GAUCHER DISEASE: A LYSOSOMAL STORAGE DISORDER WITH MANY TYPES

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Abstract

Gaucher disease is a chronic multisystem disease with a genetic background. It is inherited in an autosomal recessive way and belongs to the lysosomal cumulative diseases. The symptomatology is due to the decreased activity of the lysosomal enzyme glucocerebrosidase and the accumulation of glucosylceramide in macrophages. The disease presents three types, with the predominant type being Gaucher Disease type 1 (GD1), which does not show neurological involvement and the types GD2, GD3 that present with various, usually severe neurological symptoms. There are two main therapeutic approaches for the disease, the treatment of enzyme replacement and the one that involves the reduction of the therapeutic substrate.

INTRODUCTION

Gaucher disease is the most common sphingolipidosis. Sphingolipidoses are part of lysosomal cumulative diseases and relate to the dysfunction in the process of catabolism of certain critical metabolites that are either in the cell membrane or are regulators of signaling pathways [1].

Gaucher disease is a rare, autosomal recessive genetic disorder, first described in 1882 by Philippe Gaucher. The French dermatologist, while he was still a medical student, recognized in a 32-year-old woman a clinical picture of marked splenomegaly without leukemia, and despite attributing the clinical picture to some type of cancer, he published his findings in his doctoral thesis. Many years later the biochemical nature of the disease, which took his name, was fully understood [2].

Gaucher disease (GD) is caused by mutations in the gene for Acid beta-glucocerebrosidase or beta-glucosidase (GBA1), which is located on chromosome 1 (1q21). These mutations cause a severe decrease in the activity of the lysosomal enzyme glucocerebrosidase (GCase), which normally hydrolyzes glucosylceramide (GlcCer) to ceramide and glucose [3]. Up to date, more than 400 mutations in the GBA1 gene have been described. Mutations in the GCase activator, saposin C, and more specifically in the PSAP gene, cause a similar clinical picture, but are much rarer [3, 4].

EPIDEMIOLOGY

GD is a disease found in all nationalities and races, although it has an extremely high prevalence among Ashkenazi Jews. Specifically, among the latter, it has been detected a frequency of 1: 850, while the carriers are 1:17 [5]. In the general population, the incidence of the disease is approximately 1/40,000 to 1/60,000 births [6].

PATHOPHYSIOLOGY

Mutations in the GBA1 gene that cause a decrease in glucocerebrosidase activity lead to the accumulation of glucosylceramide in macrophages, transforming them into Gaucher cells [7]. Gaucher cells are found mainly in the bone marrow, spleen, and liver. The pathophysiological mechanism leading to the neurological complications of the disease has not yet been fully elucidated [8]. An autophagic dysfunction is hypothesized, as well as the amplification of another metabolic pathway resulting in the accumulation of glucosylsphingosine which causes neuronal dysfunction and death.

CLINICAL PICTURE

Gaucher disease is characterized by hepatosplenomegaly, cytopenia, severe bone damage and in some cases, serious neurological complications. There are three types of the disease (table 1, Figure 1).

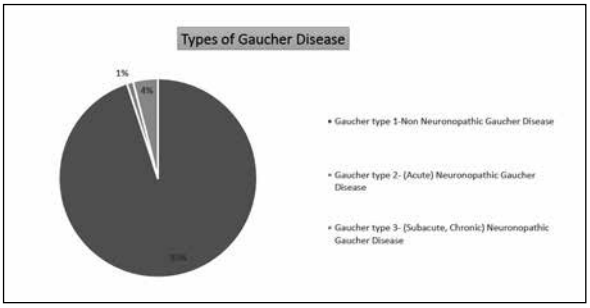
Type 1

Type I (GD1) is the most common (prevalence 90-95% in Europe and North America). It has a varied clinical picture, and its spectrum extends from asymp-

Table 1. Symptomatology of Gaucher disease types

Gaucher type 1	Gaucher type 2	Gaucher type 3
Splenomegaly	Cerebellar symptoms	Horizontal saccadic movement disorder
Hepatomegaly	Opisthotonus -trunk rigidity	Ocular muscle apraxia
Bone disease, bone pain crises	Eye movement dysfunction	Myoclonus
Anemia, cytopenia	Epileptic seizures	Epileptic seizures
Fatigue	Medullar dysfunction	Extrapyramidal symptoms
Abdominal pain	Apnea crises	Dementia

Figure 1. Diagram showing the prevalence of Gaucher Disease subtypes



tomatic patients throughout their lives to forms with early onset in childhood. The mean age of diagnosis is between 10-20 years [9].

