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Gaucher's Disease – current state of knowledge and future perspectives?

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Abstract

Introduction and purpose: Gaucher's Disease (GD), a rare genetic disorder, is a difficult challenge in genetic and metabolic disorders. The aim of this review is to provide an exploration of GD, spanning its pathophysiology to the latest advancements in diagnostic and therapeutic innovations. In this review we aimed to underscore the challenges it presents and the ongoing efforts to overcome them.

State of knowledge: GD, characterized by the accumulation of glucocerebroside, involves molecular, cellular, and systemic dysfunctions. At the molecular level, mutations in the GBA gene give rise to diverse manifestations, influencing disease severity. Cellular disruptions lead to lysosomal dysfunction, altered calcium homeostasis, and chronic inflammation, impacting various organ systems. Diagnostic approaches involve biomarkers, genetic testing, and imaging studies, each playing a crucial role in confirming the disease type and assessing its grade.

Summary: Management and treatment strategies for GD have evolved, with enzyme replacement therapy and substrate reduction therapy serving as the basics. However, challenges persist, including limited efficacy in treating neurological symptoms and the high cost of treatments. The review highlights ongoing research and future perspectives in GD therapy.

Keywords: Gaucher's Disease; lysosomal storage disorder; glucocerebrosidase; enzyme replacement therapy; substrate reduction therapy

1. Introduction

Gaucher's Disease (GD) was first described by the French physician Philippe Gaucher in 1882. Gaucher, in his observations, initially mistook the peculiar cellular pathology in a patient's spleen for cancer (1) (2). It wasn't until several decades later that the enzymatic deficiency underlying the condition was explained, marking a groundbreaking moment in the field of metabolic disorders. This discovery not only enhanced our understanding of GD but also served as a cornerstone for the broader domain of lysosomal storage diseases, converging in the fields of genetics, biochemistry, and clinical medicine (2). The aim of this review is to demonstrate the wide range of aspects related to GD, from its pathophysiological roots to the latest in diagnostic and therapeutic innovations.

2. Pathophysiology

Gaucher's disease is a rare and inherited metabolic disorder characterised by the accumulation of glucocerebroside in various organs and tissues, leading to a range of clinical manifestations (3). The pathophysiology of GD can be described into several key aspects, including the molecular, cellular, and systemic levels.

2.1 Molecular level

GD is an autosomal recessive genetic disorder caused by mutations in the GBA gene located on chromosome 1q21. The gene encodes the enzyme glucocerebrosidase (GCCase), which is essential for the breakdown of glucocerebroside, a lipid present in cell membranes (4). More than 300 mutations in the GBA gene have been identified, resulting in GD. These mutations vary from single nucleotide point mutations to larger sequence deletions or insertions (5). The severity of the disease and the specific type of GD (Type 1, 2, or 3) are determined by the nature of these mutations. N370S is commonly associated with Type 1 GD and is characterised by the absence of neurological symptoms. On the other hand, the L444P mutation is more commonly linked with the neuronopathic forms of the disease, Types 2 and 3 (6).

Although individuals may have the same genetic mutation, the severity and specific symptoms of GD can vary widely. This suggests that other genetic, environmental, or possibly epigenetic factors may influence disease expression. (7) Therefore, predicting disease severity based only on genetic information is complex, and the correlation between genotype and phenotype is not absolute (8).

2.2 Cellular level

Gaucher disease is characterised by a number of cellular abnormalities that significantly affect cellular function. The main issue is the accumulation of glucocerebroside in lysosomes due to a deficiency of the enzyme GCCase. These overloaded lysosomes become dysfunctional, leading to characteristic cellular changes, impaired calcium homeostasis and lysosomal dysfunction (9).

Impaired autophagy, caused by disrupted signalling pathways, further exacerbates the problem. Damaged organelles and cellular debris are not removed, leading to the accumulation of additional waste in the cytoplasm and overloading of lysosomes (10). The accumulation of waste becomes a stimulus for the inflammatory response, activating immune cells and exacerbating the systemic symptoms of GD (11).

Disturbances in calcium homeostasis are also a key element of the pathomechanism. Alterations in calcium channels and transporters lead to abnormal calcium release, causing endoplasmic reticulum stress and affecting signalling cascades. Lysosomal dysfunction associated with disturbances in calcium dynamics affects macrophages and contributes to the formation of Gaucher cells (12) (13) (14).

