Review article

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Diagnosis and Management of Gaucher Disease: Current Approaches and Emerging Perspectives

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Gaucher disease, the most common lysosomal storage disorder, is caused by autosomal recessive pathogenic variants in the *GBA1* gene, resulting in deficient glucocerebrosidase activity and multisystem involvement. Clinical manifestations range from non-neuronopathic disease to acute and chronic neuronopathic forms, affecting hematologic, visceral, skeletal, and neurological systems. This review provides an updated, evidence-based overview of Gaucher disease, emphasizing diagnostic strategies, genotyping, clinical spectrum, and therapeutic approaches, with the aim of promoting early recognition and precision-guided management. Diagnosis is based on demonstration of reduced enzyme activity and confirmation by *GBA1* genotyping, while disease-specific biomarkers such as Lyso-Gb1 improve diagnostic accuracy, prognostic assessment, and treatment monitoring. Non-neuronopathic disease typically presents with splenomegaly, hepatomegaly, cytopenias, and skeletal involvement, whereas neuronopathic forms are characterized by progressive neurological deterioration. Genotype–

phenotype correlations assist in predicting disease severity, assessing the risk of neurological involvement, and guiding genetic counseling. Disease-modifying therapies, including enzyme replacement therapy and substrate reduction therapy, have significantly improved visceral, hematologic, and skeletal outcomes, although neurological manifestations remain largely refractory. Emerging gene-based therapeutic strategies aim to restore glucocerebrosidase activity and address unmet clinical needs. A structured approach integrating clinical assessment, biochemical testing, molecular analysis, and individualized therapy is essential to optimize outcomes, as early diagnosis and timely treatment prevent irreversible complications.

Keywords: Gaucher disease; biomarkers; enzyme replacement therapy; substrate reduction therapy; gene therapy

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Dijagnoza i lečenje Gošeove bolesti: trenutni pristupi i nove perspektive

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Gošeova bolest, najčešća lizozomska bolest skladištenja, uzrokovana je autozomno recesivnim patogenim varijantama u genu *GBA1*, koje dovode do smanjene aktivnosti glukocerebrozidaze i multisistemskog zahvatanja organa. Kliničke manifestacije variraju od neneuronopatskog oblika do akutnih i hroničnih neuronopatskih formi, pri čemu mogu biti zahvaćeni hematološki, visceralni, skeletni i neurološki sistemi. Ovaj pregledni rad pruža ažuran, na dokazima zasnovan prikaz Gošeove bolesti, sa posebnim naglaskom na dijagnostičke strategije, genotipizaciju, klinički spektar i terapijske pristupe, sa ciljem unapređenja ranog prepoznavanja i precizno usmerenog lečenja. Dijagnoza se zasniva na dokazivanju smanjene aktivnosti enzima i potvrđuje genetičkim ispitivanjem gena *GBA1*, dok specifični biomarkeri, poput Lyso-Gb1, unapređuju dijagnostičku tačnost, prognostičku procenu i praćenje terapijskog odgovora. Neneuronopatski oblik bolesti se najčešće manifestuje splenomegalijom, hepatomegalijom, citopenijama i skeletnim promenama, dok neuronopatske forme karakteriše progresivno neurološko propadanje. Korelacije između genotipa i fenotipa omogućavaju predviđanje težine bolesti, procenu rizika za neurološko zahvatanje i pružanje adekvatnog genetičkog savetovanja.

Terapije koje modifikuju tok bolesti, uključujući supstitucionu enzimsku terapiju i terapiju redukcije supstrata, značajno su poboljšale visceralne, hematološke i skeletne ishode, dok neurološke manifestacije i dalje ostaju uglavnom refraktorne. Novi genski terapijski pristupi imaju za cilj obnovu aktivnosti glukocerebrozidaze i prevazilaženje postojećih terapijskih ograničenja. Strukturisan pristup koji integriše kliničku procenu, biohemijska ispitivanja, molekularnu analizu i individualizovano lečenje od suštinskog je značaja za optimizaciju ishoda, jer rano postavljanje dijagnoze i pravovremeno započinjanje terapije sprečavaju nastanak ireverzibilnih komplikacija.