The symptoms of the disease can vary and affect different organs, but without neurological complications. Half of the patients report intense fatigue, which affects their daily life [10]. One of the most common symptoms is osteopenia or even osteoporosis, which occurs at a much younger age than normal [11]. Pathological fractures often occur as well (mainly of the long bones and vertebrae) [12]. In addition to the reduction of bone density, that is mainly responsible for them, fractures can often be the result of focal osteolytic lesions. In cases involving mainly the lower jaw, cystic lesions locally can even lead to serious dental abnormalities [13, 14]. With the use of magnetic resonance imaging, both bone marrow infiltration and bone infarction, lytic and osteonecrotic lesions can be assessed [15]. On X-ray, lesions can be found around metaphysis/diaphysis of the femur. The deformity consists of lack of modeling of this specific area of the bone with abnormal cortical thinning and lack of the concave di-metaphyseal curve, resulting in an Erlenmeyer flask-like appearance. These lesions occur mainly in childhood [16].

Gaucher cells are also found in other organs such as the lungs, mainly in patients homozygous for the 1448G (L444P) mutation [17]. Patients with GD1 and pulmonary involvement may have a picture of interstitial lung disease, which could potentially lead to pulmonary fibrosis or pulmonary hypertension. Pulmonary hypertension is more common in patients who have had a splenectomy, especially women.

Rarely, proteinuria and hematuria are found after the infiltration of renal glomeruli by Gaucher cells [18]. Complications from the cardiovascular system, the eyes or the skin are rare in GD1 [19]. More specifically, in some cases, there is a yellow-brown pigmentation of the skin in the anterior region of the tibia as well as on the cheeks.

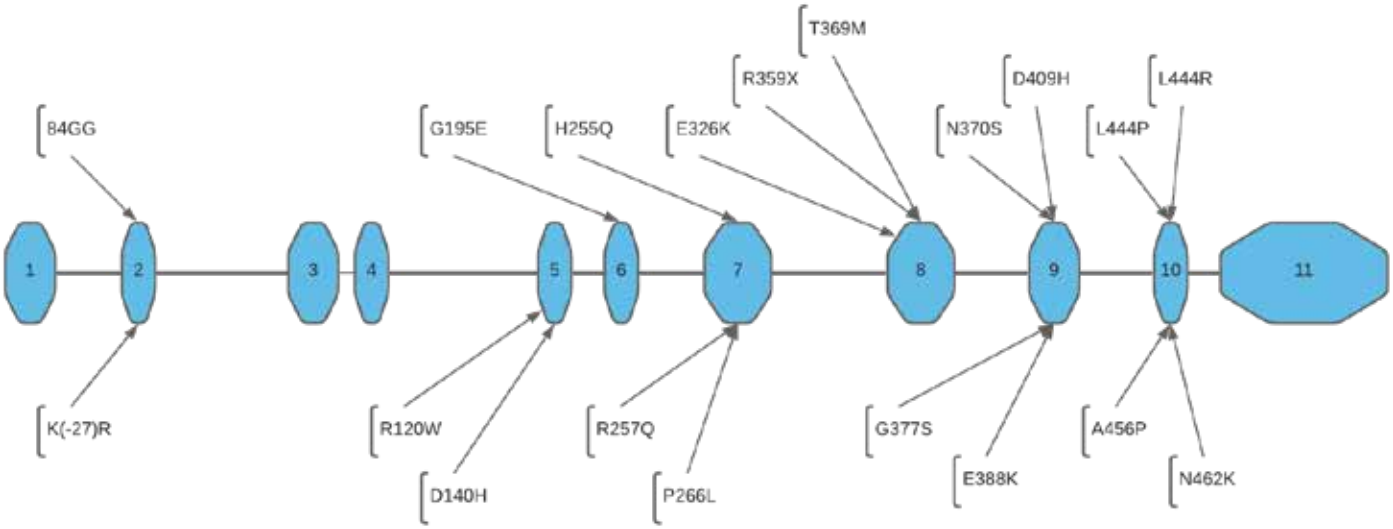
Interestingly, there is an association between GD1 disease and an increased risk of developing Parkinson's disease. Therefore, mutations in GBA are observed in 2-30% of patients with Parkinson's disease [20]. In fact, Parkinson's disease in patients with GD1 as well as in heterozygous carriers occurs at a younger age compared to the general population and often occurs with dysautonomia and dementia [21, 22].

