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# GAUCHER DISEASE: EXPLORING THE GENETIC AND CLINICAL FRONTIERS OF A MULTIFACETED CONDITION

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**Abstract:** Gaucher disease (GD) is a rare and inherited condition that manifests mainly in childhood. It is caused by the lack of the enzyme glucocerebrosidase, resulting in the accumulation of fat in the tissues, which causes osteopenia, hepatomegaly, splenomegaly, anemia, fatigue, thrombocytopenia and bruising. GD is divided into three types: type 1 is the most common and chronic, presenting bone deformities and enlarged organs; type 2 is rarer and fatal up to two years of age, with serious neurological problems; type 3, in turn, begins in childhood and includes bone, ocular and neurological symptoms, with a longer life expectancy than type 2, allowing many patients to live until adolescence or beyond. However, there is still much to be studied about GD, due to several gaps in the understanding of its mechanisms. The objective of this systematic review is to gather and analyze existing studies on this disease, aiming to expand knowledge with updated and in-depth information. To this end, a systematic review of studies found in the National Library of Medicine and Virtual Health Library (PubMed/BVS) databases was conducted. Commentaries, editorials, conference reports, and studies that did not meet the inclusion criteria were excluded: publication date after 2014, lack of empirical data, or old articles that were inaccessible in full. In total, 12,322 articles were found and, after applying the filters, inclusion and exclusion criteria, and removing duplicate articles, 29 articles were selected for the review. The articles highlighted the impact of GD on different organ systems, addressing body physiology and hepatosplenic pathology related to glucocerebrosidase deficiency, in addition to discussing aggravations, treatments, and associated diseases. As science advances, it is expected that GD will become better known, allowing for more accurate diagnoses and more effective treatments.

**Keywords:** Gaucher Disease, Enzyme Replacement, Neurological Phenotypes.

## INTRODUCTION

Gaucher disease (GD) is a rare condition that affects approximately 1 in 50,000 people, usually beginning in childhood. It is an autosomal recessive disease caused by deficiency of the beta-glucocerebrosidase enzyme, encoded by the GBA1 gene on chromosome 1p21, resulting in the accumulation of glucocerebroside in macrophages and consequent impairment of lipid metabolism (Weinreb et al., 2022; Christina et al., 2022). This accumulation, resulting from the deficiency of the glucocerebrosidase enzyme, causes systemic symptoms such as osteopenia, bone pain and fractures, hepatomegaly, splenomegaly, anemia, fatigue, thrombocytopenia, and easy bruising (Christina et al., 2022; Derralyn A. et al., 2023). GD is classified into three main types, according to severity and symptoms.

Type 1, the most common chronic form, without significant neurological involvement, usually begins in childhood, causing bone abnormalities and an increased risk of stomach and esophageal bleeding, which can progress to severe liver disease or cancer. Type 2 is the rarest and most fatal form, resulting in death by age two, and is characterized by severe neurological problems such as seizures, spasticity (muscle stiffness), and developmental delay. Type 3, chronic neuropathic, begins in childhood and includes similar bone symptoms to type 1, such as bone deformities and painful crises, as well as eye problems such as strabismus and abnormal eye movements, and severe neurological symptoms, including seizures and developmental delay, which are progressive but less acute than in type 2. People with type 3 generally have a longer life expectancy, often living into adolescence

or early adulthood (Demczco et al., 2021). According to the Clinical Protocol and Therapeutic Guidelines for Gaucher Disease (PCDT GD), accurate measurement of liver and spleen size is essential for both the diagnosis and monitoring of treatment of Gaucher disease. However, there is no consensus on the normal size of the liver, as it varies according to the age of the patient and the measurement point used, which limits the specificity of the measurement. In addition, for diagnosis, magnetic resonance imaging is recommended due to its ability to provide accurate volumetric measurements without exposure to radiation. Therefore, the combination of physical and imaging examinations is essential for an accurate diagnosis and for monitoring the response to treatment of Gaucher disease (Ministry of Health, 2014; National Gaucher Foundation, 2023). Regarding treatment, the main treatment is enzyme replacement therapy (ERT), administered intravenously, which corrects the deficiency of the enzyme beta-glucocerebrosidase. ERT reduces symptoms such as hepatomegaly, splenomegaly, bone pain, and anemia, improving patients' quality of life. In addition to ERT, substrate reduction therapy (SRT) can be considered, which decreases the production of accumulated substrate due to enzyme deficiency, and is useful for patients who do not respond well to ERT or have significant side effects. Therefore, continuous monitoring is crucial to adjust treatment and detect complications, such as progression of bone disease or neurological problems (Sam et al., 2021).

However, despite advances, significant challenges remain, such as early diagnosis and the development of more effective treatments for the most severe types of the disease. Given this context, this review aims to synthesize the available evidence on Gaucher disease and its development, providing a comprehensive and updated overview on the subject, focusing on the physiology, pathology, symptoms, diagnosis, treatments, and challenges related to this disease, highlighting significant advances and obstacles.

## METHODOLOGY

This systematic review was conducted following the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines to ensure rigor and transparency in the review process.

To search for articles, the indexing term "Gaucher Disease" was used, as well as the association of these terms and expressions: physiology, symptoms, diagnosis, treatment and types I, II and III. The searches were carried out in the electronic databases PubMed and BVS. The search was limited to articles published in English and Portuguese, from 2014 to April 2024. The search strategy combined the terms using the Boolean operators "AND" to interconnect the different domains of interest and "OR" to include synonyms or related terms within the same domain. Table 1 represents a summary of the screening of the articles used in the present study.

| INDEXING TERMS | CRITERIA APPLIED |
|---|---|
| **PubMed:**<br>- Gaucher Disease AND physiology AND pathology AND symptoms AND diagnosis AND treatment AND types I, II and III<br><br>**BVS:**<br>- Gaucher disease And physiology AND pathology AND symptoms AND diagnosis AND treatment AND types I, II and III | **Inclusion:**<br>- Review articles, systematic reviews and meta-analyses - Articles published between 2014 and 2024 - English and Portuguese<br><br>**Exclusion:**<br>- Articles that did not present empirical data or that were not fully accessible<br>- Articles unrelated to the topic<br>- Articles published before 2014 |

Table 1: Simplified methodology. Source: Authorial

Review articles, systematic reviews and meta-analyses that discussed Gaucher disease and its physiological aspects, diagnosis, symptoms and therapies in children and adults were included. Articles published before 2014, commentaries, editorials, conference reports and studies that were not directly related to the defined descriptors were excluded. Studies that did not present empirical data or that were not fully accessible were also excluded. In addition, other articles were included with the aim of contextualizing, enriching and justifying the topic addressed.

