Gaucher disease: A diagnostic approach, clinical evolution and review

https://doi.org/10.56238/sevened2023.006-006

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ABSTRACT

Introducion: Gaucher disease is an inherited metabolic disorder caused by a mutation in the GBA1 gene, resulting in deficiency of the enzyme beta-glucosidase and accumulation of glucocerebroside in tissues. This disease, which is an autosomal recessive inheritance, affects organs such as the spleen, liver, bone marrow and central nervous system. Case Presentation: A 23-year-old male was referred to the internal medicine service for evaluation of hepatosplenomegaly and anemia. She reports persistent lower extremity pain for a period of 5 years and increased abdominal volume. No history of comorbidities or regular use of medication. Discussion: There are three phenotypes of the disease with varied clinical manifestations: type I (non-neuropathic) is the most common, type II (acute neuropathic) is more severe, with acute neurological impairment and poor prognosis, and type III (chronic neuropathic) is less severe. The incidence is estimated at 1 in 60,000 in the general population. The main symptoms include hepatosplenomegaly, thrombocytopenia, anemia, and bone pain. Based on the premise that Gaucher Disease is difficult to diagnose early due to the similar clinical picture with different diseases, this work aims to delimit the signs and symptoms of the disease and its most affected age group to cover a greater recognition of this rare condition, facilitating the appropriate treatment of these patients. Conclusion: The analysis of the articles showed that the diagnosis is made through acid

beta-glucosidase enzyme activity tests or detection of Gaucher cells in tissues and its treatment involves specific enzyme replacement, such as the use of alpha- taglycerase.

Keywords: Enzyme deficiency, Rare deseases, Mutation.

1 INTRODUCTION

Gaucher disease (GD) is a rare, hereditary, autosomal recessive disorder comprising innate dysfunction of metabolism caused by functional deficiency of the acid lysosomal enzyme β-glucosidase (GBA), also known as glucosylceramidase and glucocerebrosidase (Giuffrida et al., 2023).

GBA enzyme deficiency is associated with mutations in the "GBAgene", located on chromosome 1 (1q21). The accumulation of glycosphingolipids in cells, especially in macrophages, called Gaucher cells, results in cellular dysfunction (Uzen et al., 2023).

The clinical manifestations of the disease occur due to the infiltration of gaucher cells into the main organs of the reticuloendothelial system, such as the spleen, liver, and bone marrow, causing hematopoietic depression causing thrombocytopenia (Minervini et al., 2023).

The classification of Gaucher disease (GD) is carried out in three phenotypes according to neurological involvement, comprising type 1 as non-neuropathic, and neuropathic, subdivided into 2 types, which comprise respectively acute GD, referring to type 1, and chronic GD, referring to type 2 (Giuffrida et al., 2023).

Gaucher disease (GD) type 1 is characterized by the absence of neurological manifestations during life until advanced adulthood, since adult carriers who have developed dementia and/or Parkinson's disease have been described. At present, hematological, visceral, and skeletal manifestations are predominant, and treatment through intravenous enzyme replacement or oral substrate reduction therapy is effective (Schiffmann et al., 2023).

Although the initial symptomatology of Gaucher disease (GD) is nonspecific (Giuffrida et al., 2023), GD classified as type 2 comprises an acute form of the disease due to the onset of a rapidly progressive neurodegenerative disease in childhood, characterized by high mortality in the first years of life (Schiffmann et al., 2023).

The other neuropathic form, classified as type 3, comprises a chronic form, considering that the involvement of the central nervous system can occur in months or years and progression, with longer life expectancy. Some authors consider the development of horizontal supranuclear palsy from the pathognomonic view of this type, however, different from that of the type 2, GD3 patients may have non-neurological clinical manifestations present in type 1 of the disease (Schiffmann et al., 2023).

Diagnosis can be made by measuring low levels of enzyme activity in peripheral blood cells, and molecular genotype analyses are important to assess the possible evolution of the disease (Minervini et al., 2023).

