

Gaucher disease

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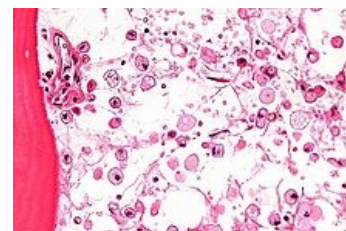
Gaucher disease is an inherited lysosomal storage disease caused by a genetic defect (deficiency or absence) of the lysosomal enzyme **glucocerebrosidase**. This enzyme is responsible for the hydrolytic cleavage of glucosylceramide to glucose and ceramide.

Gaucher disease is an **autosomal recessive** disease. It occurs in all nations, most often in Ashkenazi Jews with an incidence of up to 1: 2500. Insufficient enzymatic activity causes the accumulation of fat molecules called cerebroside - 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). Disorders of the skeletal system 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 decreasing organ size and normalization of blood counts. With early use of enzyme therapy, there may also be a positive effect on neurological symptoms.

Patophysiology and genetics

Patogenesis

The accumulating substance, **glucocerebroside**, consists of ceramide (sphingosine + fatty acid) 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 the accumulation of glucocerebroside in RES cells and the consequent damage to various organs. Retention of glucocerebroside in cells can be demonstrated histologically in the liver, spleen and other organs.



Bone marrow of a patient with Gaucher's disease- wrinkled paper macrophages can be seen.

β -glucocerebrosidase gene

- the gene is located in the long arm of chromosome 1 (1q21);
- contains 11 exons approximately 7,3 kb long;
- in it's proximity there is a pseudogene with significant homology to the functional gene;
- the highest number of gene mutations were proved in exon 2;
- three most common mutations are:
 - exchange of bases in nucleotide 5841 (1226A → G),
 - in 70 % is responsible for increased incidence in the Ashkenazi population,
 - the symptoms are usually mild,
 - 1448T → C mutation,
 - often seen in the neuropathic type Gaucher's disease,
 - insertion of 1 base in nucleotide 84 (84G → GG),
 - frame shift mutation - leads to premature termination of the enzyme synthesis with complete loss of it's activity,
 - carriers have severe symptoms, the prognosis is poor,
- in many cases, Gaucher's disease is a complex change of genes with numerous mutations, which partially affect the pseudogen and other 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 macrophages filled with lipids (Gaucher cells) accumulate. The lymphatic system, lungs, skin, eyes, kidneys, heart, and the brain and nervous system can also be affected.

The type and severity of symptoms can vary significantly from patient to patient - there are almost asymptomatic to life-threatening cases.

Depending on which organs are affected, we distinguish between two forms of Gaucher disease, visceral and neuropathic .

Visceral type

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

Skeletal system

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

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

Skin

Yellow skin pigmentation 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 are confirmed by diffuse, stained infiltrates on radiological examination.

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 / dl in men, Hb <116 g / dl in women) - accompanied by increased fatigue,
- thrombocytopenia (PLT <100 x 10⁹ / l) - tendency to bleed and hematoma,
- leukopenia (<4 x 10⁹ / l) - accompanied by frequent infections,
- increased number of reticulocytes and changes in clotting are observed.

Biochemistry

Secondary biochemical changes are a manifestation of the increasing activity of macrophages : an increase in the concentration of acid phosphatase and angiotensin converting enzyme is 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 type

Early onset

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. Significant are problems with food intake and frequent respiratory infections. Due to marked hepatosplenomegaly, the abdomen is significantly enlarged. In the second year of life, the CNS is affected. Infants tend to be spasmodic and opisthotic. Leads to dysphagia , stridor , and paralysis of the eye muscles. Seizures are mostly isolated. 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, manifested by severe hydrops .

Subacute type

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 develop 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 observed in families in northern Sweden. Myoclonus are symptoms with a poor prognosis and can result in dementia. In recent years, the incidence of Parkinson's disease , characterized by rapid onset and high resistance, has been reported in adult patients with Gaucher disease . It is believed that Gaucher's disease is not directly involved in the pathogenesis of Parkinson's disease, but only leads to increased sensitivity of the organism to it.

Diagnosis

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

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

Imaging methods findings (UZ, X-rays, 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 (districts of accumulated Gaucher bb.), 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 flask shape deformities), bone crisis (based on ischemia, bone infarction with subsequent necrosis of the relevant bone area), clinical prodrome bone crisis - severe bone pain immobilizes the patient for several days, temperatures up to septic, leukocytosis, while negative blood culture)

Treatment

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.

Enzyme replacement treatment

The first experiments to exogenously deliver 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 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 endocytosis of β -glucocerebrosidase. 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 physically better, 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. Side effects are not known, in individual cases there has been an immune response against the supplied enzyme.

References

Related articles

- Fabry disease
- Macrophages

External links

- **Medicína pro 21. století – Gaucherova choroba** (<http://www.ceskatelevize.cz/porady/10175805663-medicina-pro-21-stoleti/208572231040005-gaucherova-choroba>)

Použitá literatura

- **HOFFMANN, Georg F.** *Stoffwechselerkrankungen in der Neurologie*. 1. edition. Georg Thieme Verlag, 2004. pp. 212. ISBN 3-13-136321-5.
- www.focusongaucher.cz (<http://www.focusongaucher.cz>) (infokarty pro praktické lékaře)

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