications, it is especially important for the treatment of types 2 and 3 of the disease in children and adolescents, who are acute and have high mortality. Therefore, molecular genetic research methods should be introduced for early detection and diagnosis in patients with Gaucher disease.

Keywords: Gaucher disease, β-glucocerebrosidase, pathomorphology, cytology, splenectomy.

Introduction

Gaucher disease (HD) - (ICD-10 - E75.2 code - violation of β-glucocerebrosidase metabolism) is a rare orphan genetic lysosomal disease with an autosomal recessive type of inheritance, leading to the accumulation of lipids and impaired function of various organs. The pathogenesis of the disease is based on a hereditary deficiency in the activity of β-glucocerebrosidase, a lysosomal enzyme involved in the breakdown of products of cellular metabolism. The genetic basis consists of mutations of the glucocerebrosidase gene located in the q21 region on chromosome 1. About 200 different mutations have been studied that lead to a defect in the enzyme (a decrease in its stability or activity) and which are associated with a wide polymorphism of clinical symptoms of HD. The most common mutations are N370S, L444P, IVS2+1 and 84GG [6,9,15].

The lysosomal enzyme β-D-glucosidase is responsible for the cleavage of the complex lipid glucocerebroside into glucose and ceramide. Due to the low activity of this enzyme, complete cleavage of glucocerebroids does not occur, which leads to their accumulation in macrophages and monocytes. As a result, we observe cells “filled” with lipids - Gaucher cells [1,8,12].

Gaucher's disease is a systemic disease with similar clinical manifestations (hepatomegaly and splenomegaly, cytopenia, bone lesions), but an extremely heterogeneous clinical course. Gaucher disease was first described in 1882 by the French physician P.S. Gaucher, who identified macrophage cells accumulating lipids pathognomonic for this disease, later called Gaucher cells [4,5].

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Epidemiology

Gaucher disease affects people of any ethnic group or race. This disease is equally common among both women and men. This figure ranges from 1/40,000 to 1/60,000 births, which is less than 10,000 patients worldwide. And among Ashkenazi Jews, this figure increases to 1 case per 450-500 people. Variants of GD with primary CNS damage are found in 5-10% of patients in most countries. To date, more than 200 mutations have been identified, of which 4 are the most common and account for about 90% of all mutations in the population of patients with Gaucher disease.

The presence of two mutant alleles of the gene (homozygous inheritance) is associated with a decrease (or absence) of the catalytic activity of glucocerebrosidase, which leads to the accumulation of unused lipids in the cytoplasm of cells [4,16].

Glucocerebrosidase is found in all cells of the body, but the deficiency of this enzyme is of the greatest importance for macrophages processing antigens, since an important function of these "scavenger" cells is the degradation of blood cells that have completed their life cycle [2.11].

The absence or low activity of acidic β-glucocerebrosidase leads to the accumulation of unused lipids in the lysosomes of macrophages and the formation of characteristic accumulation cells, or Gaucher cells, of large elements ranging in size from 20 to 100 microns with a small, eccentrically located nucleus and abundant cytoplasm, which has a typical "wrinkled" or striped appearance.

The consequences of functional overload of macrophages are:

1. autocrine stimulation of monocytopoiesis and an increase in the absolute number of macrophages, which is manifested by hepatomegaly and splenomegaly, infiltration of bone marrow, lungs and other organs by macrophages;
2. violation of many physiological functions of macrophages, including regulation of hematopoiesis and bone metabolism, which presumably underlies the cytopenic syndrome and lesions of the osteoarticular system. Pathological effects of proinflammatory cytokines (IL-1, TNF-α, IL-6) and cytotoxic mediators (reactive oxygen species, nitroxide, proteolytic enzymes, additive components), which are secreted by activated macrophages overloaded with lipids [10,16].

The clinical picture

Three types of Gaucher's disease are presented here:

Type I (adult or chronic) is not a neuropathic form. The clinical manifestations of type 1 HD are diverse. The age of manifestation of the disease varies from 0 to 60 years. Type 1 GB is chronic. The most common signs and symptoms are splenomegaly (95%), hepatomegaly (87%), X-ray bone changes (81%), thrombocytopenia (50%), anemia (40%), growth retardation (34%), bone pain (27%), and bone crises (9%) [2,10,13]. Severe bone loss occurs in childhood and adolescence. The causes of bone disorders are associated with the extensive proliferation of pathological cells in the bones.

The involvement of bones in the process can be local or diffuse. At the same time, severe skeletal deformities are determined due to the development of osteoporosis, osteosclerosis, osteonecrosis, thinning of the cortical layer of tubular bones and pathological fractures.