Although there is no cure for Gaucher disease; Intravenous infusions of enzyme replacement therapy (ERT) were approved in 1991, and since then they have been used in the therapeutic planning of patients, being effective in clinical manifestations of some types of the disease (Minervini et al., 2023).

In view of the above, although Gaucher disease (GD) is a rare autosomal recessive hereditary, it includes significant morbidity and mortality, therefore, adequate knowledge about the disease is necessary for early diagnosis and implementation of effective treatment for the management of carriers. In view of this, the present research aims to describe a case report about gaucher disease (GD), as well as to explain the main types, diagnostic methods and treatment.

2 CASE PRESENTATION

A 23-year-old male patient was referred to the medical clinic for evaluation of hepatosplenomegaly and anemia. She reports persistent lower extremity pain for a period of 5 years and increased abdominal volume. No history of comorbidities or regular use of medications.

Conscious, oriented, acyanotic, anicteric, with skin-mucosal pallor (2+/4+), regular breathing. Palpable liver 4 cm below the right costal margin with moderate sensitivity to touch; Palpable spleen 8 cm below the left costal margin. Lower extremities without deformities Notable.

Ultrasound of the total abdomen showed a liver and spleen with slightly enlarged dimensions and normal sonographic texture. Remaining abdominal structures with no abnormalities. In the myelogram, normocellular bone marrow, with significant presence of cells compatible with Gaucher cells.

Diagnosis of Gaucher disease confirmed by myelogram and clinical findings.

The patient was referred for consultation with a hematologist to initiate specific treatment for Gaucher disease, which may include enzyme replacement therapy. Multidisciplinary follow-up is recommended, including regular assessment of liver function and monitoring of blood counts.

3 DISCUSSION

Gaucher disease (GD) is the most common of the glycosphingolipids and the first to have specific treatment with enzyme replacement therapy (ERT). It is an autosomal recessive, clinically heterogeneous, progressive disease caused by deficient activity of the enzyme beta-glucocerebrosidase, which compromises lipid metabolism, resulting in accumulation of glucocerebroside in macrophages. The clinical manifestations depend on the degree of deficiency of

acid beta-glucosidase, which is encoded by the GBA1 gene - located on chromosome 1p21, and the accumulation of glycolipids.

According to data from the Ministry of Health, there are 670 patients with GD under treatment in Brazil, approximately 96% of whom use ERT and 4% use substrate synthesis inhibition (ISS). When diagnosed late and/or left untreated, patients are at risk of developing significant damage and complications that can lead to death.

There are three described phenotypes of GD and although there is no perfect correlation between genotype and phenotype, at least it is possible to distinguish the non-neuropathic form from the neuropathic form. L444P in a homozygous state is more associated with early neurological symptoms and can be seen in types II and III. Thus, type 1 (non-neuronopathic or chronic non-neuronopathic adult form) is the most frequent form of GD, accounting for 95% of cases. Patients may be asymptomatic or present varying degrees of hepatosplenomegaly, hematological manifestations and bone involvement, and the survival of these patients may be similar to that of the normal population. (1)

Despite being the subtype with the highest prevalence and best clinical outcome, the lack of classic symptoms in type 1 GD leads to frequent underdiagnosis. Based on this, we emphasize the importance of considering GD as one of the diagnostic possibilities in clinical conditions that present with chronic anemia associated with splenomegaly in childhood, thus avoiding late diagnosis and treatment and the consequent progression of the disease.

The acute or infantile neuronopathic form, known as type 2, is associated with hepatosplenomegaly, severe neurological changes, and death, usually occurring in the first two years of life, usually due to pulmonary involvement. There is no evidence of efficacy of specific treatment (ERT or ISS) in this form of the disease. (2,3,4) Meanwhile, type 3, i.e., the subacute or juvenile neuronopathic form of neuropathopathy, presents with clinical manifestations (hepatosplenomegaly, anemia, thrombocytopenia, and bone involvement), which usually begin in childhood and are usually more severe than those presented by patients with type 1, in addition to being associated with slowly progressive neurological dysfunction. Death commonly occurs between the second and fourth decades of life. (4)

In contrast to other genetic diseases, there is a highly effective treatment for type 1 GD through enzyme replacement therapy (ERT) with imiglucerase. Before ERT was available, anemia and thrombocytopenia were treated with splenectomy (5). The seminal study by Barton et al. on alglucerase, for example, was performed only in patients with type 1 GD, and even so, the use of this enzyme was not limited to type 1. Thus, since the biochemical defect is the same (regardless of the type of disease), it is assumed that any of the recombinant enzymes, as well as the ISS, can be used in patients with type 3 GD, even if clinical trials have been performed only in patients with type 1.