The identified studies were initially reviewed by 2 members of the team, taking into consideration, their titles and abstracts to identify potentially relevant studies. In case of divergence of opinion among the members, a third member decided whether the article would be used.

## RESULTS

Initially, the expressions associated with the search term "Gaucher Disease" identified 12,322 articles, of which 6,899 were in PubMed and 5,423 were in the Virtual Health Library (VHL). The inclusion and exclusion criteria were then added to the database filters. In this selection, the search revealed 152 articles that were related to the object of study of this work. In the selection of duplicate articles, 8 articles were excluded, leaving 144 suitable articles. After reading the titles and abstracts, 29 articles were selected for review and detailed analysis, as shown in Figure 1.

The table 2 describes the articles based on: author, year of publication, type of study, objective, results and conclusion. These studies focus primarily on GD, providing a comprehensive analysis of this condition that is still enigmatic and little known to the general population.

This systematic review identified and analyzed 29 relevant articles on Gaucher Disease (GD), highlighting the clinical complexity and advances in the understanding of this condition. Revel-Vilk et al. (2020) discussed the importance of the biomarker Glucosylsphingosine (Lyso-Gb1) in the diagnosis and prognosis of GD, emphasizing that it is easily accessible, quantifiable, and valuable for elucidating the molecular pathogenesis of the disease. In addition, Feng et al. (2023) examined patient-reported outcomes and concluded that the heterogeneity of the disease makes it difficult to accurately measure the quality of life of those affected, which points to the need for more specific instruments for this assessment. Regarding clinical manifestations, Minervini et al. (2023) explored the oral and radiological aspects of GD, showing that the infiltration of Gaucher cells into the bone marrow causes significant bone destruction.

Wang et al. (2022) provided a comprehensive analysis of the global epidemiology of the disease, revealing that the prevalence varies significantly between regions, with an average of 14 cases per 100,000 live births. Daykin et al. (2021) discussed the challenges in diagnosing neuronopathic forms of GD, emphasizing the importance of distinguishing between acute and chronic types for appropriate therapeutic choice.

Finally, regarding treatments for GD, Augustín et al. (2023) highlighted the usefulness of Ambroxol in therapy for patients with inadequate responses to enzyme replacement therapy (ERT) or substrate reduction therapy (RRT). Sam et al. (2021) analyzed the efficacy of emerging therapies for GD, especially in pediatric populations, highlighting that new pharmacological approaches have significantly improved the prognosis of diagnosed children.