Osteonecrosis is the most significant manifestation of the disease and is accompanied by severe bone pain, which causes the greatest concern in patients. Radiographs show the expansion of the ends of long tubular bones and the thinning of their cortical layer. Splenomegaly is a permanent and earliest sign of HD; on palpation, the spleen has a dense consistency. In exceptional cases, the weight of the spleen may be 20% of the child's body weight. It occupies the entire abdominal cavity and puts pressure on the stomach, reducing appetite. Infiltration by Gaucher cells and the development of infarcts in the spleen leads to fibrosis of the organ, scarring and abdominal pain.

Hepatomegaly in HD is less pronounced than splenomegaly and usually develops later. The volume of the organ increases 1.5–2 times. Many patients develop liver fibrosis with symptoms of portal hypertension. Significant abnormalities in the hematopoiesis system are also found. Normocytic,

normochromic anemia and severe thrombocytopenia are detected, and therefore bleeding is noted. Hematological manifestations of the disease are mainly associated with infiltration of the bone marrow by Gaucher cells, displacement of normal hematopoietic elements and hypersplenism [6, 8,17].

Type II (infantile) is an acute neuropathic form. The main symptoms of the disease with this type of GB appear in the first 6 months of life.

The clinical symptom complex includes signs of damage to the nervous system and internal organs. In the early stages of the disease, muscle hypotension, delay and regression of psychomotor development are observed. As the disease progresses, spasticity appears with type 2 neck retraction, limb flexion and oculomotor disorders with the development of convergent strabismus, laryngospasm and dysphagia.

Bulbar disorders with frequent inhalations are characteristic, leading to the death of the patient from apnea, aspiration pneumonia or dysfunction of the respiratory center of the brain [7,19]. Tonic-clonic seizures usually occur in the late stages of the disease and are resistant to prescribed anticonvulsant therapy. The course of the disease progresses rapidly with fatal outcome at the age of 1-2 years [2, 5, 16].

Type III (juvenile) is a chronic neuropathic form. The main feature of the clinical manifestations of GB of this type is that along with the lesion of parenchymal organs (splenomegaly, hepatomegaly), neurological manifestations are also observed. Neurological symptoms usually appear between the ages of 6 and 15 years and later [2.13].

A characteristic symptom is paresis of the muscles innervated by the oculomotor nerve, which may be the only neurological manifestation for a long time. Myoclonus, generalized tonic-clonic seizures are possible. Gradually progressive extrapyramidal rigidity, decreased intelligence, trism, facial expressions, dysphagia and laryngospasm. Intellectual disabilities range from minor changes to severe dementia. It is possible to develop cerebellar disorders, as well as speech and writing disorders, behavioral changes and episodes of psychosis. In most cases, the disease proceeds slowly. Death occurs with severe lung and liver damage. The life expectancy of patients with type 3 GB is 12-17 years, but cases of survival up to 30-40 years have been described [2,3].

Diagnostics.

The diagnosis of Gaucher disease should be considered in a patient with unexplained splenomegaly, hepatomegaly, cytopenia and bone symptoms. The standard of modern diagnostics is the biochemical analysis of the activity of acid beta-glucocerebrosidase in blood leukocytes.The diagnosis is confirmed by a decrease in enzyme activity to 30% or less of the normal value. An additional characteristic biochemical marker is a significant increase in the activity of chitotriosidase in blood serum (an enzyme presumably secreted by activated macrophages overloaded with unused lipids is a surrogate marker of Gaucher disease activity).

The diagnosis can be confirmed by molecular analysis of the glucocerebrosidase gene: the presence of two mutant alleles confirms the diagnosis of Gaucher disease [11,16].

Morphological examination of the bone marrow makes it possible to identify characteristic diagnostic elements - Gaucher cells and at the same time excludes the diagnosis of hemoblastosis or lymphoma as the cause of cytopenia and hepatosplenomegaly. The presence of a large number of Gaucher cells in the punctate and trepanation bone marrow biopsy or liver biopsy is an obvious sign of Gaucher disease. However, single cells with similar morphology (similar to Gaucher) can also occur in other diseases accompanied by increased cell destruction, such as chronic myeloid leukemia and lymphoproliferative diseases [2,16].

Gaucher cells are easily recognized in an optical microscope due to their appearance and size. These are three-dimensional cells with a diameter of 30-100 microns of indeterminate shape, round, slightly polygonal, oval or elongated. The nucleus is small, eccentric, round or stellate, with spongy or compacted chromatin. Binuclear or multinucleated cells often appear. The cytoplasm is abundant, pale

and full of crystalline matter arranged in plates, perinuclear, in the form of "bulbous leaves" or whorls. In rare cases, the cells contain small vacuoles and have a foamy appearance. Red blood cells, erythroblasts, or pigment granules are often found in the cytoplasm. Morphological changes in the spleen are manifested by the replacement of lymphoid tissue by Gaucher cells, they are of macrophage origin, and the contents of the cells have a characteristic autofluorescence and a characteristic appearance under microscopy in polarized light.

