VIA MEDICA

REVIEW ARTICLE

Acta Haematologica Polonica 2025
Number 2, Volume 56, pages xx–xx
DOI: 10.5603/ahp.101026
ISSN 0001–5814
e-ISSN 2300–7117

Lyso-Gb1 — a highly specific biomarker for Gaucher disease

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Abstract

Gaucher disease (GD) is a rare, autosomal recessive disorder, belonging to the group of lysosomal storage diseases (LSDs). The essence of the disease is a decrease in glucocerebrosidase activity, leading to an accumulation of glucosylceramide in the liver, spleen, bone marrow, bones, and other organs. Gaucher disease presents with a wide range of phenotypic variations and is classified into three types based on the presence of neurological symptoms. Due to the heterogeneous course of the disease, accurate diagnosis is often delayed by many years. Various biomarkers are useful in diagnosing, monitoring progression and treating this disease, such as angiotensin-converting enzymes, serum ferritin, CCL18 and chitotriosidase. The search for a more specific and sensitive biomarker has led to the identification of the deacylated form of glucocerebroside, glucosylsphingosine (lyso-Gb1).

Lyso-Gb1, as a biomarker, is easily measurable in clinical samples, including dried blood spots. It has diagnostic and predictive value and also reflects therapeutic response. A rapid and significant reduction in lyso-Gb1 concentrations in plasma or cerebrospinal fluid following treatment has been reported by many researchers. The levels of lyso-Gb1 decrease during effective treatment, which allows for a determination of whether a patient is responding to treatment, and can indicate the ineffectiveness of therapy before clinical consequences appear. It has been demonstrated that biomarker levels correlate with improvements in disease parameters, including liver volume, spleen volume, hemoglobin and platelet counts. This indicates that a low plasma lyso-Gb1 concentration correlates with a higher therapeutic success rate.

The aim of this review was to present the utility of lyso-Gb1 in diagnosing, assessing disease severity, and monitoring the effectiveness of Gaucher disease therapy.

Keywords: Gaucher disease, lyso-Gb1, biomarker

Acta Haematol Pol 2025; 56, 2: xx–xx

Introduction

Gaucher disease is a rare, autosomal recessive disorder with a prevalence of 1:50,000–1:100,000 in the general population. The highest prevalence occurs in the Ashkenazi Jewish population (of Eastern European descent), where there is a frequency of 1:850 [1, 2]. Despite its rarity, GD should be considered in the differential diagnosis of other hematological disorders presenting with anemia, thrombocytopenia and hepatosplenomegaly [3].

The disease is caused by point mutations in the *GBA1* gene, which is located on the long arm of chromosome

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Received: 05.06.2024 Accepted: 06.02.2025 Early publication: xx.03.2025

1 [4]. The essence of Gaucher disease is a reduction in the activity of the enzyme glucocerebrosidase (GCase), also known as glucosylceramidase or acid β-glucosidase. Its role is to hydrolyze glucocerebroside, which is a sphingolipid present in all cell membranes, into glucose and ceramide [5]. Reduced activity of glucocerebrosidase leads to progressive accumulation of glucocerebroside and its derivative, glucosylsphingosine (lyso-Gb1), in tissue macrophages, which transform into Gaucher cells. These cells mainly infiltrate the bone marrow, spleen, and liver [6]. Symptoms of GD include hematological, visceral, skeletal, and in some forms, neurological disturbances. In the literature, three forms of the disease have been distinguished based on clinical symptoms, including the presence or absence of neurological symptoms (Fig.1) [1, 6, 7].