Finally, it has been reported an increased risk of certain malignancies, especially multiple myeloma in patients with GD1.

Type 2

Gaucher type 2 disease is very rare (affects <5% of cases in most countries) and is characterized by very serious neurological complications that begin in neonatal life, while a fetal subtype is described (extremely rare, <1% of cases and the most severe form) [23]. The neurological burden begins in infants 3-6 months of age, who most commonly initially show hepatosplenomegaly. In 60% of cases splenomegaly is associated with thrombocytopenia. The clinical triad that enhances the diagnosis of the disease consists of cervical and trunk stiffness, bulbar signs and oculomotor dysfunction. Pyramidal and extra-pyramidal signs are found in the neurological examination of newborns. Affected infants often suffer from episodes of apnea, which are associated with a gradually increasing duration of laryngeal spasm

Figure 2.



[24, 25]. Seizures, usually of the type of refractory myoclonic epilepsy and slowing of neonatal psychomotor development are common in GD2. Bone complications in type 2 are not described. There may also be involvement of the lung, most commonly with lesions resulting from repeated aspirations as well as pulmonary infiltration by Gaucher cells. Death usually results from prolonged apnea or mass aspiration and occurs before the first 3 years of patients' lives [26]. The fetal form of the disease is characterized by hydrops, hepatosplenomegaly, ichthyosis, arthrogryposis, facial deformity, and fatal thrombocytopenia. These embryos usually end up in the womb or shortly after birth. Nevertheless, the diagnosis of the disease is considered very important in order to offer the suitable genetic guidance and advice to the parents [26].

Type 3

Gaucher type 3 disease (affects 5% of cases, but there are studies describing that it can reach up to 33% of them), is a combination of type 1 and 2, as in GD3 coexist the visceral complications of type 1 and neurological complications [27]. It is often referred to as adolescent or subacute neurological GD, as it most commonly occurs before the age of 20 years. Type 3 neurological complications may be mild, such as slowed horizontal saccadic eye movement, but the disease may present with severe neurological complications such as progressive myoclonic epilepsy (affecting 16% of patients with type GD3) or cerebellar ataxia and spasticity [28-30]. Systemic complications on the other hand are usually mild (hepatosplenomegaly, bone disorders, cytopenia). Patients with the mutation c.1342G > C (D409H) show progressive calcification of the aorta and heart valves, as well as corneal and hydrocephalus lesions [31]. The patients with the rare deficiency of saposin C present with a clinical picture corresponding to GD3, having all the main neurological complications of the disease [32].

DIAGNOSIS

The diagnosis of the disease is made by measuring the activity of the enzyme glucocerebrosidase. The measurement is made in circulating leukocytes or monocytes or in fibroblast culture [33, 34]. Most commonly, the enzyme activity is at 10-15% of normal value. We can detect the decrease in the enzyme activity by checking the blood monocytes with flow cytometry, although this method remains to be certified by more centers [35].

If the activity of the enzyme glucocerebrosidase is normal, but there is a high clinical suspicion or biomarkers that point to the possibility of GD (especially when chitotriosidase is very high), then the PSAP gene should be tested for mutation in sapocin C [36].