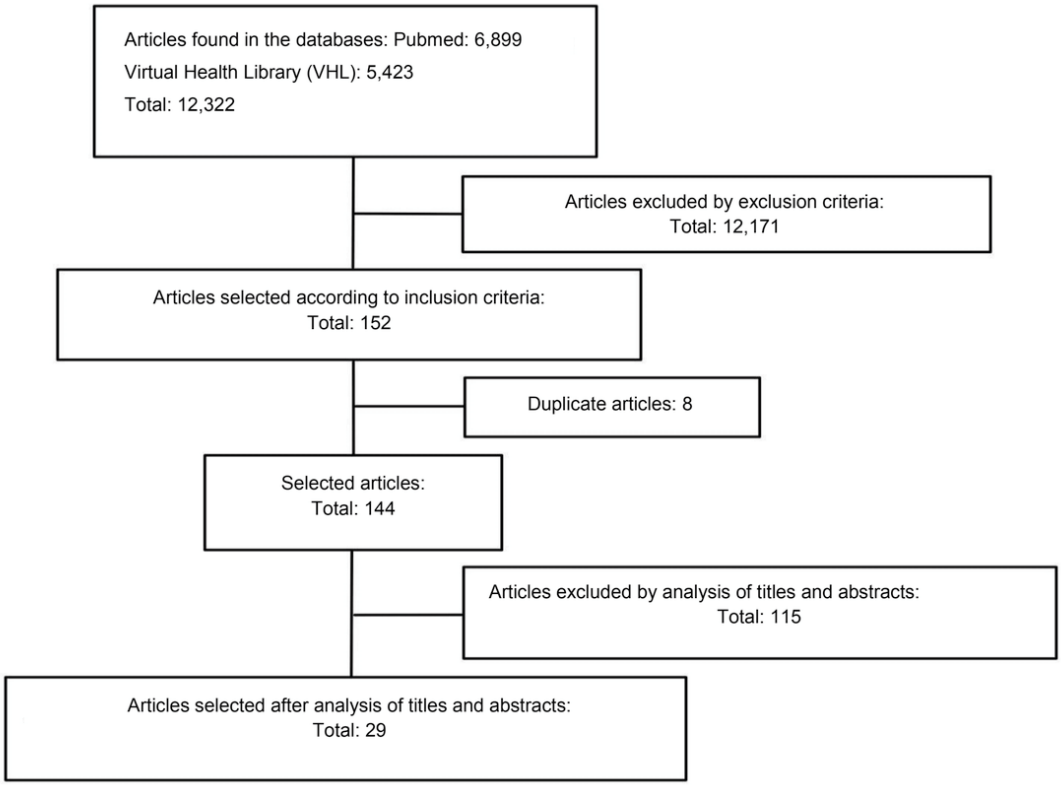


Figure 1: Flowchart of article search and selection. Source: Authorial

| Description of articles used for the review | | | | |
|---|---|---|---|---|
| **Title** | **Author and date** | **Method** | **Goals** | **Conclusion** |
| Value of Glucosylsphingosine (Lyso-Gb1) as a Biomarker in Gaucher Disease: A Systematic Literature Review | Shoshana Revel-Vilk et al. (2020). | Systematic Literature Review | To evaluate the importance of glycosylsphingosine (lyso-Gb1) as a biomarker for diagnosis and prognosis. | Lyso-Gb1 meets the biomarker criteria as it is easily accessible and quantifiable, allows elucidation of the molecular pathogenesis of GD and is diagnostically valuable. |
| Patient-reported outcomes in Gaucher's disease: a systematic review | Junchao Feng et al. (2023) | Systematic Literature Review | Identify and analyze outcomes reported by patients with GD. | Due to the heterogeneity of the disease, the instruments used to measure patient-reported outcomes are still generic. As a result, GD presents substantial difficulties in measuring patients' quality of life. |
| Gaucher: A Systematic Review on Oral and Radiological Aspects | Giuseppe Minervini et al. (2023) | Systematic Literature Review | To assess the effects of Gaucher disease on the jaw using CT scans and X-rays. | Bone manifestation occurs through the mechanism of infiltration of Gaucher cells into the marrow, causing destruction. |
| Global Epidemiology of Gaucher Disease: an Updated Systematic Review and Meta-analysis | Meimei Wang et al. (2022) | Systematic Literature Review and Meta-analysis | To address quantitative data on the global epidemiology of Gaucher disease. | Several data related to the prevalence and incidence of the disease were presented, but more than 50% of the study was carried out in Europe. The prevalence of the disease in Oceania, Europe, North America and Asia, on average, was 1.4 cases per 100,000 live births. |

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| Diagnosing neuronopathic Gaucher disease: New considerations and challenges in assigning Gaucher phenotypes | Emily C Daykin et al. (2021) | Review of Literature | Present aspects of the Gaucher phenotype that help differentiate between acute and chronic types. Highlight the challenges faced in therapies. | Gaucher disease is caused by mutations in the GBA1 gene. Distinguishing between the types of the disease is essential for choosing the correct therapy, given that the blood-brain barrier is a challenge in treatment. |
| Hepatic, Splenic, and Bone Marrow Gaucheromas: A case series and Systematic Literature Review | Bogdan Augustin Chis et al. (2023) | Systematic Literature Review | Present Gaucheromas and their ultrasound characteristics based on imaging exams. | Gaucheromas can be found in any patient with GD. Malignant neoplasms should be considered. The use of imaging studies is always useful, since histopathological examination is difficult to obtain. |
| Gaucher disease | Derralynn A Hughes et al.(2023) | Review of Literature | Display the clinical features of Gaucher Disease, such as: types, diagnosis, genes involved and therapies. | The disease is heterogeneous. The following are important for understanding the disease: genetic management, targeted therapy (enzyme replacement therapy) and monitoring of the progression of symptoms and disease (in individuals who already have the disease).). |
| Hemostatic Abnormalities in Gaucher Disease: Mechanisms and Clinical Implications | Silvia Linari et al.(2022) | Review of Literature | Highlight the pathophysiological interaction between hemostasis and inflammation, addressing the therapeutic options available to manage hemorrhagic complications. | Approaches such as ERT and TRS have demonstrated efficacy in improving peripheral and hematological symptoms, with the approach being taken individually for each patient. |
| Global Incidence and Prevalence of Gaucher Disease: A targeted Literature Review | Genaro Castillon et al.(2022) | Review of Literature. | To display a qualitative synthesis of global estimates of GD incidence and prevalence, specific to GD types1-3 and overall, published over the past 10 years. | Estimates of incidence and prevalence of GD over the past 10 years have varied considerably between regions and have been poorly documented outside Europe and North America. Data for GD2 and GD3 were limited. |
| Imaging of non-neuronopathic Gaucher disease: recent advances in quantitative imaging and comprehensive assessment of disease involvement | Andrew J Degnan et al.(2020) | Review of Literature | To review the imaging manifestations of Gaucher disease and discuss the best quantitative approaches to determine organ and bone marrow involvement. | Conventional imaging of non-neuropathic Gaucher disease underestimates multisystem organ involvement in the disease. Newer quantitative MRI methods allow more efficient assessment of fat fractions in organs and marrow. |
| A review on Gaucher disease: therapeutic potential of β-glucocerebrosidase-targeted mRNA/saRNA approach. | Shunping Feng et al.(2024) | Review of Literature. | To unlock the potential of a cost-effective mRNA/saRNA-based approach to the treatment of Gaucher Disease. | It is concluded that saRNA treatment is something revolutionary, but mRNA should continue to be used initially, as it has a reliable track record. Thus, if necessary, saRNA is a treatment breakthrough due to its high efficiency. |
| The use of Ambroxol for the treatment of Gaucher disease: A systematic review | Diego Agustín Abelleryra Lastoria et al. (2024) | Systematic Literature Review | To analyze laboratory studies that described the mechanisms by which Ambroxol can provide symptomatic relief in patients with GD. Comparing the results between types I, II and III of the disease. | Ambroxol may be considered for the treatment of neurological manifestations of GD. However, due to the heterogeneous nature of the disease, varying degrees of symptomatic improvement have been observed with treatment. |

