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Gaucher's Disease – What Should You Know

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Abstract

Gaucher's Disease (GD) has a special place among ultra-rare diseases, which is a disease that occurs in less than onein 50 000 persons. The disease is caused by a hereditary autosomal

deficiency of the lysosomal enzyme glucocerebrosidase. The pathognomonic feature of GD is the presence of storage cells or gaucher cells in spleen, liver and other organs and tissues. There are several clinical types of gaucher disease, differing in manifestation, prognosis and treatment. It is very important to diagnose the disease early so that the correct treatment can be implemented. Nowadays, it is not uncommon for general practitioners and specialists to make the wrong diagnosis due to the low probability and lack of knowledge of the disease, leading to a worsening patient's condition. A proper examination consists of a medical history, physical examination and targeted radiological examinations, which are of particular importance in the diagnosis due to changes in the body that are not otherwise detectable, but which already offer a chance to make a diagnosis. The latest treatment is based on enzyme replacement therapy, but unfortunately the prognosis in some cases is still unfavourable. This is why early diagnosis and research to find an effective treatment are so important.

KEY WORDS: glucocerebrosidase deficiency, liver disease, splenomegaly

Introduction

Gaucher’s disease (GD) is an autosomal recessively inherited lysosomal storage disease [3,11,15,16]. It is classified as an ultra-rare disease the kind of disease that occurs in less than 1 in 50,000 patients [1]. It is a metabolic disorder caused by an autosomal hereditary deficiency of the lysosomal enzyme glucocerebrosidase [3,10]. Gaucher's disease was first described by Phillipe Gaucher in his doctorate thesis [5]. Gaucher disease is the most commonly occurring disorder of glycolipid metabolism [4].

Reduced β-glucosidase activity is responsible for the pathological accumulation of glucosylceramide inside the lysosomes of Gaucher cell-producing macrophages, mainly in the reticuloendothelial system. Glucosylceramide-loaded macrophages activate their own cells by releasing cytokines, chemokines and fibroblastic factors, resulting in inflammation, fibrotic changes with irreversible tissue damage [11].

The pathognomonic abnormality of the disease is the occurrence of storage cells, which are activated macrophages (Gaucher cells) [18]. Their presence is apparent in the spleen, liver, bone marrow, lymph nodes, and occasionally in the lungs. The process is most expressed in the monocyte-macrophage system because of their increased phagocytic activity designed to eliminate aging red and white blood cells, which release large amounts of glycosphingolipids [1]. In the most severe forms of the disease, the central nervous system is involved as well [2].

Types of Gaucher's disease

We distinguish between 3 clinical types of Gaucheries disease [2].

Most patients suffer from the chronic, non-neuropathic form, known as type 1 [4,11]. Which is the least severe but most common type of the disease and is characterized by a slower progression. Gaucher's disease type 1 primarily affects organs such as the liver and spleen. In this type, the most common symptoms are thrombocytopenia, anemia, splenic enlargement, skeletal involvement or liver enlargement, rarely complicated by cirrhosis and portal hypertension [15]. In this type, the most common symptoms are thrombocytopenia, anemia, splenic enlargement, skeletal involvement and liver enlargement but rarely complicated by cirrhosis or portal hypertension [2,11]. This type neither decrease lifespan of patients nor affect the central nervous system [4,12].

Type 2 and type 3 Gaucher's disease involve various central nervous system symptoms [2,4]. Acute neuropathic Gaucher disease (GD type 2) is the most severe and rapidly progressing type of GD. It also may manifests in infancy. Neurological aggravation progresses rapidly. It affects the brain and peripheral nervous system [15]. Symptoms include progressive cognitive decline, muscle stiffness, impairment of motor skills and coordination, respiratory difficulties,

swallowing disorders accompanied by general systemic manifestations. Patients typically die before the age of 2 (lifespan is 3 to 55 months) [5,15].

The chronic neuropathic form of the disease called type 3 has a slower neurological progression and usually occurs during adolescence [5]. It most commonly starts in childhood, in the first decade of life. It affects both internal organs and the central nervous system. This type includes patients with neurological symptoms that do not fit the criteria for type 2 [15].