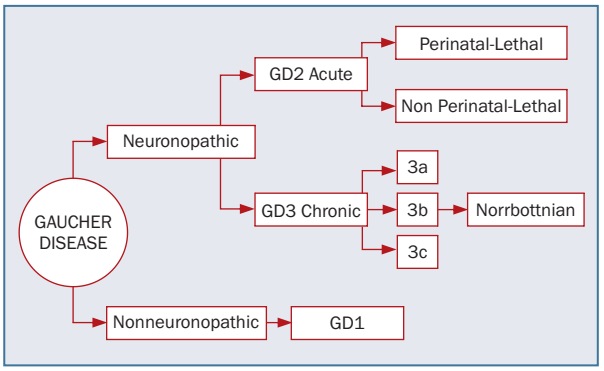

Figure 1. Schematic division of Gaucher disease

Type 1 (also known as GD1/non-neuronopathic) is the most common form. Its clinical presentation is diverse, ranging from asymptomatic throughout life to onset in childhood. Typical but nonspecific symptoms include hepatosplenomegaly causing abdominal enlargement and discomfort. The most commonly encountered symptoms in the course of GD are splenomegaly and thrombocytopenia, which is why this disease is often diagnosed by hematologists. Due to the abnormal number and activity of osteoblasts and osteoclasts, bone involvement occurs, including bone modeling disorders, fractures, and osteolytic changes. There are acute, painful bone crises, mainly in the pelvis and lower limbs [1, 5, 6]. It is generally believed that in this type of disease, there is no involvement of the nervous system [7]. However, in the last decade, there has been intensive research into a connection between GD1 and Parkinson's Disease (PD). Literature reports indicate that patients with GD1 exhibit a 26-fold increased risk of developing PD over their lifetime compared to the general population [8].

Type 2 (also known as GD2/acute neuronopathic) is rare and the most severe form, characterized by neurological changes in the fetal period or in the first months of life. There is no effective treatment for this form of GD. Patients typically die before the age of 3, most commonly due to prolonged spontaneous apnea. In the lethal perinatal form, there is generalized edema (hydrops fetalis), which can result in fetal demise *in utero*. The same visceral and hematological symptoms as seen in GD1 also occur. Additionally, there is progressive and aggressive neurodegenerative progression characterized by a triad of symptoms including body stiffness (opisthotonus), bulbar symptoms such as swallowing difficulties or laryngeal stridor, and oculomotor paralysis [1, 9, 10].

Type 3 (also known as GD3/subacute neuronopathic) is a combination of the visceral presentations of type 1 GD with the neurological features of type 2 GD. The first symptoms appear in childhood, usually before the age of 2, and less commonly may manifest in teenagers [11]. Involvement of the central nervous system can manifest as horizontal saccadic eye movements. This variant is often separated into three subtypes. Subtype 3a is characterized by mild visceral disease along with progressive neurological symptoms. It presents with oculomotor apraxia, progressive myoclonic epilepsy, and dementia. In subtype 3b, there is massive visceral disease, skeletal symptoms, and slow involvement of the nervous system. The main neurological symptom is horizontal supranuclear gaze palsy. Subtype 3c is an atypical and rare variant characterized by aortic and cardiac valve calcification [7, 8, 12]. The Norrbottnian type of GD occurs relatively frequently in the northern part of Sweden and affects about 40% of all known cases in the country. This is associated with the founder effect of the L444P mutation, which may have appeared in this area in the sixteenth century or earlier. The Norrbottnian subtype manifests with a wide range of neurological symptoms such as horizontal supranuclear gaze palsy, ataxia, spastic paralysis, cognitive dysfunction, and seizures. There are also hematological and visceral disturbances with significant hepatosplenomegaly and kyphoscoliosis [13, 14].

The gold standard diagnostic method for identifying GD is the detection of reduced activity of β-glucocerebrosidase in fresh blood leukocytes. Over the last decade, attention has been focused on the tandem mass spectrometry method for screening for lysosomal disorders to adapt it for efficient newborn screening [15, 16]. As a result of these efforts, a simplified and rapid screening method has been developed. It involves measuring the activity of β-glucocerebrosidase using dried blood spots (DBS) on filter paper [17]. In cases where reduced enzyme activity is detected, confirmation of the disease is necessary through the identification of characteristic mutations in the *GBA1* gene [4].

Treatment involves intravenous enzyme replacement therapy (ERT) using imiglucerase, velaglucerase, or taliglucerase. These preparations are recombinant forms of β-glucocerebrosidase administered via intravenous infusions. An alternative is oral substrate reduction therapy

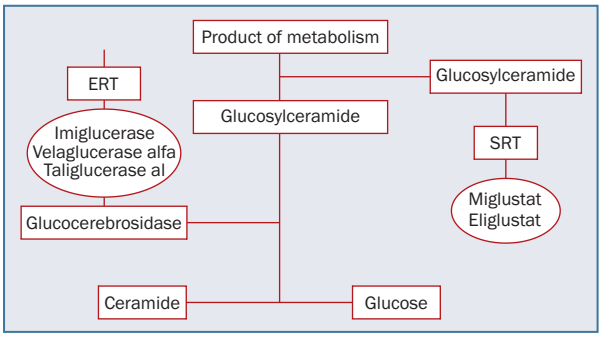

Figure 2. Available therapies for Gaucher disease. ERT — enzyme replacement therapy; SRT — substrate reduction therapy