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| Natural history and management of liver dysfunction in lysosomal storage disorders | Moinak Sen Sarma et al. (2022) | Review of Literature | Analyze lysosomal storage disorders (LSD) that cause liver dysfunction. | In Gaucher disease, there are two liver presentation phenotypes. The first is milder with hepatomegaly, focal nonmalignant liver lesions, and fibrosis. The other is severe, presenting as cirrhosis, portal hypertension, and potential hepatocellular carcinoma (HCC). |
| β-Glycosphingolipids as Mediators of Both Inflammation and Immune Tolerance: A Manifestation of Randomness in Biological Systems | Yaron Ilan. (2019) | Review of Literature | The review evaluates the concept of randomness in biological systems exploring the example of glycosphingolipids - natural killer T cells (NKT) and their influence on the immunological alterations present in Gaucher disease. | Gaucher disease not only affects the lipid metabolic system, but also triggers a series of alterations in the immune system, leading to chronic inflammation and immune dysfunction. In addition, the complexity of study models and the individuality of each patient highlight the need for a personalized approach to the treatment of GD.. |
| Gaucher Disease for Hematologists | Gül Nihal Özdemir et al. (2022) | Review of literature | Analyze the types of Gaucher disease and mention its main symptoms, diagnosis and how the disease works in more detail. | It was found that there is a phenotypic diversity in Gaucher disease that cannot be explained. Splenomegaly was the most common finding, and other symptoms and their frequencies of occurrence were cited. |
| Neuroinflammation in Gaucher disease, neuronal ceroid lipofuscinosis, and commonalities with Parkinson's disease | Laetitia Francelle et al. (2022) | Review of literature | To analyze the role of glial cells and neuroinflammation in PD and LSDs, including Gaucher disease (GD) and highlight the inflammation pathways that lead to neuron loss. | There are links between multiple LSDs and common neurodegenerative diseases such as Parkinson's disease (PD). PD is related to Gaucher disease because of the interaction between the genes of each. |
| Protocolo Clínico e Diretrizes Terapêuticas para Doença de Gaucher | Conitec (2014) | Information report | Recommendations on GD: diagnosis and treatments. | It assumes that all recombinant enzymes involved in the disease can be used in patients with GD3. Treatment with enzyme replacement therapy is only performed for patients who have all the major criteria and at least one of the minor ones. |
| Demographic shifts and healthcare: A review of aging populations and systemic challenges. | Jane Osareme et al. (2024) | Review of literature | Assess the relationship between population aging and the challenges faced by health systems | With the increase in chronic diseases and conditions related to the aging of the population, the health system experiences a greater demand for specialized care, requiring larger infrastructures and staff. |
| Advances in the treatment of autosomal recessive congenital ichthyosis, a look towards the repositioning of drugs. | Sheila I Peña-Corona et al.(2023) | Review of literature | Address repositioning strategies with drugs and biological substances for ichthyosis. | The prospect for drug repositioning for ichthyosis is still limited, dose and frequency are the main challenges to be established, while maintaining patient safety. |
| Gaucher disease: a diagnostic approach, clinical course and review. | Bárbara Pereira Silva et al. (2023) | Case report | Delimit the signs and symptoms of the disease and the age group most affected. | Diagnosis is made through tests that analyze the activity of the beta-glucosidase enzyme or detection of Gaucher cells in tissues. Treatment involves enzyme replacement, such as the use of alpha-taglycerase. |

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| Gaucher disease: clinical phenotypes and refining GBA mutational spectrum in Thai patients. | Tim Phetthong et al. (2021) | Review of literature | To describe clinical features of Thai GD in patients diagnosed during 2010-2018, including analysis of previously uninvestigated GBA recombinant alleles. | Neuronopathic GD was prevalent among the Thai affected population and the p. L483P homozygote was the most common genotype in Thai patients. In addition, the Rec1a allele and splice mutations were associated with GD2 and severe cases of GD3. |
| Hematopietic stem cell transplantation for Gaucher Disease | Usha R Somaraju et al.(2017) | Review of literature | To analyze the role of TCHS in people with Gaucher disease in relation to: mortality risk, effectiveness in modifying the course of the disease or regression of neurological manifestations. | HCT is a treatment that offers the potential for permanent cure. However, there are no clinical trials that have analyzed the safety and efficacy of this treatment in comparison with other measures, such as enzyme replacement therapy and substrate reduction therapy. |
| High-Dose Ambroxol Therapy in Type 1 Gaucher Disease Focusing on Patients with Poor Response to Enzyme Replacement Therapy or Substrate Reduction Therapy. | Majdolen Istaiti et al.(2023) | Experimental study | To evaluate the efficacy of 12 months of daily ambroxol in three groups of patients with type 1 GD with an excellent response to enzyme replacement therapy (ERT) or substrate reduction therapy (TRS). | Patients exposed to high doses of ABX have shown good efficacy. It would be interesting to add off-label ABX to the therapeutic armamentarium for patients with GD1 with an optimal response or those who fail to receive ERT or RRT. |
| Current and emerging pharmacotherapy for Gaucher disease in pediatric populations. | Sam Richard et al.(2021) | Review of Literature | To assess the efficacy of currently available therapies for the treatment of GD and to describe new pharmacotherapies under development, especially for young patients. | The prognosis for children diagnosed with GD in the 21st century exceeds previous expectations, due to the variety of existing approaches, and other therapies in development. |
| Gaucher Disease Treatment. | National Gaucher Foundation | Informative study | It explains the two main types of treatment for Gaucher disease—enzyme replacement therapy (ERT) and substrate reduction therapy (RRT)—highlighting their functionalities, methods of administration, and benefits in minimizing symptoms and permanent damage to the body. | Both enzyme replacement therapy (ERT) and substrate reduction therapy (RRT) are effective in treating Gaucher disease, with the choice of treatment depending on individual patient preferences and needs. ERT involves regular intravenous infusions, while RRT offers a more convenient oral option. |
| The Two Substrate Reduction Therapies for Type 1 Gaucher Disease Are Not equivalent. Comment on Hughes et al. Switching between Enzyme Replacement Therapies and Substrate Reduction Therapies in Patients with Gaucher Disease: Data from the Gaucher Outcome Survey (GOS). | Pramod K. Mistry et al.(2023) | Experimental study. | To evaluate the reasons and consequences for patients with type 1 Gaucher disease switching from intravenous enzyme replacement therapy (ERT) to oral substrate reduction therapy (RRT) and vice versa, highlighting the differences between the two main oral RRTs, eliglustat and miglustat, in terms of efficacy, tolerability and side effect profile. | The article concludes that due to the superior tolerability profile and greater efficacy of eliglustat compared to miglustat, eliglustat has become the first-line therapy for type 1 Gaucher disease. Miglustat, with a higher incidence of gastrointestinal and other side effects, is recommended only for patients who cannot tolerate ERT. Clear distinction between the two RRTs is crucial to inform physicians and patients about treatment options. |