Ključne reči: Gošeova bolest; biomarkeri; supstituciona enzimska terapija; terapija redukcije supstrata; genska terapija

Introduction

Gaucher disease (GD) is the most common sphingolipidosis and a prototypical lysosomal storage disorder, characterized by marked clinical heterogeneity and frequent diagnostic delay. It is caused by autosomal recessive pathogenic variants in the *GBA1* gene, resulting in deficient lysosomal glucocerebrosidase activity and progressive accumulation of glucosylceramide within macrophages. This leads to multisystem involvement, predominantly affecting the hematologic, skeletal, hepatic, and pulmonary systems (1,2). Although GD is rare, with an estimated incidence of 0.39–5.8 per 100,000 live births, its prevalence is markedly higher among individuals of Ashkenazi Jewish ancestry (≈1:350–450) (1,2).

Clinically, GD is classified based on neurological involvement. Type 1 GD, the most prevalent form, lacks primary central nervous system involvement, whereas types 2 and 3 represent acute and chronic neuronopathic forms with poorer prognoses (1–3). While certain *GBA1* variants are associated with specific phenotypes, substantial intra- and interfamilial variability limits reliable genotype–phenotype prediction (4–6).

Despite well-characterized molecular mechanisms and the availability of disease-specific biomarkers, early diagnosis remains challenging due to non-specific initial manifestations such as cytopenias, organomegaly, and skeletal symptoms (1,6–10). Importantly, GD is a rare genetic disorder for which effective disease-modifying therapies are available. Enzyme replacement and substrate reduction therapies have transformed outcomes in non-neuronopathic GD, enabling near-normal life expectancy when initiated early; however, neurological disease remains largely unresponsive to current treatments (1–5).

GD remains underdiagnosed despite available disease-modifying therapies, largely due to its heterogeneous and often subtle clinical manifestations. Increased clinician awareness, systematic inclusion in differential diagnoses, and the use of targeted biomarkers are essential to reduce diagnostic delays. This review provides an updated, evidence-based synthesis of GD, emphasizing diagnosis, genotyping, clinical spectrum, and therapeutic strategies, including enzyme replacement, substrate reduction, and emerging gene therapies. Its goal is to enhance clinician awareness, highlight key diagnostic considerations, and promote early recognition and precision-guided management, ultimately supporting improved long-term outcomes in patients with this rare metabolic disorder.

Clinical presentation

Type 1 Gaucher disease (GD1) accounts for approximately 90–95% of cases and is defined by the absence of primary neurological involvement (11). Clinical presentations are highly heterogeneous. Splenomegaly (>90%) and hepatomegaly (60–80%) are the most common findings, frequently accompanied by cytopenias, particularly thrombocytopenia and anemia (2,3,6). Skeletal involvement ranges from osteopenia to severe bone crises and osteonecrosis, often contributing substantially to morbidity (3). Additional features include fatigue, growth delay in children, and pubertal delay (6). Patients with GD1 have an increased risk of Parkinsonism and certain hematologic malignancies, while biochemical abnormalities such as hyperferritinemia and gammopathies are common (11,12). Genotype influences disease expression, with the N409S variant strongly associated with non-neuronopathic disease. With timely therapy, life expectancy is generally normal.

Type 2 Gaucher disease (GD2) is a rare (<1%), acute neuronopathic form with onset in infancy and rapid neurological deterioration, leading to early mortality, usually before three years of age (13–15). Neurological manifestations include bulbar dysfunction, oculomotor abnormalities, opisthotonos, and refractory seizures, while visceral involvement such as hepatosplenomegaly and thrombocytopenia is typically severe. Type 3 Gaucher disease (GD3), accounting for approximately 5% of cases, presents chronic and progressive neurological involvement, including oculomotor abnormalities, ataxia, seizures, and cognitive impairment, alongside visceral and skeletal manifestations like GD1. Clinical severity and survival are highly variable, with some patients reaching adulthood (15–17).