(SRT), which relies on drugs that reduce the production of glucocerebroside (eliglustat and miglustat) (Fig. 2) [9, 10]. The emergence of new therapies has led to an increased demand for the identification of specific biomarkers to facilitate the diagnosis and monitoring of GD. As numerous studies have shown, glucosylsphingosine (lyso-Gb1) is currently the most promising and reliable marker for GD [18–20].

The aim of this review was to present the biomarker lyso-Gb1 and its utility in diagnosing, assessing severity, and monitoring the effectiveness of Gaucher disease therapy.

Hematological symptoms of Gaucher disease

Gaucher disease has traditionally included three main clinical types with various symptoms and course dynamics. However, in light of the latest data, it now seems probable that the mentioned phenotypes occur as a continuation of the disease process, rather than as separate entities [7, 21].

The storage of Gaucher cells in the bone marrow leads to hematopoiesis disorders, and therefore the disease may manifest itself in the form of cytopenias. Although the symptomatology is diverse, in each case (mostly in type 1), hematological symptoms may occur i.e. thrombocytopenia, anemia, leukopenia, as well as splenomegaly and hepatomegaly [5, 21, 22].

Isolated thrombocytopenia, being the most common cytopenia in the course of GD [19], can result from bone marrow infiltration or infarction, hypersplenism, platelet storage in the spleen, and autoimmunization against thrombocytes. Due to thrombocytopenia, impaired platelet function and reduced synthesis of coagulation factors, bleeding complications may occur [22, 23].

Anemia is a less common symptom of GD, and typically manifests as mild, normocytic, and coexisting with thrombocytopenia. The pathogenesis is usually multifactorial, and it may be similar to that of thrombocytopenia. This can result from bone marrow infiltration and hypersplenism, but may also be caused by vitamin B12 and iron deficiency. Hyperferritinemia, correlated with increased hepcidin levels, is also a common manifestation [6, 24].

Moreover, patients tend to develop malignant tumors more frequently than in the general population. Studies confirm a correlation between the occurrence of GD and multiple myeloma (MM), as well as monoclonal and polyclonal gammapathy. The presence of atypical Gaucher cells and pseudo-Gaucher in the bone marrow in patients with MM or other hematological diseases, without coexistent storage disease, may raise diagnostic doubts [25, 26]. A connection between Gaucher disease and the development of lymphomas, as well as non-hematological cancers i.e. hepatocellular carcinoma, pancreatic cancer, melanoma and lung cancer, is currently subject to a good deal of research [6, 25, 27, 28].

Established plasma markers of Gaucher disease

Biomarkers are various chemical molecules, including simple metabolites and complex proteins, which indicate the presence of a biological process associated with the symptoms of a specific disease [29]. They serve as useful clinical tools in diagnosing, monitoring progression and treating diseases, as well as in newborn screening programs for lysosomal disorders [29, 30].

An ideal biomarker should possess several characteristics confirming its clinical validity (Fig. 3). In the diagnosis and monitoring of Gaucher disease, several biomarkers are used: angiotensin-converting enzymes (ACE), ferritin, chitotriosidase (ChT) and chemokine CCL18/PARC (pulmonary and activation-regulated chemokine) [29, 31–34].

Angiotensin-converting enzyme (ACE) plays a crucial role in many physiological processes. This enzyme is involved in controlling blood pressure, vascular remodeling, and immune processes. In healthy people, ACE enters circulation mainly from the endothelium of pulmonary blood vessels and reaches very low concentrations. However, in cases of GD, ACE levels may be increased by 3–5 times. According to Danilov et al. [29], the increased level of ACE in the blood of patients originates from activated macrophages in the spleen and/or liver. It is worth noting that elevated levels of ACE in serum can accompany various diseases involving the activation of the monocyte/macrophage line, including: sarcoidosis, tuberculosis, berylliosis, and histoplasmosis [35]. Therefore, this enzyme is a nonspecific marker of GD with variable expression related to genetic polymorphism and the use of ACE inhibitors. Currently, ACE is not used in the diagnosis and monitoring of Gaucher disease, especially as a single biomarker [31].