Chronic inflammation is an important factor of GD in cells. The interaction between accumulated lipids and immune cells triggers the release of inflammatory mediators, including cytokines and chemokines. Elevated proinflammatory cytokines, such as TNF- α and IL-6, are characteristic (15). TNF- α serves as a central mediator in the inflammatory cascade, activating transcription factors like NF- κ B and inducing additional proinflammatory cytokines and adhesion molecules (16) (17). Apart from the local tissue damage, chronic inflammatory state causes systemic manifestations, contributing to the multisystemic nature of GD, and impacting overall immune system function (18).

2.3 Systemic level

At the systemic level, GD impacts various organ systems. The aberration at the molecular and cellular levels, marked by deficient GCCase activity, sets the stage for a cascade of effects throughout the body (1).

The accumulation of Gaucher cells in the bone marrow significantly disrupts the body's normal production of blood cells, leading to a wide range of haematological problems. These specialised cells, which are filled with undegraded glucocerebroside, crowd out healthy bone marrow cells and can also contribute to the destruction of red blood cells. As a result, people with GD often suffer from anaemia due to both the displacement of healthy bone marrow cells and the potential destruction of red blood cells. In addition, the infiltration of Gaucher cells into the bone marrow reduces platelet production, leading to thrombocytopenia. In addition to red blood cells and platelets, the production of white blood cells is also affected, resulting in leukopenia (19).

The infiltration of Gaucher cells into the bone marrow leads to significant bone complications, most notably bone pain. The presence of Gaucher cells disrupts the normal bone architecture, resulting in pain that is often severe and recurrent, manifesting clinically as a "bone crisis" (20). Fractures are another consequence of Gaucher cell infiltration into the bone marrow. The compromised structural integrity of the affected bones makes them more susceptible to fracture, contributing to the skeletal fragility observed in people with GD (21).

Osteonecrosis, characterised by the death of bone tissue due to impaired blood supply, is a major complication in GD. The infiltration of Gaucher cells disrupts the vascular supply to bone tissue, leading to areas of necrosis (22) (23).

Hepatosplenomegaly in GD results from the accumulation of lipid-laden macrophages, known as Gaucher cells, in these organs. The enlarged spleen can lead to increased sequestration and destruction of blood cells, worsening haematological conditions such as anaemia and thrombocytopenia (24). Splenomegaly can also cause discomfort, early satiety and potential nutritional problems (1) (25), while hepatomegaly can cause abdominal discomfort and, in advanced stages, liver dysfunction including fibrosis or cirrhosis and possibly portal hypertension (15).

Although less common than the haematological or skeletal manifestations, pulmonary symptoms of Gaucher disease can have a significant impact on the patients. These complications result from the deposition of Gaucher cells in the lung tissues (8). The accumulation of these cells can obstruct and disrupt the function of the alveoli, reducing the efficiency of gas exchange and leading to reduced oxygen uptake. This process can also trigger inflammation and fibrosis, or scarring, of the lung tissue, which further impairs lung function and contributes to the respiratory symptoms experienced by some patients (26) (27). One of the more serious respiratory complications associated with Gaucher disease is pulmonary hypertension (8).

Moreover, the systemic effects extend to the nervous system, particularly in the context of neuronopathic forms of the disorder. The infiltration of Gaucher cells into the central nervous system (CNS) instigates a cascade of intricate pathophysiological events, resulting in neurological complications (28) (29). Cognitive decline is a prominent manifestation of GD's impact on the nervous system. The infiltration of Gaucher cells into the CNS disrupts normal neuronal function and connectivity, leading to progressive cognitive impairment. This decline includes various cognitive domains, affecting memory, attention, and executive functions, and contributes to the overall neurological burden experienced by individuals with neuronopathic GD (30). Seizures represent another neurological complication in GD, arising from the disrupted neuronal activity associated with the infiltration of Gaucher cells. Movement disorders, including a spectrum of motor abnormalities, further characterise the neurological complications in GD. The disrupted neuronal circuitry, influenced by Gaucher cell infiltration, can lead to conditions such as dystonia, ataxia, and spasticity (29).

3.Types of Gaucher's Disease and Their Pathophysiological Differences

GD is classified into three primary types based on the presence or absence of neurological involvement. Each type has distinct characteristics, symptoms, and progression patterns, which affect patients differently (31).