Bone marrow biopsy is not a necessary test to confirm the diagnosis of GD. In fact, as Gaucher-type cells can be seen in certain hematological diseases such as lymphoma, chronic lymphocytic leukemia, and others, it is advisable to avoid the test, as it may be misguiding [37].

The genotyping of the GBA1 gene encoding GCase will confirm the diagnosis and identify the responsible mutation. More than 400 mutations of the disease have been described in the GBA1 gene, the most common of which are the following: c.1226A > G (N370S), c.1448T > C (L444P), c.84dup, c.115 + 1G > A (IVS2 + 1G > A) and R120W/RecNciI (39.40) (Figure 2).

Biomarkers of the disease

Chitotriosidase is an enzyme produced by activated macrophages, and in the case of GD by Gaucher cells.

Its levels in patients with GD who do not receive treatment are particularly high and therefore can act as a biomarker of the disease, as well as an indicator of the response to treatment [36]. The limitation of the usefulness of the measurement of chitotriosidase is its presence in other lysosomal cumulative diseases (such as Niemann-Pick, although in this case it is at lower levels), in granulomatous diseases, such as sarcoidosis and other diseases (b thalassemia, Alzheimer's disease, multiple sclerosis) [38]. Also, there is a mutation in chitotriosidases' gene that lead to a deficiency in the activity of the enzyme in the general population. This fact makes it difficult to use the enzyme measurement as a biomarker for the disease and especially as a biomarker between patients with GD, measuring the severity of their disorder or their response to treatment. Finally, there are different techniques for measuring the enzyme levels, which may also worsen the comparison of the results between different reference centers [39].

Another biomarker of GD is the chemokine CCL18/PARC, which like chitotriosidase is secreted by Gaucher cells. In the plasma of patients with GD this chemokine is found 20 to 50 times higher than normal [36].

The transmembrane protein gpNMB (glycoprotein nonmetastatic melanoma protein B) has also been found to be increased 50-fold in the plasma of patients with GD1 [40]. A recent study has confirmed this association, while another study describes the presence of elevated levels of this protein in the CNS of patients with GD3 [41].

Glucosylsphingosine is a biomarker under investigation, which appears to be more specific for the disease than chitotriosidase and CCL18. While further studies are needed to support the wider use of glucosylsphingosine, it has recently been found to make a significant contribution to monitoring patients' response to treatment [42, 43].

Finally, ferritin, although not a specific indicator of the disease, seems to provide useful information at different stages of the disease. It is elevated in most patients with GD, with serum iron levels and transferrin saturation being normal [44, 45]. Iron stores are mainly found in the liver and bone marrow, so ferritinemia also functions as a predictor of the onset of bone complications of the disease. Splenectomized patients with GD also have high ferritin.

TREATMENT

There are two types of treatment for Gaucher disease. The treatment is not suitable for all types of the disease, nor for all its stages. It is important to diagnose the disease early, before permanent and irreversible complications of the disease, such as osteoarthritis, vertebral fractures, osteonecrosis as well as massive fibrous splenomegaly, hepatic or pulmonary fibrosis [46, 47].

Enzyme replacement therapy

The principle of enzyme replacement concerns the supply to the cells of the glucocerebrosidase that they lack. The drugs on the market are analogs of recombinant DNA produced by the human enzyme β-glucocerebrosidase (imiglucerase, velaglucerase) but also by plant-derived glucocerebrosidase (taliglucerase) [48-50]. The administration of the above treatments is intravenous, while the dosage and frequency of administration are determined based on recommendations from the International Working Group on Gaucher Disease (ICGG), as well as the guidelines and the treatment goals. A typical starting dose for children and adults with severe symptoms is 60 U/Kg body weight every 2 weeks, with the dose reduced by half when a therapeutic effect is achieved [51]. Lower doses may reduce the cost of treatment and are recommended for use in patients with a stable clinical picture of GD1. The evaluation of the response to treatment is done by controlling a blood analysis report of the patients, the bone density and their quality of life in general through various scales (pain, etc.) [52].