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| Outcomes after 8 years of eliglustat therapy for Gaucher disease type 1: Final results from the Phase 2 trial, | Elena Lukina et al.(2018) | Experimental study | To report the final results of a Phase 2 clinical trial and its extension (NCT00358150), which evaluated the efficacy and safety of eliglustat as first-line oral therapy for adults with previously untreated Gaucher disease type 1 (GD1). | The study concludes that eliglustat is an effective and well-tolerated therapy for type 1 Gaucher disease (GD1), resulting in significant improvements in clinical parameters and quality of life over 8 years of treatment. Most adverse events were mild or moderate, and the treatment was shown to be sustainable in the long term, especially benefiting the most severely affected patients. |
| Hematopoietic Stem Cell Transplantation for Storage Disorders: Present Status. | Soumalya Chackraborty et al.(2024) | Review of literature | To discuss the current evidence for hematopoietic stem cell transplantation (HSCT) in the treatment of various lysosomal storage diseases, and to assess the suitability of hematopoietic stem cells as a therapy option. | Hematopoietic stem cell transplantation (HSCT) is a viable and attractive treatment option for lysosomal storage diseases, particularly in low- and middle-income countries. This is due to the single-intervention nature of these cells and improvements in patient outcomes resulting from advances in peri-transplant medical care and conditioning regimens. |
| Exploring the efficacy and safety of Ambroxol in Gaucher Disease: an overview of clinical studies. | Feda E Mohamed, Fatma Al-Jasmi.(2024) | Review of literature | Highlight the potential of ABX as a pharmacological chaperone therapy for GD and emphasize the importance of addressing feasibility of response in clinical trials to improve the management of this rare and complex disorder. | They noted that although the treatment may be considered ambitious, it is also associated with a sense of ambivalence, due to persistent uncertainty surrounding several critical clinical issues. |

Table 2: Description of Articles Used for the Review. Source: Authorial

Mistry et al. (2023) compared the two main TRSs, Eliglustat and Miglustat, concluding that Eliglustat has a superior efficacy and tolerability profile, being recommended as the first line of treatment for type 1 GD.

## DISCUSSION

### GAUCHER DISEASE AND PHYSIOLOGY

Changes in demographic patterns in several countries since the last decades of the 20th century, including increased life expectancy and the phenomenon of population aging, have emerged as significant challenges for the health domain, particularly in the context of public and universal health systems, as in Brazil. In this context, Gaucher Disease, with its clinical manifestations and etiologies, assumes a prominent role when viewed from a comparative perspective with other more common diseases, since the subject is little discussed and its clinical signs are aggravating (Osareme et al., 2024).

It is important to emphasize that GD is a rare disease represented by a lysosomal disorder with autosomal recessive genetic transmission that generates many clinical signs, which must be observed to avoid complications. Bone, liver, and splenic disorders related to GD are the most common findings and cause multiple complications that affect the patient's quality of life (Christina et al., 2022; Derralyn A. et al., 2023).

Regarding physiology, GD is caused by mutations in the GBA1 gene, located on chromosome 1, which is responsible for encoding the lysosomal enzyme β-glucocerebrosidase (GCase) (Revel-Vilk et al., 2020; Feng et al., 2024). This enzyme

is matured in the Golgi apparatus and is subsequently delivered to the lysosomes with the help of the lysosomal integral membrane protein-2 (LIMP-2) molecule. Once in the lysosome, the enzyme hydrolyzes its substrate, glucosylceramide (GlcCer), which comes from the breakdown of the membrane of red blood cells and leukocytes, into glucose and ceramide through acidic pH (Sen et al., 2022; Francelle et al., 2022).

The mutation in the GBA1 gene results in a marked decrease in the GCase enzyme, that is, it leads to a significant accumulation of substrate (GlcCer) in macrophages, which forms fibrillar aggregates in their cytoplasm. Macrophages filled with unprocessed GlcCer are called Gaucher cells. The accumulation occurs mainly in the mononuclear phagocytic system, which acts in the defense of the organism. For example, histiocytes, lymph nodes, Kupffer cells, osteoclasts, microglia in the central nervous system (CNS) and alveolar macrophages. The infiltration of Gaucher cells occurs mainly in the spleen, liver and bone marrow (Linari et al., 2022; Feng et al., 2024; Sen et al., 2022).

In the bone marrow, the accumulation of glycosphingolipids causes an imbalance between osteoclasts and osteoblasts. Osteoblasts are cells responsible for the formation of new bone tissue, while osteoclasts perform the function of reabsorption from the demineralization and degradation of the bone matrix. The process of hematopoiesis, known for dividing, differentiating and maturing cells, from the most primitive, is also affected. The result of this imbalance is: bone thinning, fragility and development of osteolytic lesions (Sen et al., 2022).

Regarding the brain, the pathophysiological mechanisms of the occurrence of GD still do not have enough studies to be analyzed. This occurs because the turnover of GlcCer in the brain is lower, so lysosomal accumulation is less frequent, except in some manifestations of the disease. However, it is known that GCase dysfunction hinders the degradation of α-Synuclein (α-Syn) in lysosomes and leads to the accumulation of oligomers in the substantia nigra of the brain, resulting in neurotoxicity (Francelle et al., 2022).

Splenomegaly is a consequence of the infiltration of Gaucher cells into the spleen, which act by abnormally releasing inflammatory cytokines, exhibiting expression of surface markers and sequestering iron (Sen et al., 2022).

In some cases, GD is caused by a deficiency of saposin C, a protein responsible for activating GCase. Saposins (A-D) have the main role of degrading sphingolipids and digesting membranes. Saposin C is one of four homologous proteins that derive from the cleavage of the prosaposin precursor protein (Feng et al, 2024).