Diagnosis of Gaucher disease

Gaucher disease is confirmed by demonstrating reduced glucocerebrosidase (GCase) activity and/or biallelic pathogenic *GBA1* variants. Enzymatic testing in leukocytes or fibroblasts (≤15% of normal) is diagnostic, while dried blood spots (DBS) serve primarily for screening and require confirmatory analysis (10,11). Glucosylsphingosine (Lyso-Gb1) is a highly sensitive and specific biomarker for screening and monitoring, outperforming traditional markers such as chitotriosidase (10,18). Molecular analysis supports definitive diagnosis, genotype–phenotype correlations, and prognostic assessment. Ancillary assays may refine diagnosis but are not routine, and bone marrow biopsy is reserved for excluding alternative hematologic conditions. Prenatal testing is feasible in

families with known variants, while laboratory testing and imaging studies complement but do not replace enzymatic or genetic confirmation (6,11).

Genotyping of GBA1

Molecular analysis of *GBA1* is essential for confirming Gaucher disease, informing prognosis, guiding therapy, and supporting genetic counseling. Genotyping is recommended after biochemical confirmation, typically starting with targeted PCR for common pathogenic variants, followed by comprehensive sequencing to detect rare variants or variants of uncertain significance (VUS) (2,3,11). Over 500 *GBA1* variants are reported, with genotype–phenotype correlations aiding prediction of neurological involvement and disease severity (6,11). The c.1226A>G (N409S) variant predicts non-neuronopathic GD1, whereas homozygous c.1448T>C (L444P) or biallelic null variants are linked to acute or severe chronic neuronopathic disease (5,6). Population-specific distributions are recognized, notably in Ashkenazi Jewish individuals. Contemporary methods include Sanger sequencing, next-generation sequencing, RNA-based and multiplex ligation-dependent probe amplification approaches. Cascade testing of family members and prenatal or preimplantation genetic counseling are recommended for families with known pathogenic variants (5,6,9,11).

Biomarkers

In Gaucher disease, glucosylsphingosine, chitotriosidase, and CCL18 are the most clinically useful biomarkers, reflecting Gaucher cell burden and informing diagnosis, disease severity, and therapeutic response, though they do not replace enzymatic or genetic confirmation. Lyso-Gb1 is highly disease-specific, with plasma levels ~100-fold higher in affected individuals, correlating with thrombocytopenia, hepatomegaly, and skeletal involvement, and declining with effective therapy (18–21). Chitotriosidase serves as a surrogate marker of Gaucher cell mass but is limited by CHIT1 gene polymorphisms and elevations in other lysosomal or inflammatory disorders (22,23). CCL18 provides a complementary measure, unaffected by genetic variation but also elevated in chronic inflammation (23,24). Integrating biomarker data with clinical, imaging, and molecular results is recommended, and standardization across centers is essential for multicenter studies and phenotypic stratification (18,19,23,24).

Laboratory findings

Laboratory tests provide supportive information on disease burden and systemic complications in Gaucher disease but are not diagnostic alone. Hematologic abnormalities are common, with thrombocytopenia in ~90% of patients, anemia in 30–50%, and leukopenia uncommon; cytopenias arise from hypersplenism and marrow infiltration by lipid-laden macrophages (24–26). Bone marrow examination is rarely required, reserved for excluding alternative hematologic disorders, as Gaucher cells may resemble pseudo-Gaucher cells (27). Coagulation abnormalities, hyperferritinemia, polyclonal hypergammaglobulinemia, mild cholestasis, low HDL cholesterol, and vitamin D deficiency are frequent and warrant monitoring (24–30). Prenatal or preimplantation diagnosis is feasible in at-risk families following identification of pathogenic variants. Laboratory parameters aid in disease characterization, severity assessment, and therapy monitoring but must be interpreted alongside enzymatic, genetic, and clinical data (9,24,25).

Radiological imaging

Radiological imaging is essential for evaluating organ involvement, disease burden, and complications in Gaucher disease, primarily for baseline assessment and longitudinal monitoring rather than diagnostic confirmation. Bone MRI is the reference standard for skeletal evaluation, allowing detection of marrow infiltration, edema, osteonecrosis, cortical thinning, lytic lesions, and structural sequelae, including metaphyseal–diaphyseal widening ("Erlenmeyer flask" deformity), while whole-body MRI enables concurrent assessment of skeletal and visceral involvement (25,31–34). Conventional radiography is reserved for symptomatic complications, and DEXA is recommended for monitoring bone mineral density (33,34). Abdominal MRI allows reproducible liver and spleen volumetrics and identification of focal splenic nodules ("gaucheromas") (25,35). When MRI is unavailable or contraindicated, abdominal ultrasound is an acceptable alternative (25). Imaging complements laboratory, enzymatic, and genetic assessments to guide management.