3.1 Type 1 Gaucher's Disease - non-neuronopathic form

Type 1 GD is the most common variant of this genetic condition and is characterised by the absence of central nervous system involvement. It can manifest at any stage of life and showcases a broad spectrum of symptoms and severity levels. Common symptoms of the disease include splenomegaly and hepatomegaly, which cause abdominal discomfort and a sensation of fullness. Bone disease is also a substantial feature, with individuals experiencing bone pain, crises, and an elevated risk of fractures due to bone weakening as the disease progresses. Blood disorders are prevalent, with anemia and thrombocytopenia causing fatigue, weakness, and an increased propensity for bruising and bleeding, which can further complicate the patient's condition. GD1 also has an increased risk of parkinsonism, peripheral neuropathy, portal hypertension and respiratory complications (25).

The non-neuronopathic form has a higher prevalence among the Ashkenazi Jewish population (32). Enzyme replacement therapy (ERT) and substrate reduction therapy (SRT) have transformed the treatment of type 1 GD and have significantly alleviated symptoms and improved the quality of life for those affected (33).

3.2 Type 2 Gaucher's Disease - acute neuronopathic form

Type 2 GD is the rarest and most severe variant of the condition. It is characterized by early onset, typically manifesting in infancy, and rapid progression, presenting a challenging prognosis for affected individuals. It often leads to life-threatening complications within the first few years of life (34) (35). Type 2 GD is characterized by severe neurological involvement, including dysfunction of the brain stem, which significantly affects basic life functions such as swallowing, breathing, and maintaining muscle tone. In addition to these neurological challenges, patients may also experience abnormalities in eye movement, particularly with horizontal eye movements. Due to the lack of effective treatments for the neurological aspects of type 2 GD, management strategies primarily focus on providing supportive care. The aim of this care is to improve the quality of life for patients by addressing their symptoms (36).

3.3 Type 3 Gaucher's Disease - chronic neuronopathic form

Type 3 Gaucher's Disease which is characterized by neurological symptoms that are less severe and progress at a slower rate compared to the acute neuronopathic manifestations seen in Type 2 GD. This form of the disease typically emerges in childhood or adolescence and presents with systemic symptoms common to Type 1 Gaucher's Disease, such as organomegaly and bone disease, as well as specific neurological involvements (37). Eye movement abnormalities, such as slow horizontal saccades, are a noticeable challenge for those affected by Type 3 GD (37) (38). Patients may also experience varying degrees of cognitive impairment, which can impact their daily lives and development (30). Seizures may also occur in some individuals with this condition (39).

The prognosis of Type 3 Gaucher's Disease varies significantly among patients. While some individuals are able to live into adulthood, the course of the disease can differ notably. This variability indicates progress in treatment and management strategies that have emerged over the years. Treatment for Type 3 GD often involves ERT and SRT to address the systemic aspects of the disease. In addition to these targeted therapies, supportive care is crucial in managing the symptoms, particularly the neurological manifestations that define this subtype (40) (41).

4. Diagnostic Approaches

The diagnosis of GD often takes place several years after the onset of the first clinical and laboratory signs (42). Diagnosing GD is a multi-step process that involves a combination of clinical evaluation, laboratory tests, genetic testing, and imaging studies. The aim is to identify the presence of the disease, determine its type, and assess the extent of organ involvement and damage (43).

4.1 Biomarkers and Biochemical Tests

The primary biochemical test for diagnosing GD is measuring the activity of the glucocerebrosidase enzyme in leukocytes or fibroblasts. Individuals with GD have significantly reduced enzyme activity compared to healthy individuals (43). The residual enzyme activity is usually approximately 10%–15% of the normal value (1).

Chitotriosidase is the most widely used biomarker for monitoring GD. This enzyme is produced in large quantities by Gaucher cells. Its levels are significantly elevated in most individuals with GD due to the activation of macrophages engorged with glucocerebroside.

Chitotriosidase activity correlates with disease burden and has been shown to decrease in response to effective therapy, such as ERT or SRT (44). However, approximately 6% of the general population has a genetic polymorphism that results in a deficiency of chitotriosidase, making this biomarker less useful in those individuals (45).

Glucosylsphingosine, also known as Lyso-Gb1, has emerged as a highly sensitive and specific biomarker for GD (46). It is a deacylated form of glucocerebroside, the substrate that accumulates in GD, and its levels are elevated in the plasma of affected individuals. Lyso-Gb1 has been shown to correlate with disease severity and treatment response, making it a valuable tool for diagnosis and monitoring, particularly in individuals who are chitotriosidase-deficient (47).