## CLINICAL PHENOTYPES

The disorder is divided into three clinical types based on the presence and progression of neurological manifestations: type 1 (non-neuronopathic), type 2 (acute neuronopathic), and type 3 (chronic neuronopathic) (Revel-Vilk et al., 2020; Daykin et al., 2021; Derralynn et al., 2023).

In addition, it is also classified according to its two clinical forms: perinatal-lethal form (usually associated with ichthyosiform skin anomalies) and cardiovascular form (characterized mainly by calcification of the aortic and mitral valves) (Derralynn et al, 2023).

Even within its divisions, this disorder presents wide phenotypic heterogeneity, which cannot be fully explained by genotype. Table 4 illustrates the frequency of clinical data. The most frequent clinical aspect of the disease is Splenomegaly (85%), followed by Thrombocytopenia (68%) and Hepatomegaly

(63%). Regarding the most common bone findings, Osteopenia (55%), bone pain (33%), pathological fractures (7%), bone crises (7%), and growth retardation and delayed puberty (36%) were described (Nihal et al., 2022).

| Gaucher Disease: Included Phenotypes | |
|---|---|
| Main clinical phenotypes | Gaucher disease, type 1Gaucher disease, type 2 (acute, infantile)Gaucher disease, type 3 (chronic, juvenile) |
| Variant phenotypes | Perinatal-lethal form Cardiovascular form |

Table 3: Adaptation of Derralynn a Hughes' Table et al., 2023.

| Frequency of symptons | |
|---|---|
| Splenomegaly | 85% |
| Hepatomegaly | 63% |
| Thrombocytopenia | 68% |
| Anemia | 34% |
| Bleeding | Frequente |
| Osteopenia | 55% |
| Bone pain | 33% |
| Pathological fractures | 7% |
| Bone crises | 7% |
| Growth retardation | 36% |

Table 4. Adaptation and signboard Gül Nihal Özdemir et al., 2022.

The GD1 is the most frequent of the 3 types, accounting for approximately 90% of cases of the disease (Feng et al., 2023). According to the Clinical Protocol and Therapeutic Guidelines for GD, the non-neuronopathic form, also known as the adult chronic form, is the most common and least severe, because GCase enzyme activity is not so reduced. Patients may be asymptomatic or present with hepatosplenomegaly, hematologic manifestations, and bone involvement. Survival may be similar to that of the normal population. Approximately 70% to 100% of individuals with GD1 have evidence of bone disease, which can range from asymptomatic osteopenia to focal lytic or sclerotic lesions and osteonecrosis (Minervini et al., 2023; Derralynn et al., 2023). Bone involvement in GD can cause acute or chronic pain, pathological fractures, and subchondral joint collapse with secondary degenerative arthritis, and is often the most debilitating feature of GD type 1 (Derralynn et al., 2023; Nihal et al., 2022). Gaucher cell infiltration into the bone marrow, extending from the axial to the appendicular skeleton, destroys the bone architecture, especially in the lower extremities and occasionally in the mandible, affecting the patient's oral health (Minervini et al., 2023; Derralynn et al., 2023). In addition to bone complications, GD can cause disorders of the spleen and liver. Splenomegaly increases the size of the spleen from 50-200cc to 1,500-3,000cc, and can cause infarctions and acute abdominal pain. Hepatomegaly is the most common hepatic manifestation, while cirrhosis and liver failure are rare (Minervini et al., 2023).

Cytopenias, such as thrombocytopenia, anemia, and leukopenia, are common in almost all patients with GD. Thrombocytopenia is one of the first signs and may be associated with bruising or overt bleeding, with an increased risk in the presence of coagulation abnormalities. Anemia may result from hypersplenism, hemodilution, iron or vitamin B12 deficiency, and Gaucher cell infiltration of the bone marrow. Leukopenia rarely requires intervention (Derralynn et al., 2023). Although GD1 does not have a primary CNS disease, it may present with secondary neurological complications, such as spinal cord compression. The most frequent neurological manifestation in GD1 is Parkinson's disease, while in types 2 and 3, dementia and epilepsy are more common, requiring a multidisciplinary approach (Minervini et al., 2023).

Types 2 and 3 GD, in addition to presenting splenomegaly, hepatomegaly, and cytopenia, have neurological characteristics and are

considered acute and chronic nephropathies, respectively. GD2 is the most severe form of the disease, characterized by primary disease of the central nervous system, limited psychomotor development, and a rapidly progressive course with death by two years of age. It can present in several ways, including prominent visceral involvement, fetal hydrops, congenital ichthyosis, thrombocytopenia, growth retardation, strabismus, and dysphagia. In addition, it can also present bulbar signs (stridor, strabismus, and difficulty swallowing) and pyramidal signs (opisthotonus, head retroflexion, spasticity, and trismus) (Daykin et al., 2021; Derralynn et al., 2023).

Regarding the incidence and intensity of the disease, GD3 is considered intermediate between the three types. It is characterized by primary central nervous system disease with onset in childhood, a slower progressive course, and survival into the third or fourth decade in some cases. Symptoms such as oculomotor apraxia, failure of saccadic initiation, and optokinetic nystagmus are also common in GD3. Oculomotor involvement may be found as an isolated sign of neurological disease in individuals with a chronic progressive course and severe systemic involvement (e.g., massive hepatosplenomegaly). Dementia and ataxia have been observed in the more advanced stages of chronic neurological disease (Daykin et al., 2021; Derralynn et al., 2023).

The main difference between the three phenotypes is the presence and progression of neurological complications, in addition to the symptoms that may appear in childhood. The definitive diagnosis is the enzymatic measurement of BGA activity in leukocytes or skin fibroblasts; molecular analysis serves as a complementary verification of the diagnosis (Silva et al., 2023).

**VARIANT PHENOTYPES**

Among the variant phenotypes, the perinatal one is associated with hepatosplenomegaly, pancytopenia, and abnormalities in the stratum corneum of the skin (due to the altered ratio of glucosylceramide to ceramide). It is characterized clinically as: ichthyosiform skin abnormalities, collodion, or non-immune hydrops. Arthrogryposis and dysmorphic facial features are observed in 35%-43% of affected individuals; these babies are usually stillborn or die shortly after birth (Derralynn et al., 2023).