Differential diagnostic approach

Early recognition of Gaucher disease is facilitated by structured diagnostic frameworks integrating clinical features and risk factors. A Delphi consensus highlights enzymatic and genetic testing in individuals with unexplained splenomegaly, cytopenias, or other suggestive findings (36), while the Gaucher Earlier Diagnosis Consensus (GED-C) scoring system has demonstrated utility as a

case-finding tool in real-world settings (37). A systematic approach is essential given the disease's clinical heterogeneity and overlap with other inherited and acquired conditions. Hepatosplenomegaly, cytopenias, and skeletal involvement are shared features of several lysosomal storage disorders and metabolic diseases, including acid sphingomyelinase deficiency (Niemann–Pick disease type A/B) and Niemann–Pick type C (24,25,38). Ultra-rare disorders such as saposin C deficiency and Fabry disease may mimic Gaucher disease, while hematologic malignancies can further complicate diagnosis (39–41). In adults, neurological presentations may overlap with Parkinson's disease due to GBA1-associated risk (42). Integration of clinical evaluation, enzymatic assays, disease-specific biomarkers (Lyso-Gb1), imaging, and molecular analysis is therefore critical for accurate diagnosis and management (24,25).

Therapeutic strategies

Treatment of Gaucher disease has progressed from supportive care to disease-specific interventions targeting the underlying lysosomal defect. Goals include symptom relief, prevention of irreversible organ damage, and improvement of long-term quality of life, with therapy tailored to disease subtype, severity, organ involvement, and patient-specific factors (6,43). Enzyme replacement therapy (ERT) remains the first-line disease-modifying approach, restoring β-glucocerebrosidase activity and reducing glucosylceramide accumulation. Substrate reduction therapy (SRT) offers an oral alternative for selected patients, including those unsuitable for ERT (44,45). Early initiation is critical to prevent skeletal, visceral, and hematologic complications, while long-term monitoring ensures efficacy, dose optimization, and detection of disease progression or adverse effects, supporting individualized, outcome-driven care (46).

Enzyme replacement therapy

Enzyme replacement therapy is the cornerstone of disease-specific management for Gaucher disease and the first-line treatment for non-neuronopathic forms. ERT involves intravenous administration of recombinant β-glucocerebrosidase, internalized by macrophages via mannose receptors and delivered to lysosomes, promoting degradation of accumulated glucosylceramide and improving systemic manifestations (47). Approved ERT products—imiglucerase, velaglucerase alfa, and taliglucerase alfa—demonstrate comparable efficacy and favorable safety across clinical trials and real-world studies (48–50).

ERT produces sustained improvements in hepatosplenomegaly, hematologic abnormalities, skeletal involvement, and health-related quality of life in type 1 GD (47,48). Long-term registry data show reductions in skeletal morbidity, with bone pain prevalence declining from ~49% to 30% after one year, alongside fewer bone crises during follow-up (48). Early initiation further lowers the risk of irreversible skeletal complications, including avascular necrosis and progressive marrow infiltration (51,52). Prolonged therapy improves bone mineral density, particularly in children and young adults, and reduces osteoporosis prevalence in treated populations (53).

Limitations of ERT include lifelong intravenous administration, high cost, and occasional anti-drug antibody development. Critically, ERT does not cross the blood–brain barrier, limiting efficacy in neuronopathic GD (54–56). Nevertheless, it remains the standard of care for systemic disease, providing durable clinical benefit across diverse patient populations (48–50). Ongoing research seeks improved formulations and alternative delivery systems, alongside biomarker-guided monitoring, to optimize dosing, assess response, and enhance long-term outcomes.