CCL18/PARC (Pulmonary and Activation-Regulated Chemokine) is another biomarker that has been associated with GD. CCL18 levels may also be increased in chronic inflammatory diseases such as idiopathic pulmonary fibrosis, some cancers and scleroderma. Its levels are also increased in allergic reactions, insulin resistance and obesity. In GD patients, CCL18 plasma levels are 10–50 times higher than in healthy individuals. Although not as widely used as chitotriosidase or Lyso-Gb1, CCL18/PARC can serve as an alternative or additional marker for assessing disease burden and monitoring treatment efficacy. High levels of CCL18 are associated with a poorer prognosis (1) (48).

4.2 Genetic Testing

Genetic testing is crucial in diagnosing GD as it confirms the presence of mutations in the GBA gene. The GBA1 gene, which spans 11 exons and encodes the GCCase, is located on the long arm of chromosome 1 at the 1q21 location. However, recombination events between GBAP, a highly similar pseudogene located 16 kb downstream of GBA1, and GBA1 can occur, resulting in the RecNciI allele. The GBA1 gene has over 400 identified mutations, with certain mutations occurring more frequently. These include c.1226A>G (N370S), c.1448T>C (L444P), c.84dup, c.115+1G>A (IVS2+1G>A), and RecNciI (1).

Certain mutations are associated with responsiveness to specific therapies, such as ERT or SRT. Patients with one or two copies of the N370S mutation generally respond well to ERT. ERT can significantly improve hematological parameters, reduce liver and spleen size, and ameliorate bone disease in these patients (33). Genetic testing is performed in subjects displaying absent or low residual BGLU activity in cells to support the diagnosis and provide appropriate genetic counseling to family members (49).

4.3 Imaging Studies and Their Roles

Imaging studies play an important role in assessing the extent of organ involvement and monitoring disease progression in GD. Magnetic Resonance Imaging (MRI) is the preferred modality for this purpose, providing an evaluation of bone marrow infiltration, liver and spleen size, and the identification of bone lesions. Furthermore, MRI proves valuable in tracking the response to treatment over time (1).

MRI not only assesses the bone marrow but also enables the diagnosis of pathological fractures, bone necrosis, lytic lesions, and Erlenmeyer flask deformation. Additionally, it is more accurate than ordinary radiography in detecting early changes in the skeleton (23).

Osteopenia is almost always present in GD and serves as an indication of reduced bone mineral density. A substantial decline in bone density must occur before osteopenia becomes evident on radiographs, resulting in its limited sensitivity for detecting this anomaly. For the assessment of osteopenia and bone mineral density, the current preferred method is Dual-Energy X-ray Absorptiometry (DEXA). However, it is essential to exercise caution during DEXA evaluations to avoid areas of osteonecrosis (50).

In addition to MRI and DEXA, radionuclide scans using ^{99}Tcm methylene-diphosphonate (^{99}Tcm -MDP) offer insights into osteoblastic activity, providing a potential means to evaluate bone turnover in Gaucher disease. Despite their high sensitivity, these nuclear techniques have a notable limitation in terms of lower specificity and spatial resolution compared to MRI (51).

4.4 Prenatal Diagnosis

The prenatal diagnosis of GD can be conducted through genetic testing, which can utilize samples from either chorionic villus sampling (taken between 10 to 12 weeks of gestation) or cells from amniotic fluid (obtainable from as early as 16 weeks of gestation). Additionally, the activity of the GCase can be assessed directly by analyzing either fresh samples from the chorionic villi or cultured cells derived from amniotic fluid (1) (19).

5. Management and Treatment Strategies

Management and treatment strategies for GD have significantly evolved recently. The primary treatments for GD include ERT and SRT, supported by various adjunctive and supportive care measures. Treatment must generally be administered for life once initiated (52). The aim is to treat patients before complications arise. These complications can be disabling or may not improve with further treatment.

Examples of such complications include massive fibrous splenomegaly, avascular necrosis, secondary osteoarthritis, vertebral compression and other fractures, hepatic fibrosis, and lung fibrosis (53) (54) (55).

5.1 Enzyme Replacement Therapy

ERT is a main treatment for GD, particularly effective for Type 1 and some patients with Type 3 GD (36). It involves the intravenous administration of recombinant GCase to supplement the deficient enzyme in patients. ERT has been shown to significantly reduce liver and spleen size, improve blood counts, and enhance bone density, thereby alleviating many of the systemic symptoms of GD. The therapy is typically administered every two weeks and is considered a lifelong treatment. While ERT is highly effective for systemic manifestations of GD, it does not cross the blood-brain barrier and, therefore, is less effective for the neurological symptoms associated with Types 2 and 3 GD (56).