An X-ray of skeletal bones is used to identify and assess the severity of damage to the musculoskeletal system. Densitometry and MRI are more sensitive methods and make it possible to detect bone lesions (osteopenia, bone marrow infiltration) in the early stages, which are not available for imaging using radiography.

Differential diagnosis.

Gaucher's disease should be differentiated from all diseases that are accompanied by hepatosplenomegaly, cytopenia and bone damage [2,16]:

- hemoblastoses and lymphomas;
- chronic cholestatic liver diseases;
- cirrhosis of the liver as a result of chronic viral and non-viral hepatitis;
- other hereditary fermentopathies (Niemann-Pick disease);
- thalassemia and other forms of hereditary erythron pathology;
- rheumatic diseases (Felty syndrome).

Diagnosis of GD currently consists of several successive stages:

1) identification of characteristic clinical signs of the disease;
2) measurement of β-D-glucosidase activity in leukocytes; identification of characteristic Gaucher cells;
3) pathomorphological examination of biopsy samples;
4) molecular genetic analysis [1,3,5]

Treatment.

Treatment of Gaucher's disease consists in lifelong enzyme replacement therapy (HRT) with recombinant glucocerebrosidase (imiglucerase, cerezim, velaglucerase or tal-iglucerase). Glucosylacetamine biosynthesis inhibitors (miglustat or eliglustat) can also be used orally. In severe Gaucher disease (type I) in adults, the initial dose of Cerezim is 30 units / kg / infusion. The drug is administered intravenously drip with an interval of 2 weeks. (2 times a month). In some cases, for example, with severe damage to the bones of the skeleton with multiple pathological fractures, the dose of cerezim can be increased to 60 units/kg per dose (120 units/ kg per month) [2,11,16,18].

Treatment goals include: 1) prevention of irreversible damage to the musculoskeletal system and other vital organs (liver, lungs, kidneys); 2) regression or weakening of cytopenic syndrome;

3) reducing the size of the spleen and liver. Monitoring the effectiveness of enzyme replacement therapy includes monitoring of hemogram parameters, blood biochemistry, including determination of a surrogate marker of macrophage activity - serum chitotriosidase; determination of the size of the spleen and liver; assessment of the state of the bone and joint system (densitometry, MRI, bone radiography once every 1-2 years). When these goals are achieved, maintenance treatment with cerezim is prescribed at a dose of 10-15 U / kg in the form of an infusion 2 times a month (for life).

Discussion

Gaucher disease is one of the most common accumulation diseases inherited in an autosomal recessive way. The disease is definitively

diagnosed by detecting mutations and enzyme deficiency in patients who show symptoms and signs [4,6].

In the oncology clinic, enzyme levels are first determined in patients with suspected HD, and genetic analysis is performed in patients with low enzyme levels. The Gaucher Registry study, published in 2000, collected data from 522 clinicians and 1,698 HD patients from 38 different countries. Genetic analysis was performed on 766 of these patients, and the N409S (N370S) mutation was detected in 53% of the 1,532 patients. The L483P (L444P) mutation was the second most common (16%). In the Gaucher Registry study, osteopenia was observed in 42% of patients, and bone damage was higher in the group without a spleen than in the group with a spleen. In our study, with the exception of two patients, the z-score in the lumbar region was < -1 in five patients and ≤ -2.5 in six patients. [19].

For a complete diagnosis of this type of pathology, it is necessary to conduct a molecular genetic study, which, unfortunately, is not available in our clinic. With more thorough collection of anamnesis, bone densitometry, trepanobiopsy of the liver and/or bone marrow, as well as pathomorphological and molecular genetic studies, it may be possible to avoid surgical intervention with the removal of the spleen and refer it to a specialist for conservative enzymatic therapy [9,13,15].

Conclusions

Thus, Gaucher disease is a rare disease that belongs to the group of lysosomal accumulation diseases and is characterized by polymorphic clinical symptoms with damage to many organs and systems and a progressive course without adequate rehabilitation therapy. Timely diagnosis of the disease in children is associated with certain difficulties associated with the lack or insufficiency of information from pediatricians and general practitioners.

The polymorphism of clinical manifestations and the absence of pathognomonic symptoms make it difficult to diagnose in the early stages, and the polysystemic nature of the lesion masks Gaucher's disease under various diseases.

Hereditary diseases that lead to disability and a decrease in the quality of life of the population have social significance and financial consequences for both the patient and the state. In this regard, it is advisable to carry out early diagnosis using molecular genetic research methods and conduct timely pathogenetic therapy to prevent disability.

HD is a rare lysosomal accumulation disease affecting many body systems. It can cause irreversible complications in patients who are diagnosed late. The main treatment method is enzyme replacement therapy. Since this is a rare and multisystem disease, patients should be monitored in centers with experience in the treatment of Gaucher disease.

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