Symptoms

Gaucher's disease is a multisystem disorder. Depending on the subtype of the disease, symptoms can appear at any age [5]. Typical symptoms seen in GD include thrombocytopenia, anemia and splenomegaly. In addition, it is assumed that the accumulation of glucocerebroside in Gaucher cells causes the osteoskeletal lesions by compression on blood vessels, and this in turn causes necrotic changes [1].

Liver enlargement sometimes can be found only using imaging scans, when the liver is not palpable [7].

In most patients, it is observed that the liver is affected by the disease giving specific symptoms:
-liver enlargement with or without liver enzyme changes,
-fibrosis or cirrhosis,
-hepatic portal hypertension,
-focal liver lesions,
-cholelithiasis
[13]

In addition, the disease is associated with several biochemical changes of potential concern to the hepatologist and gastroenterologist. These include hypergammaglobulinemia, hyperferritinemia and metabolic abnormalities that can lead to misdiagnosis of chronic liver diseases with a common etiology, such as primary hemochromatosis, autoimmune liver disease, nonalcoholic steatohepatitis or fatty liver disease [13].

The studies conducted showed a correlation of magnetic resonance elastography of the liver and spleen volume with the severity of the disease. Which gives the assumption that they may be biomarkers of disease severity [14].
Bone involvement is also a frequent symptom in patients. It causes deformities and leads to limitation of daily physical activities and deterioration of quality of life. Gaucher cells occupy all long bones which is for example the mandible [17].
Oral lesions are often asymptomatic. The most common signs of oral involvement include occasional gums bleeding, yellowish skin pigmentation, lesions on the oral mucosa, or delayed eruption of teeth [17].

Diagnosis

Unfortunately, due to nonspecific physical and subjective symptoms and lack of awareness, patients with type 1 often experience a delay in diagnosis.

Splenomegaly and thrombocytopenia are the predominant clinical manifestations in many patients with Gaucher's disease. These symptoms cause concern in patients and lead to visits to the doctor. Diagnostic difficulties result from limited knowledge and lack of awareness of the disease [1]. Therefore, hepatologists and gastroenterologists in particular need to be aware of this disease [13].

The diagnosis of the disease is based on glucocerebrosidase activity measured in leukocyte samples. Spleen tissue or liver biopsy material may show characteristic, generally oligonucleated, storage cells showing striped cytoplasm in Leishman stain. Molecular analysis can identify mutated glucocerebrosidase alleles causing the disease and can help diagnose and screen family members at risk for this recessive disease [18].

Although type 1 of Gaucher's disease is most often diagnosed in childhood or early adulthood the condition can be manifested at any age due to the gradation of residual enzyme activity and phenotypic variability [4].

Due to the significant clinical variation in type 1, it is difficult to predict the course of the disease based on genotype alone. Because of the importance of early intervention to maximize

treatment response, current guidelines recommend regular monitoring of symptomatic pediatric patients with type 1 of the disease for visceral, hematologic and bone involvement.

The latest guidelines recommend: physical examinations (including a detailed history and careful monitoring of height and growth rate), hematological examinations, including complete blood count (CBC) and biomarkers such as chitotriosidase activity, every 6-12 months, also monitoring of liver and spleen volume every 6-12 months, preferably by volumetric magnetic resonance imaging (MRI), and skeletal evaluation, including dual energy X-ray absorptiometry (DXA) every 12 months and MRI of the spine and femur every 12-24 months [9].

Treatment

Currently, the primary therapeutic method is enzyme replacement therapy, which involves intravenous administration of recombinant glucocerebrosidase. Treatment of milder forms of the disease also includes oral therapy that inhibits the production of glucocerebrosidase. (2) Treatment is available in the form of intravenous enzyme replacement therapy or, in adults, substrate reduction therapy [9].

Patients with asymptomatic disease initially do not need to receive treatment. However, active bone disease and significant hepatosplenomegaly are considered an indication for starting enzyme replacement therapy in asymptomatic children.

Before the invention of enzyme replacement therapy (ERT), treatment was largely based on symptom management with splenectomy performed because of the extensive splenic invasion in severe patients with a bad prognosis [4,5,6].

Before the ERT, treatment was palliative and supportive. This is still the case in most developing countries. It is estimated that only 10% of potential patients worldwide receive dedicated treatment [18].

