

Gaucher's disease

Gaucher disease is an inherited lysosomal storage disease that is caused by a genetic defect (deficiency or absence) of the lysosomal enzyme glucocerebrosidase. This enzyme is responsible for the hydrolytic cleavage of glucosylceramide to glucose and ceramide.

Gaucher disease is an autosomal recessive disease. It occurs in all nations, most often in Eastern European Jews with an incidence of up to 1: 2500. Insufficient enzymatic activity causes the accumulation of fat molecules called cerebrosides - glucosylceramide (glucocerebroside) in the cells of the reticuloendothelial system (RES) and leads to enlargement of the liver and spleen with symptoms of hypersplenism (anemia and thrombocytopenia). Skeletal system disorders occur - due to the infiltration of these RES cells into the bone marrow. Rarely does the disease manifest in the lungs and CNS. Based on enzyme therapy there can be a significant improvement with perverted organ enlargement and normalization of the blood count. With the timely use of enzyme therapy, there may also be a positive effect on neurological symptoms.

Pathophysiology and genetics

Pathogenesis

Bone marrow in a patient with Gaucher disease The accumulating substance, glucocerebroside, consists of ceramide (sphingosine + MK) and glucose. It is an intermediate in the biosynthesis or degradation of complex membrane components - eg globoside in erythrocytes. Glucocerebrosidase, a predominantly lysosomal lipid hydrolase, cleaves glucose from ceramide. Decreased enzymatic activity leads to accumulation of glucocerebroside in RES cells and consequent damage to various organs. Retention of glucocerebroside in cells can be demonstrated histologically in the liver, spleen and other organs.

B - glucocerebrosidase gene edit source]

- It is located on the long arm of chromosome 1 (1q21);
- contains 11 exons approximately 7.3 kb in length;
- a pseudogen that has high homology to a functional gene occurs nearby;
- most gene mutations were detected in exon 2;
- the most common three mutations include:
 - base exchange nucleotide 5841 (1226A → G),
 - is 70% responsible for the increased incidence of the disease in the Jewish population,
 - it is generally accompanied by a mild course of the disease,
 - mutation 1448T → C,
 - often proven in the neuropathic form of Gaucher disease,
 - single base insertion in nullotide 84 (84G → GG),
 - leads to a shift in the reading frame and thus to the premature termination of enzyme synthesis with full loss of activity (zero allele),
 - its carriers are severely affected,
 - a homozygote for this null allele has not yet been observed,
- in many cases of Gaucher disease it is a complex change of genes with numerous mutations, which partially affect pseudogene and other neighboring genes,

B-glucocerebrosidase requires an activator for its hydrolytic function, the defect of which also leads to Gaucher's disease.

Clinic

It affects various organs, especially the spleen, liver and bone marrow, where lipid-filled macrophages (so-called Gaucher cells) accumulate. The lymphatic system, lungs, skin, eyes, kidneys, heart, and rarely the brain and nervous system can also be affected.

The type and severity of symptoms can vary significantly from patient to patient - we know almost asymptomatic to life-threatening disease.

The first type of Gaucher disease begins to manifest at different ages, severities, and symptom progressions.

Depending on the organs affected, we distinguish between two forms of Gaucher's disease, visceral and neuropathic.

Visceral form

The patient has symptoms caused by infiltration of various organs by storage cells. Outbreaks, as well as clinical manifestations, vary from case to case.

Skeleton

On radiological examination, it is possible to observe loosening in the phalanges, jaws and vertebral bodies .

- *Inflation at the distal ends of the femur in the shape of an Erlenmeyer flask* is characteristic .
- Due to circulatory disorders, acute or chronic ischemia may occur at a young age with the subsequent development of femoral head necrosis - *aseptic necrosis of the large joint heads, avascular necrosis* .
- Destruction and compression of vertebral bodies (*pathological fractures and compression fractures of vertebrae*).
- *Chronic bone or joint pain* .
- *Bone crises* - may be accompanied by fever.
- At the early onset of the disease, *children are short and dystrophic* .
- *Osteonecrosis , osteopenia , osteoporosis and cortical bone thinning* may occur .

Leather

Yellow skin discoloration and brown conjunctival pigmentation, so-called Pingueculae , are common symptoms of Gaucher disease in adults.

Internal organs

Spleen

- Splenomegaly can occur in early childhood , leading to hypersplenism with anemia , leukocytopenia and thrombocytopenia . The size of the spleen can interfere with food intake and is more often a heart attack of the spleen.

Liver

- Despite hepatomegaly, dysfunction and portal hypertension are rare. Hepatic impairment may be manifested by abnormalities in proteosynthesis. Fibrosis to cirrhosis of the liver, esophageal varices in portal hypertension may be present.

Lungs

- Cough and recurrent pneumonia are symptoms of lung involvement that confirm diffuse, stained infiltrates on radiology.

Kidneys

- Lipid accumulation in the kidneys does not lead to any clinical manifestations.

Changes in elderly patients

There is frequent development of malignant tumors, such as Hodgkin's lymphoma or myeloma . Another complication observed is pulmonary hypertension without a previously clarified origin.