Serum ferritin is the main marker of tissue iron overload. As reported in the literature, elevated serum ferritin concentration is a common phenomenon in previously

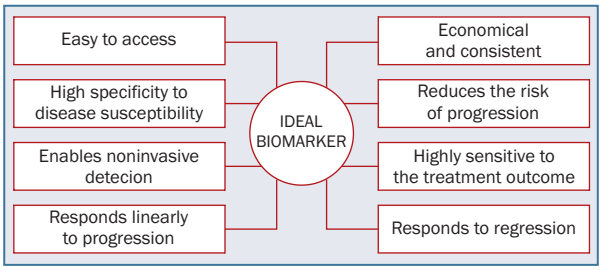

Figure 3. Features of ideal biomarker

untreated patients with GD. The first study describing hyperferritinemia in patients with GD was published in 1983 [36] and it paved the way for many other publications presenting ferritin level results in various cohorts worldwide [37–41]. Although hyperferritinemia occurs in the majority of patients with GD1, the increase in serum ferritin concentrations is secondary, and is driven by elevated levels of certain cytokines [42]. The chronic inflammatory state observed in GD, along with the excessive expression of IL-6, IL-10, and macrophage inflammatory proteins (MIPs), can lead to increased hepcidin synthesis, resulting in reduced plasma iron levels and elevated serum ferritin concentrations [31, 32]. As reported by Stein et al. [37], chitotriosidase and the chemokine CCL18 are significantly superior to ferritin. Those authors demonstrated that the correlation of ferritin with disease severity indicators was relatively weak compared to other biomarkers.

Chitotriosidase (ChT) is an enzyme produced and secreted by activated macrophages that phagocytose glycosphingolipids [43]. However, increased ChT activity is observed in various pathological conditions, and recently ChT has been proposed as a sensitive biomarker for active sarcoidosis [35]. Chitotriosidase is currently the most commonly measured biomarker for GD, and its activity allows for the assessment of disease severity. In patients with GD, ChT activity is c.1,000 times higher than normal values, and drastically decreases in response to ERT treatment [44]. However, the use of chitotriosidase as a marker for monitoring GD activity has specific limitations. Approximately 6% of the European population is homozygous and has a deficiency in chitotriosidase activity due to a mutation (24 bp duplication) in the *CHIT1* gene. Meanwhile, about one in three patients with heterozygous mutations show approximately half the activity of this enzyme [6, 43, 44].

Similar to the previous marker, serum concentrations of CCL18 in patients with GD are elevated 10–50 times above normal values. Therefore, in patients with chitotriosidase deficiency, this marker has been proposed as an alternative [45]. However, CCL18 levels are also high in other pathologies such as inflammatory conditions or cancer processes. Increased expression of CCL18 has been demonstrated in cancers such as esophageal squamous cell carcinoma, oral squamous cell carcinoma, ovarian cancer, and pancreatic cancer [46, 47]. The routinely used biomarkers ChT and CCL18 therefore do not reflect the pathophysiology of GD and are not specific to it. Taking into account that glucosylsphingosine is a deacylated form of glucocerebroside directly involved in the pathological pathway of GD, it has an advantage over other markers such as ChT and CCL18 [48].

Lyso-gb1 in diagnosis of Gaucher disease

In patients with Gaucher disease, the delay in making an accurate diagnosis can be as long as 10 years, often leading to the initiation of therapy at an advanced disease stage [42, 49]. Early diagnosis and prompt treatment are essential to prevent irreversible complications such as avascular necrosis [50]. There is a clear need for a sensitive and specific biomarker for GD diagnosis. Recently, lyso-Gb1, a downstream metabolite of glucosylceramide, has emerged as a promising such biomarker [20, 51–53].

Elevated concentrations of lyso-Gb1 were first described over 40 years ago by Raghavan et al. [54], who identified this product in the spleens of adult GD patients [54]. This discovery was confirmed by Nilsson and Svennerholm, who demonstrated elevated levels of lyso-Gb1 in the brain and cerebellum of five infants and young patients with the neuronopathic form of GD [55]. Over the years, it has been repeatedly suggested that elevated concentrations of lyso-Gb1 may underlie some neurological and skeletal symptoms [56, 57].