The earliest effective ERT, alglucerase, was introduced in the 1990s and dramatically changed the prognosis of the disease. Successive, newer forms of ERT with improved

manufacturing techniques and safety profiles have been approved. The newer oral substrate reduction therapy (SRT) works earlier in the biochemical pathway to mitigate glucosylceramide accumulation. Both therapies are expensive and each one has drawbacks that must be considered: ERT requires intravenous infusion every few weeks, while SRT has a narrower safety profile, given CYP2D6 and CYP3A metabolism, and is only approved for use in adults [4,5,6].

Eliglustat is an oral substrate-reducing therapy approved in the European Union and the United States as a first-line treatment for adult patients with Gaucher's disease type 1 who have a compatible CYP2D6 metabolic phenotype [6]. It was approved in 2014 [19].

Eliglustat is a selective, strong inhibitor of glucosylceramide synthase, the enzyme responsible for the biosynthesis of glucosylceramides that accumulate in GD. The intense metabolism of eliglustat by CYP2D6 and, to a lesser extent, CYP3A of the cytochrome P450 pathway, requires careful consideration of the patient's CYP2D6 metabolizer status and simultaneous use of drugs metabolized by these pathways [6].

Eliglustat is a daily oral therapy as an alternative to enzyme therapy administered every 2 weeks. The recommended eliglustat dose is 84 mg twice daily in people with rapid metabolism. With intermediate metabolism it is reduced to 84 mg once daily. In practice, it is important to note that each eliglustat capsule contains 100 mg of eliglustat tartrate, which is equivalent to 84 mg of eliglustat [6].

Enzymatic replacement therapy, intravenous infusion of recombinant glucocerebrosidase (imiglucerase, velaglucerase alfa, taliglucerase alfa) has been shown to be safe and effective in reducing the morbidity associated with the heterogeneous clinical manifestations of type 1 disease: hematologic cytopenia , symptomatic hepatosplenomegaly , bone pain, bone necrosis and osteopenia. Oral substrate reduction therapy (SRT) by inhibiting glucosylceramide synthase (miglustat and eliglustat tartrate) is also used in a select group of GD1 patients [8].

Current treatments, such as enzyme replacement therapy (ERT), are not effective for GD2 and GD3 due to their inability to cross the blood-brain barrier (BBB) [15].

Models of medical care clearly vary in different health care systems around the world. Patients are most often under the primary care of hematologists, metabolic specialists, geneticists, pediatricians, gastroenterologists or rheumatologists. Supportive care is also provided by orthopedic surgeons, neurologists and other specialists [18, 20].

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Bibliography

[1]

Sumskiene E, Machaczka M. Jak rozpoznawać i leczyć chorobę Gauchera: zarys patofizjologii, objawów klinicznych, metod diagnostycznych i leczenia. *Acta Haematologica Polonica*. 2017;48(3):165-173. doi:https://doi.org/10.1016/j.achaem.2017.07.003

[2]

Hasiński P, Bik-Multanowski M, Koba-Wszędobył M, et al. Choroba Gauchera – zalecenia dotyczące rozpoznawania, leczenia i monitorowania. *Acta Haematologica Polonica*. 2017;48(4):222-261. doi:https://doi.org/10.1016/j.achaem.2017.10.001

[3]

Suelen Porto Basgalupp, Altmann V, Filippo, et al. GBA1 variants in Brazilian Gaucher disease patients. *Molecular genetics and metabolism reports*. 2023;37:101006-101006. doi:https://doi.org/10.1016/j.ymgmr.2023.101006

[4]
Degnan AJ, Ho-Fung VM, Ahrens-Nicklas RC, et al. Imaging of non-neuronopathic Gaucher disease: recent advances in quantitative imaging and comprehensive assessment of disease involvement. *Insights into Imaging*. 2019;10(1). doi:https://doi.org/10.1186/s13244-019-0743-5

[5]
Dandana A, Ben Khelifa S, Chahed H, Miled A, Ferchichi S. Gaucher Disease: Clinical, Biological and Therapeutic Aspects. *Pathobiology*. 2015;83(1):13-23. doi:https://doi.org/10.1159/000440865

[6] Belmatoug N, Di Rocco M, Fraga C, et al. Management and monitoring recommendations for the use of eliglustat in adults with type 1 Gaucher disease in Europe. *European Journal of Internal Medicine*. 2017;37:25-32. doi:10.1016/j.ejim.2016.07.011