Substrate reduction therapy

Substrate reduction therapy provides an effective oral alternative to enzyme replacement therapy for type 1 Gaucher disease by inhibiting glucosylceramide synthase (GCS), reducing glucocerebroside biosynthesis, and rebalancing substrate production with residual lysosomal GCase activity (57,58). Oral SRT agents, including miglustat and eliglustat, improve systemic manifestations such as anemia, thrombocytopenia, and organomegaly (59,60).

Miglustat, a reversible and non-specific GCS inhibitor capable of crossing the blood–brain barrier, is generally reserved for patient's intolerant to ERT due to modest efficacy and frequent gastrointestinal and neurological adverse effects (61,62). Eliglustat, a potent and selective ceramide analogue, demonstrates efficacy comparable to ERT, stabilizing hematologic parameters, organ volumes, and quality of life in both treatment-naïve (ENGAGE) and ERT-stabilized (ENCORE) patients (59,63). SRT also improves bone mineral density and reduces biomarkers such as chitotriosidase, though it does not address neuronopathic complications (58,61).

Limitations include incomplete efficacy in neuropathic GD, potential drug–drug interactions, and CYP2D6 genotype-guided dosing for eliglustat to ensure optimal pharmacokinetics and safety. Ongoing research focuses on the development of next-generation GCS inhibitors with improved selectivity and enhanced blood–brain barrier penetration, as well as personalized therapeutic strategies integrating pharmacogenomic profiling and biomarker-guided monitoring. Overall, SRT represents a convenient and effective disease-modifying oral therapy for selected adults with type 1 GD, particularly for those unable or unwilling to receive ERT.

Pharmacological chaperone therapy

Pharmacological chaperone therapy is a mutation-specific, mechanism-based approach for Gaucher disease that stabilizes misfolded β-glucocerebrosidase, enhances lysosomal trafficking, and increases residual enzymatic activity (64,65). Unlike enzyme replacement or substrate reduction therapies, chaperones augment endogenous enzyme function, reducing intracellular glucosylceramide and glucosylsphingosine accumulation (66).

Early proof-of-concept was provided by N-octyl-β-valienamine, which increased GCase activity in cells with the F213I mutation (67). Ambroxol, an orally bioavailable mucolytic repurposed as a chaperone, demonstrates mutation-dependent efficacy, significantly enhancing GCase activity in cells carrying L444P/L444P, RecΔ55, RecNciI, and L444P/D409H genotypes, with limited effect in others mutational contexts (65). Clinically, high-dose ambroxol has improved hematologic and visceral parameters in GD1, including increases in hemoglobin and platelet counts, reductions in spleen volume, and improvements in liver function, with reported benefits for skeletal manifestations, particularly in pediatric patients (68).

Ongoing trials (NCT01463215, NCT03950050, NCT04388969) confirm dose-dependent increases in GCase activity and reductions in cerebrospinal fluid glucosylsphingosine, demonstrating CNS penetration (66). Pharmacological chaperones are generally well tolerated, with mild gastrointestinal symptoms being the most common adverse events. Although their applicability is limited by mutation-specific responsiveness and incomplete coverage of all genotypes, chaperones represent a promising adjunctive or alternative strategy for selected patients, particularly those with neuronopathic involvement or inadequate response to standard therapies (64,69).

Gene therapy

Gene therapy represents a potentially transformative, disease-modifying strategy for Gaucher disease by directly correcting the underlying GBA1 defect and restoring lysosomal β-glucocerebrosidase activity. Current approaches include in vivo and ex vivo strategies. In vivo therapy primarily uses systemic adeno-associated viral (AAV) vectors, which efficiently transduce target tissues and, with selected serotypes, may cross the blood–brain barrier, offering potential benefit for neuronopathic disease. Ex vivo approaches involve lentiviral modification of patient-derived hematopoietic stem cells followed by autologous transplantation, enabling sustained systemic GCase expression (70).