To test the potential of lyso-Gb1 in serum as a biomarker, Dekker et al. [51] prospectively recruited 64 GD patients, 34 carriers, and 28 healthy individuals as a control group. The authors demonstrated that patients with GD1 had an average 200-fold increase in plasma lyso-Gb1 levels compared to the control group. Lyso-Gb1 concentrations also correlated with established biomarkers ChT and CCL18. However, in patients homozygous for the 24 bp duplication in the *CHIT1* gene, plasma lyso-Gb1 concentrations showed a weaker correlation [51].

This study was confirmed by Rolfs et al. [53] who retrospectively analyzed non-Jewish Caucasian patients, showing elevated lyso-Gb1 concentrations >12 ng/ml in patients with Gaucher disease (GD), but not in healthy controls, GD carriers, or patients with other lysosomal storage disorders [52]. Another study also confirmed that lyso-Gb1 as a key diagnostic biomarker; however, the threshold value of 4 ng/ml, with 100% sensitivity and specificity, differentiated patients with GD from healthy individuals in the control group [53]. The LYSO-PROOF study, an international multicenter effort, further assessed lyso-Gb1 as a GD biomarker with predictive value for clinical severity. The study, involving 160 untreated GD patients from 22 research

centers, reported lyso-Gb1 concentrations ranging from 13 to 1,520 ng/ml. Statistically significant differences were observed between mild GD1 patients (mean = 167 ng/ml) and severe GD1 patients (mean = 320 ng/ml). These results confirmed lyso-Gb1's utility as a sensitive biomarker and its potential to predict disease severity in patients with unclear genotypes and clinical status [58]. Hurvitz et al. [18] explored the relationship between GD genotype and lyso-Gb1 concentrations in the pediatric population, observing significantly higher lyso-Gb1 levels in children with severe GD1 compared to those with mild GD1 [18]. The prevalence of GD in the pediatric population was highlighted in the recent GAU-PED study, which included 154 patients referred to a pediatric hematology department due to unexplained organomegaly and thrombocytopenia. Pession et al. [42] reported that GD was diagnosed and confirmed in 14/154 patients (9.09%). In this study, *GBA1* gene sequencing was performed in 16 patients with a positive enzymatic test result, confirming GD in 10 patients. In the remaining six patients, a wild-type *GBA1* gene sequence was found, with normal lyso-Gb1 concentrations and no symptoms, which posed a diagnostic challenge. Lyso-Gb1 was particularly useful in this subgroup of patients, as despite low β-glucosidase enzyme activity in DBS and enzymatic tests, GD diagnosis could not be confirmed, requiring more extensive diagnostics. This study demonstrates that lyso-Gb1, as a second-tier test combined with DBS analysis, is a valuable tool that enhances GD diagnostics [42].

Recently, monitoring lyso-Gb1 through the analysis of dried blood spots (DBS) on filter paper has become an important alternative for the rapid diagnosis of GD [59–61]. The advantages of this method include easy sample collection using capillary blood and the small volume of blood required [58, 59]. Both lyso-Gb1 concentrations and molecular analysis can be performed on the same small volume of a blood sample [58]. The diagnosis of GD based on lyso-Gb1 measurements combined with *GBA1* mutation analysis in DBS has been described as setting a new standard for screening patients [59, 62]. Rossi et al. reported a case of two siblings with hepatosplenomegaly and cytopenia, whose initial clinical presentation suggested a possible GD diagnosis. The diagnosis was confirmed using a screening protocol that included the measurement of β-glucocerebrosidase activity and lyso-Gb1 concentrations from the same DBS sample, along with molecular testing [63]. Moreover, lyso-Gb1 in DBS may be a promising screening tool in newborns, and may be beneficial in monitoring the course of the disease, with significantly higher plasma lyso-Gb1 concentrations detected in patients with neuronopathic forms of GD compared to non-neuronopathic GD patients [64]. However, as the latest guidelines indicate, further extensive studies are necessary to document the impact of transport and storage conditions on the sensitivity of lyso-Gb1 in DBS [65].

Lyso-gb1 in assessment of treatment response

Various studies on the utility of lyso-Gb1 as a sensitive and reliable biomarker of the response to treatment have been conducted. Making treatment decisions based on lyso-Gb1 is crucial, not only because of its role as a biomarker, but also due to its involvement in pathogenesis [20, 66].