Hematology

Typically, patients experience:

- anemia (Hb <135 g / l in men, Hb <116 g / l in women) - accompanied by increased fatigue,
- thrombocytopenia (PLT <100 x 10⁹ / l) - tendency to bleed and hematoma formation,
- leukopenia (<4 x 10⁹ / l) - accompanied by frequent infections.

As a rule, we find an increased number of reticulocytes and changes in clotting are observed.

Biochemical changes

Secondary biochemical changes are a manifestation of the increasing activity of macrophages : an increase in the concentration of acid phosphatase and angiotensin converting enzyme has long been known. An even more sensitive parameter is the measurement of chitotriosidase activity: this enzyme, the physiological significance of which is not yet known, shows up to a thousand times the normal activity in patients with Gaucher disease.

Neuropathic form

Early form

In the early form of the disease (according to the old nomenclature referred to as type II), it develops between the 2nd and 3rd month of life. Problems with food intake and frequent respiratory infections are characteristic. Due to pronounced hepatosplenomegaly, the abdomen is significantly arched. In the second year of life, the symptoms affecting the CNS come to the fore. Infants are becoming increasingly tragic and opisthotic. Dysphagia , stridor and

paralysis of the eye muscles occur . Seizures are mostly rare. The process of degradation progresses rapidly, the final stage is characterized by severe cachexia, joint contracture and treatment-resistant infections. Death occurs most often between 2-3. year of life. Neonatal manifestations of the disease were also observed in individual cases, but they were not compatible with life. Like other lysosomal storage diseases, Gaucher's disease has a congenital form, which is manifested by severe hydrops .

Subacute form _ _ edit source]

The subacute neuropathic form (according to the old nomenclature type III) differs from type II by a later onset and a slower course. The high variability of the clinical picture indicates considerable heterogeneity within the group. Between the 2nd and 3rd year of life, children have a fever of unclear origin and increased bleeding, enlargement of the liver and spleen causes severe abdominal pain . Bone marrow infiltration causes pancytopenia, which is also supported by hypersplenism. Other symptoms include mental retardation along with prominent behavior, choreoathetosis, and seizures. As the disease progresses, patients become more spastic, rarely reaching the second year of life. The subacute form of Gaucher disease is most commonly seen in families in northern Sweden. Myoclonus are symptoms with a poor prognosis and can result in dementia. In recent years, Parkinson's disease , which is characterized by rapid onset and high resistance, has been reported in adult patients with Gaucher disease . Gaucher's disease is not thought to be directly involved in the pathogenesis of Parkinson's disease, but only to increase the body's sensitivity to it.

Diagnostics _ _ _ edit source]

Diagnosis is easily made by measuring β -glucocerebrosidase activity in leukocytes . No bone marrow biopsy is required for this. Gene analysis has only limited use. The determination of the enzyme chitotriosidase is suitable for monitoring the course of the disease and determining appropriate doses in enzyme therapy.

The clinician will determine suspected Gaucher disease based on hepatomegalosplenism, anemia, thrombocytopenia, and bone pain. The final diagnosis must be made enzymatically.

Findings on imaging methods (ultrasound, X-ray, MRI):

- *liver* - hepatomegaly, rounding of the lower angle of the liver, higher echogenicity of the parenchyma, later inhomogeneous parenchyma with nodules, fibrosis;
- *spleen* - splenomegaly (spleen may extend to the small pelvis and in front of the midline), hyperechogenic parenchyma diffusely, later inhomogeneous parenchyma with nodules (distorts accumulated Gaucher cells), spleen infarctions, branching and wavy linear veins in incipient portal hypertension
- *bones* - fractures (long bones, ribs, compression fractures of vertebral bodies), osteolysis, osteonecrosis, remodeling of long bones (femur - Erlenmeyer flasks), bone crisis (based on ischemia, bone infarction with subsequent necrosis of the relevant bone area), clinical pro bone crisis - severe bone pain immobilizes the patient for several days, temperatures up to septic, leukocytosis, while negative blood culture)

Therapy

Symptomatic treatment

Severe bone pain is treated with corticosteroids . Prior to the introduction of enzyme therapy, splenectomy was the only way to improve symptoms (anemia, thrombocytopenia), and its effect was not permanent. Liver cells subsequently took over the storage function. At present, splenectomy is no longer indicated due to the concomitant increased risk of pulmonary hypertension.

Enzymatic therapy

The first experiments to exogenously supply the missing enzyme were performed more than 20 years ago, but failed to incorporate the enzyme into liver cells instead of storage cells (macrophages) and therefore there was no improvement in symptoms .

The breakthrough came after the discovery of membrane receptors for mannose on the surface of macrophages, which are suitable for targeted β -glucocerebrosidase endocytosis. Native β -glucocerebrosidase, a glycoprotein, has been modified to be mannose as the terminal sugar. This allowed multiple incorporation of the enzyme into macrophages. After only a few months of treatment, patients feel better physically, the pressure in the abdomen subsides along with the shrinking liver and spleen, and the problems with increased bleeding cease. Thanks to long-term enzyme replacement therapy, bone pain also disappears and children grow to normal heights. The side effects are not known, in individual cases there has been an immune response against the supplied enzyme.

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- [Medicine for the 21st century - Gaucher's disease](#)

References

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- www.focusongaucher.cz (info cards for general practitioners)