Other phenotypic features may include intracranial calcifications, cardiomegaly, and severe respiratory dysfunction, which contribute to high perinatal mortality. The variation in phenotypic expression may be attributed to different genetic mutations that affect the specific metabolic pathway involved in the synthesis of ceramide and other lipids essential for skin integrity and cellular function. Recent studies also highlight the importance of genetic screening and counseling for families with a history of variant phenotypes, as early identification can help in family management and planning (Peña-Corona et al., 2023).

In terms of the cardiovascular phenotype, individuals homozygous for the GBA1 variant develop cardiovascular disease with calcification of the mitral and aortic valves at puberty. Mild splenomegaly, corneal opacities, and supranuclear ophthalmoplegia are additional findings that develop earlier and may go unnoticed. These findings are consistent with the cardiovascular calcification syndrome observed in patients with Gaucher disease, which includes a variety of cardiopulmonary complications (Peña-Corona et al., 2023).

Research indicates that valve calcification in patients with Gaucher is caused by abnormal accumulation of glucosylceramide

in the heart valves, leading to stiffness and dysfunction.

Supranuclear ophthalmoplegia and corneal opacities result from similar deposits in ocular tissues. Management of this phenotype requires a multidisciplinary approach, including cardiologists, ophthalmologists, and hematologists. Regular monitoring of cardiac and ocular function is essential to detect complications early and initiate appropriate treatments, such as surgical interventions to correct valvular heart disease and enzyme replacement therapies to reduce glucosylceramide burden in tissues (Phetthong et al., 2021).

## SYMPTOMS AND DISEASES RELATED TO GD

The sign of hepatosplenomegaly is undoubtedly one of the most classic and aggravating signs of GD, usually present from childhood, in addition to being one of the signs that leads most to death in patients suffering from the disease. It has been questioned that this considerable increase in organs may be caused by the accumulation of substrate (glucocerebroside) in the reticuloendothelial system within the Gaucher cells of the spleen and liver, in addition to pro-infiltrative and pro-inflammatory factors (Augustin, et al., 2023; Degnan et al., 2019).

Furthermore, portal hypertension and liver cirrhosis are considered rare signs of GD, but there is a higher risk of liver fibrosis in these cases, which is even more common in patients who have previously undergone splenectomy (surgical procedure to remove the spleen). This fibrosis can increase the risk of cirrhosis, HCC (hepatocellular carcinoma) and can lead to death. This occurs mainly due to the deposition of Gaucher cells, which can establish a fibrogenic (contaminated) environment (Degnan et al., 2019).

Another important laboratory finding that stands out in Gaucher disease is hematological abnormalities, such as anemia. In this finding, ferritin levels are also higher in patients who have partially lost their splenic function (asplenic), a finding that can be confused with greater severity of the disease, which often causes patients to require blood transfusions (Degnan et al., 2019).

Furthermore, a very common disease that develops in cases of Gaucher disease is progressive myoclonic epilepsy, more specifically type 1 (PME1).

It presents clinically as a neurodegenerative disease that occurs in most cases between 6 and 15 years of age, and is characterized by myoclonus (involuntary muscle contraction, tremor or spasm) and chronic epileptic seizures. A few years after the onset of these signs, ataxia, incoordination, intentional tremor and dysarthria may also occur. Seizures are well controlled in most cases with anticonvulsant medication (Degnan et al., 2019).

With regard to bone signs and symptoms, they are more common in GD1. This knowledge of musculoskeletal dysfunctions in GD is very important to differentiate it from other very similar pathologies, such as hematopoietic neoplasms and rheumatic problems. Implantation of Gaucher cells with osteopenia (loss of bone mineral density) in the bone marrow progressively compromises bone density with a prominence of the lower extremities of the femur and proximal tibia. Involvement of the upper extremities, although uncommon, also contributes to musculoskeletal morbidity (Minervini et al. 2023; Degnan et al., 2019).

Early analyses of bone involvement in GD believed that bone changes were irreversible. However, recent studies have shown that some treatments result in an improvement in early bone marrow changes. The prognosis

of skeletal involvement remains poor and marrow responses take longer than organ responses. Bone turnover biomarkers have failed to reduce the risk of stratifying patients, making imaging assessment essential for clinical management (Degnan et al., 2019).

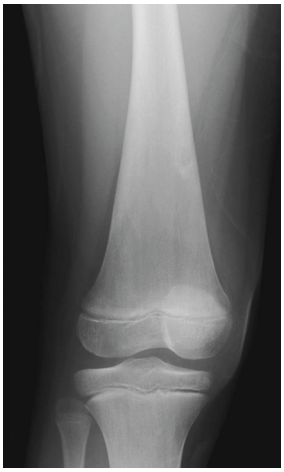

Figure 4: Frontal radiograph of the right knee in a 12-year-old patient with Gaucher disease with widening of the distal femoral shaft and metaphysis.
Source: Adapted from Andrew J. Degnan, 2019

## TREATMENTS

Treatment for GD involves four main types: enzyme replacement therapy (ERT), substrate reduction therapy (SRT), hematopoietic stem cell transplantation (HSCT), and Ambroxol. Patients with type 2 GD are not classified as suitable patients for these therapies because, although these treatments have the possibility of prolonging the patient's life, they will not alter the severe neurological damage (Somaraju et al., 2018; Taiti et al., 2023).

### ENZYME REPLACEMENT THERAPY (TRE)

According to the Clinical Protocol and Therapeutic Guidelines for GD, ERT is a treatment established since 1991, which consists of the intravenous administration of the recombinant enzyme β-glucocerebrosidase, which patients with GD do not produce adequately. This therapy significantly reduces clinical symptoms, including hepatosplenomegaly and bone complications. The most common drugs used in ERT are imiglucerase, alfavelaglicerase and alfataliglicerase, each differing in aspects of production and glycosylation (Ministry of Health, 2014).