Many authors have reported a rapid and significant reduction in lyso-Gb1 concentrations in plasma or cerebrospinal fluid following treatment with ERT or SRT, either alone or in combination [18, 19, 44, 53, 67, 68]. In a retrospective analysis from phase III clinical studies of GD1 patients treated with velaglucerase alpha, baseline plasma lyso-Gb1 concentrations decreased over time in both treatment-naïve patients (30.7% reduction from baseline to week 13) and those previously treated with imiglucerase (16.5% reduction). In this study, despite prior treatment with imiglucerase for at least two years, further reduction of lyso-Gb1 was achieved in the group of patients after switching to velaglucerase alpha. This demonstrated that dynamic changes in lyso-Gb1 allow for determining whether a patient is responding to treatment and can indicate the ineffectiveness of therapy before clinical consequences appear [67]. A study by Rossi et al. [63] proved reduction of the accumulated biomarker during the first ERT administrations, with its concentrations reaching stability after the first four treatments. Moreover, the platelet count improved gradually during therapy and a significant correlation of lyso-Gb1 concentrations and platelet count was found [63].

Arkadir et al. [19] also demonstrated that changes in lyso-Gb1 concentrations after the initiation of ERT preceded improvements in hematological parameters, including platelet count and spleen volume, and proved that it is a pharmacodynamic biomarker responsive to therapeutic intervention [19]. This was also confirmed by a study on the long-term efficacy and safety of taliglucerase alpha in a pediatric population with GD1, in which patients involuntarily interrupted treatment for about three months. As a result, the concentration of lyso-Gb1 more than doubled compared to the measurement before the interruption, while neither clinical symptoms nor hematological parameters changed. This also demonstrates that monitoring lyso-Gb1 allows for the detection of insufficient treatment before clinical consequences occur in the patient [69]. Studies on the impact of ERT treatment in pediatric GD patients were also conducted by Hurvitz et al. [18] In this study, the lyso-Gb1 concentration increased in eight children treated with ERT, which was linked to probable weight gain (>15%) and either a lack of dosage adjustment or non-adherence to recommendations. This highlights lyso-Gb1 as a potential tool for monitoring adherence to treatment guidelines in this age group [18].

Lyso-Gb1 concentrations can vary depending on the type of GD and the chosen treatment approach. A study by Smid et al. [44] compared the biochemical response in patients with GD1 to treatment with SRT (miglustat and eliglustat) and ERT. Lyso-Gb1 levels were similar in previously untreated patients who received eliglustat or ERT for two years, but the response to miglustat was lower [44]. In a multicenter pilot study evaluating the efficacy of an ambroxol addition in GD, the combination of ERT with ambroxol reduced the concentration of lyso-Gb1 in cerebrospinal fluid by 25.7% compared to baseline values in patients with the neuronopathic form of GD [70]. Recently, the measurement of lyso-Gb1 concentrations in cerebrospinal fluid has been used in numerous studies assessing the efficacy of this drug in patients with the neuronopathic form of GD [71–73]. A new report from the Brazilian Rare Disease Center reveals that the type of disease affects the post-treatment reduction of lyso-Gb1 concentrations. In the treated GD1 group, biomarker levels were significantly lower (m = 112 nmol/L) than in the treated GD3 group (m = 877 nmol/L) [74].

Lyso-gb1 in monitoring disease progress

Due to the significant variability in the clinical presentation of GD, guidelines for assessing disease burden pose a challenge. Monitoring disease progression in GD patients includes indirect markers such as liver/spleen size, platelet count, and radiological imaging of the skeletal system [75]. It has been shown that lyso-Gb1 concentrations are associated with disease severity in patients with GD [51, 52]. The pathophysiological role of lyso-Gb1 in GD was demonstrated in a study by Lukas et al. [76], where mice received subcutaneous lyso-Gb1 for 12 weeks. After four weeks of treatment, lyso-Gb1 accumulated in all major tissues of the mice, and lyso-Gb1 concentrations in the blood increased to over 500 ng/ml. After eight weeks of treatment, the mice developed hematological and visceral symptoms, including a decrease in hemoglobin and hematocrit levels and an increase in spleen size [76].