FLT201, the first AAV-based candidate for GD1, encodes an engineered GCase variant (GCase85) with enhanced intracellular stability, delivered via a liver-selective AAVS3 capsid. Preclinical studies demonstrated durable GCase activity and effective glucosylceramide clearance across liver, spleen, bone marrow, and lungs, exceeding outcomes with enzyme replacement therapy (71). Early clinical data from the phase 1/2 GALILEO-1 trial showed that a single intravenous dose in adults previously treated with ERT or SRT resulted in sustained Lyso-Gb1 reductions, normalization of hemoglobin, stabilization of platelet counts, and maintenance of organ volumes for up to 21 months without ongoing therapy (72). The ongoing phase 3 GALILEO-3 trial is evaluating safety and efficacy in adults transitioned from stable ERT or SRT, including hematologic stability, biomarker reduction, organ volumes, and patient-reported outcomes (73).

CNS-directed preclinical strategies using dual AAV9 vectors delivering GBA1 with neurotrophic factors improved survival, motor function, and neuropathology in neuronopathic models, addressing key limitations of current therapies (74). While long-term safety, durability, and immunogenicity require further study, gene therapy holds promise as a one-time intervention capable of delivering sustained systemic—and potentially neurological—benefit in Gaucher disease.

Prognosis and long-term outcomes

The prognosis of Gaucher disease depends on disease subtype, age at diagnosis, and timing of therapeutic intervention. In non-neuronopathic GD1, early initiation of enzyme replacement or

substrate reduction therapy has markedly improved survival, allowing most patients to achieve near-normal life expectancy. Long-term registry data demonstrate sustained normalization of hematologic parameters, reduction of organomegaly, and stabilization of skeletal disease, including in patients switching therapies. Outcomes are optimal when treatment precedes irreversible damage, although residual skeletal complications and comorbidities may persist (75,76). In contrast, neuronopathic GD2 and GD3 are associated with poorer outcomes due to progressive central nervous system involvement, which remains largely unresponsive to current therapies. Emerging therapeutic strategies, including pharmacological chaperones and gene-directed therapies, are currently under investigation to address central nervous system pathology and improve outcomes in neuronopathic disease (77).

Limitations of the study

This review has several limitations. The available evidence is largely focused on non-neuronopathic Gaucher disease (GD1), which limits extrapolation to neuronopathic forms (GD2 and GD3). Long-term outcomes are primarily derived from observational registries and single-arm studies, making them vulnerable to selection and reporting bias. Furthermore, variability in imaging methodologies, biomarker assessments, and clinical endpoints hampers direct comparison across studies.

Evidence regarding emerging therapeutic approaches, including pharmacological chaperones and gene-based therapies, remains preliminary, precluding firm conclusions on long-term efficacy and safety. Finally, publication bias toward positive findings may result in an overestimation of treatment benefits. Well-designed randomized and multicenter studies are needed to validate long-term outcomes, harmonize outcome measures, and optimize individualized management across all Gaucher disease subtypes.

Conclusions

Gaucher disease illustrates both the substantial therapeutic advances and the ongoing challenges characteristic of rare metabolic disorders. Despite well-defined molecular mechanisms and the availability of effective disease-modifying therapies, diagnosis is often delayed due to heterogeneous and frequently subtle clinical manifestations. Early recognition is therefore critical to prevent irreversible organ damage and improve long-term outcomes. Enhanced clinician awareness,

systematic inclusion of Gaucher disease in relevant differential diagnoses, and broader access to disease-specific biomarkers are key strategies to reduce diagnostic delay.

Enzyme replacement therapy remains the standard of care for non-neuronopathic Gaucher disease, while substrate reduction therapy offers an effective oral alternative for selected patients. Emerging approaches, including pharmacological chaperones and gene-based therapies, aim to broaden therapeutic options and address neurological involvement; however, challenges related to blood–brain barrier penetration, long-term efficacy, and equitable access remain. These developments highlight the need to integrate advancing scientific knowledge into structured clinical care pathways.

Future progress will depend on improved phenotypic stratification, standardized and predictive biomarkers, and the generation of robust long-term data through international collaboration. Coordinated efforts within expert networks, such as the International Working Group on Gaucher Disease, are essential for harmonizing clinical practice and guiding research priorities. Ultimately, sustained innovation, increased clinical awareness, and longitudinal follow-up are crucial to ensure optimal outcomes and quality of life for patients with Gaucher disease.

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