Safety is generally good. Between 2% and 14% of patients develop antibodies against the enzyme, typically without exhibiting any clinical symptoms. Allergic reactions are rare, occurring in less than 1.5% of patients, and may include urticaria, diarrhea, hypotension, or laryngeal discomfort (1).

5.2 Substrate Reduction Therapy

SRT can be used as an alternative or addition to ERT, particularly for patients who may not tolerate ERT or for whom ERT is less effective. SRT inhibits the synthesis of GCase, the lipid that accumulates due to GCase deficiency. By reducing the production of this substrate, SRT helps to prevent its accumulation and mitigate symptoms. SRT is administered orally, making it a more convenient option for some patients. Similar to ERT, SRT is more effective in treating systemic symptoms and has limited efficacy in treating neurological manifestations (56).

5.3 Other Specific Treatments

In addition to established therapies, ongoing research and experimental treatments are expanding the spectrum of GD treatment. One of the most promising avenues is gene therapy, which has the potential to introduce a healthy GBA gene variant into patients and deliver a long-term cure. This innovative approach could enable the natural production of GCase, addressing the root cause of the disease.

Pharmacological chaperones and small molecule therapies are currently being investigated to improve enzyme stability and function, or to decrease substrate accumulation through innovative mechanisms (57).

5.4 Supportive Care

Supportive care for individuals with GD aims to enhance their quality of life, manage symptoms, and address the psychological and social challenges associated with living with this chronic condition. Unlike ERT and SRT, which directly address the biochemical imbalances underlying GD (2), supportive care takes a comprehensive approach to the patient's well-being (58).

Individuals diagnosed with GD commonly experience bone and joint pain, as well as discomfort resulting from splenomegaly (33). To alleviate these symptoms, a variety of pain management strategies are employed, including the use of analgesics, ranging from non-steroidal anti-inflammatory drugs to more potent painkillers, based on the severity of the pain. Physical therapy, through exercises, strengthens muscles and improves joint functionality, providing significant pain relief (59). Moreover, in cases of severe bone complications such as fractures or bone necrosis, orthopedic interventions may be necessary. Given the prevalence of osteopenia, osteoporosis, bone crisis, and fractures, bone health is a major concern in GD. Regular bone density monitoring via DEXA scans is necessary to detect any damage or weakness (23), and calcium and vitamin D supplementation is recommended to bolster bone strength. Bisphosphonates may also be administered to some patients to further reduce fracture risks (23) (58).

The management of haematological issues, such as anaemia and thrombocytopenia, is crucial due to their impact on fatigue, weakness, and bleeding tendencies. Strategies include blood transfusions to rapidly increase cell counts in severe cases (43).

For patients experiencing organomegaly, regular monitoring through ultrasound or MRI is essential to assess organ size and function (60). The disease can cause patients to suffer from both malnutrition and obesity, so dietary counselling may be beneficial (61) (62).

In addition to the physical symptoms of GD, it is important to consider the psychological and social impacts of the condition. Therefore, supportive care should include mental health support to assist patients and their families in managing the emotional challenges of GD (29) (63).

6. Challenges and Future Directions

Although current treatments have been groundbreaking, they do have limitations. ERT and SRT, which are the mainstays of treatment, provide significant symptom relief and improve the quality of life for many patients. However, the efficacy of these therapies is mainly limited to systemic manifestations of the disease. Treating neurological symptoms in types 2 and 3 Gaucher's disease is limited (52). Moreover, the high cost and limited accessibility of these treatments pose significant barriers, restricting their availability to a broader patient population. Therefore, more accessible and cost-effective solutions are sought. (64).

Full understanding of genetic and biochemical mechanisms responsible for GD could lead to novel therapies, including gene therapy and other genetic-based treatments that address the cause of the disease (2). However, the development of these therapies is hindered by scientific challenges and ethical dilemmas, particularly regarding the long-term effects and potential unintended consequences of genetic modification (34). Further investigation into the disease's progression, its variability in expression, and the development of neuroprotective therapies are critical areas that could yield significant benefits (2) (65).

7. Conclusion

GD presents a significant challenge in the field of genetic and metabolic disorders.. It is characterized by a spectrum of clinical presentations and a diverse range of management strategies. Despite recent advances, managing GD remains challenging due to the variability in disease expression caused by a wide array of GBA mutations. The introduction of new therapies has undoubtedly improved the prognosis for many with GD, particularly those with non-neuronopathic or less severe neuronopathic forms. However, the management of neurological symptoms in advanced stages of GD remains a challenging objective, and exploring novel treatment options is necessary.

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Authors contribution

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