It has been demonstrated that lyso-Gb1 concentrations correlate with improvements in disease parameters, including liver volume, spleen volume, hemoglobin and platelet counts [18, 19, 67, 77, 78]. In a retrospective analysis of phase III clinical trials involving patients with GD1 treated with velaglucerase alpha, the lyso-Gb1 concentration in treatment-naïve patients was significantly correlated with an increase in platelet count and a decrease in spleen volume [67]. Furthermore, a retrospective analysis of 25 patients with GD who received ERT confirmed that changes in lyso-Gb1 concentrations precede splenomegaly and thrombocytopenia, allowing for the prediction of treatment response [19]. In a multicenter, observational cohort study involving 20 Japanese patients with GD treated with velaglucerase alpha, the relationship between lyso-Gb1 and the achievement of all therapeutic goals (improvement in hepatomegaly, splenomegaly, anemia, thrombocytopenia, bone pain, and bone crisis) was assessed. It was shown that low plasma lyso-Gb1 concentration correlates with a higher therapeutic success rate, highlighting the significant role of this biomarker in evaluating treatment response [77]. In another study, the results of eight years of treatment with eliglustat in treatment-naïve adults with GD1 were presented. They showed a change in lumbar spine T-scores from the osteopenic range to normal as plasma lyso-Gb1 concentrations decreased [68]. In addition, a study conducted by Vernet et al. [74] analyzed the relation between lyso-Gb1 level and the concentration of other Gaucher disease markers in a group of 32 patients, 29 treated with GD and three untreated. The research showed a positive correlation with ChT and immunoglobulin concentration, and negative correlation with patient age among the group of 29 treated patients. The authors suggest that the connection between Ig and lyso-Gb1 concentrations might correspond with the risk of development of MM or monoclonal gammopathy of undetermined significance (MGUS), and especially that hypergammaglobulinemia in the course of GD might be due to chronic B lymphocyte stimulation by lyso-Gb1 [74].

It has been found that plasma lyso-Gb1 reflects the severity of individual genetic variants. Hurvitz et al. [18] demonstrated significantly lower lyso-Gb1 concentrations in children with the mild form of GD1 (N370S homozygotes mutations) compared to those with the severe form of GD1 (N370S heterozygotes mutations), consistent with the relationship between genotype and lyso-Gb1 concentrations observed in adults [18, 51–53]. Rolf et al. [52] demonstrated higher plasma lyso-Gb1 concentrations (median, 185 ng/mL) in patients with the L444P mutation, which is associated with a severe form of the disease, compared to patients with the milder N370S mutation (median, 143 ng/mL) [52].

Conclusions

GD is a rare, lysosomal storage disease characterized by high phenotypic and genotypic variability. Its broad clinical spectrum makes diagnosis and treatment challenging. Biomarkers play a crucial role in diagnosing, monitoring disease progression and assessing treatment response. Older GD biomarkers have low specificity and may be subject to polymorphic changes. Numerous studies have shown that lyso-Gb1 is a selective and sensitive biomarker, directly involved in the disease's pathophysiology. Elevated lyso-Gb1 concentrations early in life enable the use of glucosylsphingosine assays with DBS in newborn screening programs and prenatal settings. The important role of lyso-Gb1 in guiding therapeutic decisions, including treatment initiation and monitoring response, has also been demonstrated. However, it is necessary to define a specific

cut-off value for lyso-Gb1 concentrations as an absolute indication for initiating therapy. Equally, standardization of the units of measurement for lyso-Gb1 is required across all laboratories, because currently concentrations can be expressed in either ng/mL or nmol/L. Dynamic changes in this biomarker offer the potential to monitor adherence during pharmacotherapy in pediatric GD patients.

Numerous correlations between lyso-Gb1 concentrations and disease burden and clinical severity have been described in the literature, confirming the role of lyso-Gb1 as a prognostic marker predicting disease course before the onset of clinical symptoms. This marker may also help clinicians optimize individualized dosing regimens, supporting a personalized medicine approach.

Article information and declarations

Authors' contributions

All authors discussed results, developed/performed experiments/calculations/simulations, analysed data, wrote manuscript, contributed to final version of manuscript, and supervised project.

Funding

The authors did not receive support from any organization for the submitted work. No funding was received to assist with the preparation of this manuscript. No funding was received for conducting this study.

Acknowledgments

None.

Conflicts of interest

The authors certify that they have NO affiliations with, or involvement in, any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaux; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or in materials discussed in this manuscript.

Supplementary material

None.

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