Patients who meet all the major criteria (clinical and biochemical diagnosis) and at least one of the minor criteria will be included in the Protocol for treatment with ERT. The importance of palliative care for patients with GD types 2 and 3 and those who did not have timely access to specific treatment is emphasized (6).

It is worth mentioning that the treatment is continuous. Discontinuation should be considered if there is a worsening of the clinical picture after 24 months of regular treatment and with all possible adjustments of dose and drug substitution, and if there is poor adherence to treatment (here defined as the occurrence of less than 50% of the infusions planned for a period of 6 months, in the case of recombinant enzymes, or ingestion of less than 50% of the miglulist's capsules planned for a period of 6 months; or less than 50% of the consultations planned within a year; or failure to perform the tests requested to monitor the evolution of the disease). In cases of low adherence, the patient should be included in an educational program to ensure his or her immediate return to treatment when there is a guarantee of improved adherence.

Imiglucerase is the recombinant DNA modified form of glucocerebrosidase, and its replacement has significantly changed the evolution of type 1 GD, and most treated patients present symptom reversal or blockade of the disease. The drug should be administered in a hospital setting, under medical supervision, by intravenous infusion of 30 U/kg every 15 days (7, 8).

A retrospective study conducted in the United Kingdom by Wyatt et al., which included 175 patients with GD of different age groups (155 receiving ERT, 142/155 with imiglucerase), concluded that the time on ERT is associated with a significant increase in the number of platelets and hemoglobin and a decrease in the probability of occurrence of hepatosplenomegaly and bone pain. All analyses also suggested that the period of substantial improvement included the first 5-10 years of treatment, followed thereafter by a plateau period (6).

4 CONCLUSION

Gaucher disease (GD) is a recessive genetic condition that affects both sexes, with a slight predominance in females. Early diagnosis and follow-up of bone changes are essential to provide adequate therapy and prevent complications, even in asymptomatic patients. This has a positive impact on the prognosis and well-being of GD patients (MELLO et al., 2021).

Gaucher has three main types: type 1 is the most common, with non-neuropathic symptoms; type 2 is an acute form with severe neurological symptoms and high mortality; Type 3 is a chronic form with milder neurological symptoms and longer life expectancy. Diagnosis involves enzymatic measurement and molecular analysis (FERREIRA et al., 2011).

The investigation of Gaucher disease involves a bone marrow biopsy, identifying large cells with dark nuclei and few vacuoles in the cytoplasm, as well as elongated lysosomes loaded with lipids.

It is important to differentiate from other lysosomal storage conditions and hematologic disorders. Measurement of the action of beta-glucocerebrosidase on blood leukocytes aids in the suspicion of GD, but definitive analysis requires a complementary molecular study (VALDÉS-DÍAZ et al., 2022).

The therapy involves enzyme replacement (ERT), which reduces the accumulation of the substrate in the cells and improves the well-being of patients. In the course of treatment, an increase in body weight is observed, as the drug decreases metabolic expenditure that was elevated before enzyme replacement. This contributes to a better metabolic balance and overall well-being of patients (CORADINE; PIANOVSKI, 2015).

Therefore, it is essential to understand not only the genetic causes of GD, but also the factors that contribute to the condition, to make a rapid diagnosis and provide effective treatment. Identifying the macroscopic changes that lead to structural and functional changes is crucial for a favorable prognosis and adequate treatment of the disease. In addition to enzyme replacement treatment, recognized in the literature, it is important to consider complementary measures, such as nutritional adaptation, for a comprehensive treatment of GD (OLIVEIRA et al., 2015).

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