[7]
Adar T, Ilan Y, Elstein D, Zimran A. Liver involvement in Gaucher disease – Review and clinical approach. *Blood Cells, Molecules, and Diseases*. 2018;68:66-73. doi:https://doi.org/10.1016/j.bcmd.2016.10.001

[8]
Weinreb NJ, Barbouth DS, Lee RE. Causes of death in 184 patients with type 1 Gaucher disease from the United States who were never treated with enzyme replacement therapy. *Blood Cells, Molecules & Diseases*. 2018;68:211-217. doi:https://doi.org/10.1016/j.bcmd.2016.10.002

[9]
Yang AC, Bier L, Overbey JR, et al. Early manifestations of type 1 Gaucher disease in presymptomatic children diagnosed after parental carrier screening. *Genetics in Medicine*. 2017;19(6):652-658. doi:https://doi.org/10.1038/gim.2016.159

[10]
Abdel A, Abdalla A, Barakat T, Heba El-Taher, Ali K. Assessment of the liver and spleen in children with Gaucher disease type I with diffusion-weighted MR imaging. *Blood cells, molecules, & diseases/Blood cells, molecules & diseases*. 2018;68:139-142. doi:https://doi.org/10.1016/j.bcmd.2016.12.004

[11]
Webb M, Ari Zimran, Dinur T, et al. Are transient and shear wave elastography useful tools in Gaucher disease? *Blood cells, molecules, & diseases/Blood cells, molecules & diseases*. 2018;68:143-147. doi:https://doi.org/10.1016/j.bcmd.2016.12.010

[12]
Serai SD, Naidu AP, Andrew Burrow T, Prada CE, Xanthakos S, Towbin AJ. Correlating liver stiffness with disease severity scoring system (DS3) values in Gaucher disease type 1 (GD1) patients. *Molecular Genetics and Metabolism*. 2018;123(3):357-363. doi:https://doi.org/10.1016/j.ymgme.2017.10.013

[13]
Carubbi F, Cappellini MD, Fargion S, Fracanzani AL, Nascimbeni F. Liver involvement in Gaucher disease: A practical review for the hepatologist and the gastroenterologist. *Digestive and Liver Disease*. Published online February 2020. doi:https://doi.org/10.1016/j.dld.2020.01.004

[14]
Daniella Braz Parente, Chagas F, Renata, et al. Multiparametric magnetic resonance imaging of the liver and spleen in Gaucher disease. *Abdominal radiology*. Published online April 20, 2024. doi:https://doi.org/10.1007/s00261-024-04293-w

[15]
Feng S, Nino Rcheulishvili, Jiang X, et al. A review on Gaucher disease: therapeutic potential of β-glucocerebrosidase-targeted mRNA/saRNA approach. *International journal of biological sciences*. 2024;20(6):2111-2129. doi:https://doi.org/10.7150/ijbs.87741

[16]
Liang M, Zhu S, Liu S, et al. Gaucher disease in a patient with membranoproliferative

glomerulonephritis: case report. *BMC Nephrology*. 2023;24(1). doi:https://doi.org/10.1186/s12882-023-03163-9

[17]

Minervini G, Franco R, Maria Maddalena Marrapodi, et al. Gaucher: A Systematic Review on Oral and Radiological Aspects. *Medicina*. 2023;59(4):670-670. doi:https://doi.org/10.3390/medicina59040670

[18]

Hughes D, Mikosch P, Belmatoug N, et al. Gaucher Disease in Bone: From Pathophysiology to Practice. *Journal of Bone and Mineral Research*. 2019;34(6):996-1013. doi:https://doi.org/10.1002/jbmr.3734

[19]

Mistry PK, Lopez G, Schiffmann R, Barton NW, Weinreb NJ, Sidransky E. Gaucher disease: Progress and ongoing challenges. *Molecular Genetics and Metabolism*. 2017;120(1-2):8-21. doi:https://doi.org/10.1016/j.ymgme.2016.11.006

[20]

Mehta A, Kuter DJ, Salek SS, et al. Presenting signs and patient co-variables in Gaucher disease: outcome of the Gaucher Earlier Diagnosis Consensus (GED-C) Delphi initiative. *Internal Medicine Journal*. 2019;49(5):578-591. doi:https://doi.org/10.1111/imj.14156