All enzyme replacement therapies can be given to patients suffering from GD1, who are symptomatic or have laboratory/biological abnormalities, and only imiglucerase has been officially approved for GD3 [53, 54]. Up to date, no cure has been found for GD2, that can reverse, stabilize or delay the course of the disease. This is partly due to the very rapid progression of the disease and the serious neurological complications. Enzyme replacement therapy is usually well tolerated, with 2-14% of patients developing antibodies to the enzyme after a while. Allergic reactions are rare [55].

Substrate reduction therapy

Substrate reduction therapies aim to reduce the excess glucosylceramide, substantially reducing its production. Miglustat, which is an inhibitor of glucoceramide synthase, works by reducing its production in Gaucher cells [56]. It is prescribed in mild to moderate GD1, when it has failed or for some reason no enzyme replacement therapy can be given [57]. The most important benefit of the drug is the control of the increase in the size of the liver and spleen, while it also reduces the levels of chitotriosidase. Its effectiveness in hematological and bone complications of the disease seems to be limited [58]. It is an oral medicine, and the recommended dose is 100 mg, three times a day. It should not be given during pregnancy and patients should take contraceptive measures when they are on medication [59].

Eliglustat is a newer drug, which is a potent and specific inhibitor of glucosylceramide synthase and acts as a substrate reduction therapy for patients with GD1 [60]. It is classified as a first-line treatment, and while it appeared to be similar to Miglustat in most comparisons, eliglustat appeared to provide higher protection to patients with respect to GD1's bone complications [61]. Special care should be taken before initiating the drug, as it has serious side effects when administered to patients with rapid or intermediate metabolism of CYP2D6. In every case and before the first dose, patients should be tested by CYP2D6 genotyping to determine metabolic status [62]. Eliglustat is contraindicated in patients with severe heart disease or in patients receiving class IA and III antiarrhythmics drugs.

Substrate reduction therapies do not appear to help in cases of GD2, GD3, specifically in the neurological complications of the disease, although Miglustat appears to cross the blood-brain barrier.

Treatment with small accompanying molecules -chaperones

Chaperones are small molecules that bind to proteins in the endoplasmic reticulum, helping target proteins to form properly and thus stabilizing their structure. This is a treatment that helps to enhance the activity of the enzyme, in this case glucocerebrosidase, as mutations in the GCase gene often causean abnormal folding of the protein, resulting in its early degradation [63]. Ambroxol has been studied in high doses in combination with enzyme replacement therapy with good results [64]. Isophagomine is still being studied with encouraging in vitro results [65].

Gene therapy

The first results from the use of gene therapy in Gaucher disease were not very encouraging. Human glucocerebrosidase cDNA was successfully transferred to mouse and human hematopoietic stem cells and progenitors, with satisfactory expression of glucosidase in transplanted mice, but with a low rate of expression in vivo, and therefore no clinical benefit reported [66]. The above study was performed in patients with GD3.

Symptomatic treatments

Following the widespread use of enzyme rehabilitation therapies, routine splenectomy in patients with GD1 has been abandoned. It is now recommended in rare cases of non-response to enzyme therapy or in cases of splenic rupture [67].

For bone pain attacks, short-term bed rest and strong analgesic treatment are recommended. Orthopedic surgical evaluation is imperative in cases of pathological fractures and osteonecrosis. Regarding the use of bisphosphonates, they do not seem to improve bone density, considering that the pathophysiological mechanism has not been clarified yet. However, they are mainly given to postmenopausal women, more commonly in the case of severe osteoporosis [68]. Patients with GD should always be tested for possible coagulation disorders before any invasive procedure.

DISEASE MONITORING

Gaucher disease is a chronic, multisystemic disease. Patients with GD need both clinical monitoring (by a physician, hematologist, neurologist in the case of GD2, 3), as well as regular laboratory and imaging tests.

Enzyme replacement therapy can improve hematological disorders, reduce biomarker levels, control hepatosplenomegaly and long-term bone density disorder. Regular monitoring is also recommended for asymptomatic patients in diagnosis.

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