ERT is one of the main treatments for GD, specifically for types 1 and 3. It involves the intravenous administration of exogenous enzymes to overcome blockages in the catabolic pathway and remove the stored substrate, glucosylceramide (GL1). The dose of ERT is typically adjusted based on patient response, with an initial regimen of 15–60 enzyme units per kg administered every two weeks. This regimen can be adjusted as needed based on clinical response, such as reduction in liver and spleen volume and mass (Sam et al., 2021; National Gaucher Foundation, 2023).

Studies have shown that ERT is safe and effective in reversing liver and spleen changes caused by GD, as well as reducing the rate of bone degradation and improving pain. However, response to treatment can vary, and dose optimization remains a topic of debate among experts. Higher doses may lead to faster reduction in chitotriosidase levels and improved bone response, although the high cost of treatment is a significant consideration (Mistry, et al., 2023; Sam et al., 2021).

### SUBSTRATE REDUCTION THERAPY (TRS)

RRT is an oral approach that aims to restore metabolic homeostasis by decreasing the amount of glucosylceramide synthesized.

This reduction allows the mutated enzyme, with residual hydrolytic activity, to effectively eliminate the accumulated substrate (Feng et al., 2023; Mistry et al., 2023). RRT includes the drugs Miglustat and Eliglustat, which have distinct mechanisms of action and are indicated for different patient profiles.

Miglustat, marketed as Zavesca®, is an oral therapeutic option used primarily for adult patients with mild to moderate GD 1 who cannot be treated with ERT. Studies show that the drug can significantly reduce the size of the liver and spleen after 6 to 18 months of treatment. However, it has considerable gastrointestinal side effects, including diarrhea, abdominal pain, and weight loss, which may limit its tolerability (Mistry et al., 2023; National Gaucher Foundation, 2023). Eliglustat, sold as Cerdelga®, is a glucosylceramide synthetase inhibitor approved as first-line treatment for adults with type 1 GD who have metabolic profiles consistent with CYP2D6. Eliglustat has been shown to be safe and effective, with significant improvements in bone density and reduction in the size of affected organs. Side effects of Eliglustat are generally mild and include less severe gastrointestinal symptoms compared to those observed with Miglustat (Mistry et al., 2023; Lukina et al., 2019).

Although both drugs are glucosylceramide synthetase inhibitors, they differ significantly in terms of efficacy and side effect profile. Eliglustat is more specific and potent than Miglustat, with a superior tolerability profile, making it a preferred choice for many patients with type 1 GD (Mistry et al., 2023).

## HEMATOPOIETIC STEM CELL TRANSPLANTATION (TCTH)

HSCT offers a potential cure for GD by replacing the patient's hematopoietic stem cells with healthy cells from a donor. This procedure, although promising, is high-risk and generally reserved for specific cases due to its complications, such as rejection and infections. HSCT is an option most often considered in settings where other therapies have failed (Chakraborty et al., 2024; Donald et al., 2022).

In most cases of HSC transplantation, individuals have chronic and progressive neurological GD that has not responded as expected to ERT and RRT treatments.

This therapy also allows for combination treatments, such as ERT combined with HSCT or RRT (Chakraborty et al., 2024; Donald et al., 2022). According to the study by Chakraborty et al (2024), in the nine reported patients, neurological disease continued to progress even after transplantation, manifesting as seizures, cerebellar disease, and tone and reflex abnormalities.

## AMBROXOL

Ambroxol is an oral mucolytic that acts as a pharmacological chaperone for mutant glucocerebrosidase (GCase), facilitating its correct folding and stabilizing its functionality. This drug has shown efficacy in Gaucher disease (GD) types 1 and 3, with few significant adverse effects. Studies indicate that Ambroxol may improve the neurological manifestations of GD, offering an advantage over ERT due to its oral administration (Mohamed et al., 2024).

The use of Ambroxol in GD has been evaluated in several clinical studies. A recent systematic review highlighted the variability in response to Ambroxol treatment, observing response rates of 36% to 55% in patients with GD type 1, 22% in GD type 2, and 29% in GD type 3, with neurological improvements reported. No serious adverse events have been associated with the use of Ambroxol, making it a safe and effective option for many patients (Mohamed et al, 2024; Zhan et al., 2023).

Thus, the analysis of the selected articles demonstrates the complexity of Gaucher Disease and the importance of early diagnosis and appropriate treatment. Existing therapies, such as enzyme replacement therapy (ERT) and substrate reduction therapy (SRT), have proven effective in improving the quality of

life of patients, despite the challenges that persist, especially in neuronopathic cases. Recent studies highlight the continued need for research to develop more effective and specific treatments, in addition to exploring new therapeutic approaches, such as the use of Ambroxol. As science advances, it is expected that the understanding and management of GD will continue to improve, allowing for more accurate diagnoses and personalized treatments that can provide a better quality of life for patients affected by this rare and complex genetic condition.

## CONCLUSION

This systematic review highlights the complexity and severity of Gaucher disease, a rare hereditary condition that affects multiple organ systems. The review of the selected articles highlighted the importance of early diagnosis and continuous monitoring for the effective management of the disease, caused by the deficiency of the enzyme beta-glucocerebrosidase, and which results in diverse and potentially debilitating symptoms, such as hepatomegaly, splenomegaly, osteopenia, anemia and neurological complications.

Enzyme replacement therapy and substrate reduction therapy are emerging as fundamental treatments, providing significant improvements in the quality of life of patients. However, challenges persist, especially regarding the treatment of neuropathic forms of the disease, which have more severe prognoses and limited therapeutic options. In addition, recent advances in understanding the molecular mechanisms of GD and in the development of new therapies offer hope for more accurate diagnoses and more effective treatments. The integration of personalized therapeutic approaches, based on the genetic and clinical profile of patients, is crucial to optimize outcomes.

Furthermore, continued research is essential to fill the existing gaps in knowledge about GD, particularly regarding neurological aspects and the development of new therapeutic strategies. As science and medicine advance, it is expected that GD will be increasingly recognized and effectively treated, significantly improving the quality of life of patients affected by this challenging condition.

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