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Gaucher disease – a comprehensive review of clinical characteristics, diagnostic algorythms and current therapies

Alicja Kotula
Infant Jesus Clinical Hospital UCC MUW,
Lindleya 4, 02-005 Warszawa
kotulaalicja5@gmail.com
https://orcid.org/0009-0008-9718-1667

Natalia Kucy
Infant Jesus Clinical Hospital UCC MUW,
Lindleya 4, 02-005 Warszawa
tusia.noelle@icloud.com
https://orcid.org/0009-0007-5468-6289
Adrianna Czachor
Infant Jesus Clinical Hospital UCC MUW,
Lindleya 4, 02-005 Warszawa
adriannaczachor@gmail.com
https://orcid.org/0009-0001-8596-9341

Paula Kula
Central Clinical Hospital in Warsaw,
Banacha 1a, 02-097, Warszawa
paulakula98@gmail.com
https://orcid.org/0009-0004-7503-2602

Mateusz Haber
Central Clinical Hospital in Warsaw
Banacha 1a, 02-097, Warszawa
mhaber.mateusz@gmail.com
https://orcid.org/0009-0002-8441-4931

Olga Grelewicz
National Medical Institute of the Ministry of the Interior and Administration,
Wołoska 137, 02-507 Warszawa
olga.grelewicz@gmail.com
https://orcid.org/0000-0001-5738-9262

Elwira Servaas
National Medical Institute of the Ministry of the Interior and Administration,
Wołoska 137, 02-507 Warszawa
servaaselwira@gmail.com
https://orcid.org/0009-0004-8432-7824
Adam Juśkiewicz
National Medical Institute of the Ministry of the Interior and Administration,
Wołoska 137, 02-507 Warszawa
ad.juskiewicz@gmail.com
https://orcid.org/0000-0001-9884-3513
Alicja Pilcicka
Military Institute of Medicine,
Szaserów 128, 04-349 Warszawa
alicja.pil1640@gmail.com

https://orcid.org/0009-0003-3581-4928

Abstract

Gaucher disease (GD) is an autosomal recessive lysosomal storage disorder caused by mutations in the GBA1 gene, which encodes the enzyme glucocerebrosidase. This enzyme is crucial for breaking down glucocerebrosides, and its deficiency leads to their accumulation in the monocyte-macrophage system, forming Gaucher cells. These cells build up in the bone marrow, spleen, and liver, causing various clinical manifestations. GD is classified into three types based on clinical features and progression: GD1 (non-neuronopathic), GD2 (acute neuronopathic), and GD3 (subacute neuronopathic).

GD1, the most common form, usually presents with splenomegaly, hepatomegaly, anemia, thrombocytopenia, and skeletal symptoms and has a relatively mild course. GD2 is marked by severe neurological involvement, with a poor prognosis and a maximum survival of three years. GD3 features a mix of visceral, hematological, neurological, and skeletal symptoms, with a variable prognosis depending on the subtype.

Epidemiologically, GD is rare in the general population but more common among Ashkenazi Jews, who have a higher carrier frequency and prevalence. The genetic basis of GD is well-documented, with several mutations associated with different disease severities and outcomes. Diagnostic procedures include a comprehensive medical history, imaging studies, and biochemical and genetic tests to confirm reduced glucocerebrosidase activity and identify GBA1 mutations.

Current treatments focus on enzyme replacement therapy (ERT) and substrate reduction therapy (SRT), with supportive care for specific symptoms. ERT is the primary treatment for all children with GD1 and GD3 and for adults who meet certain criteria, while SRT is an alternative for milder forms of GD1. Despite advances in treatment, managing GD remains complex, requiring a multidisciplinary approach to address the diverse clinical manifestations and improve patient outcomes.

Keywords : lysosomal storage disease, Anemia, diagnostic algorithms, splenomegaly, enzyme replacement therapy, genetic diseases

Introduction

Gaucher disease (GD) is one of the genetically determined lysosomal storage diseases. It is inherited in an autosomal recessive manner and is caused by a mutation in the gene encoding glucocerebrosidase (GBA1), an enzyme responsible for breaking down the beta-glycosidic bonds of glucocerebroside lipids (components of cell membranes). This leads to the accumulation of glucocerebroside in cells, particularly in the monocyte-macrophage system, also known as Gaucher cells. These glucocerebroside-laden cells primarily accumulate in the bone marrow, spleen, and liver, causing an inflammatory response in these organs and manifesting in a range of clinical symptoms. The clinical presentation varies depending on the specific type of the disease and can range from mild to severe, affecting individuals of different ages and backgrounds. The disease is named after the French physician Philippe Gaucher, who first described it in 1882. The current knowledge about the disease is the result of research combining elements of genetics, biochemistry, and clinical medicine.

Etiology

The primary cause of all forms of GD is a mutation in the gene encoding glucocerebrosidase (GBA1), located in the q21 region of chromosome 1. This mutation results in a lysosomal deficiency of glucocerebrosidase activity. In 80% of cases, the disease is caused by a point mutation in GBA1 [14], and over 600 alleles are currently known to potentially lead to its development [18]. Four of these alleles are responsible for 50-60% of cases: p.N370S, c.84_85insG, p.L444P, and IVS2+1G>A. Among Ashkenazi Jews, these mutations are present in up to 90% of affected individuals [28]. Despite a thorough understanding of the genetic basis of the disease, the exact etiology remains unclear. There is significant phenotypic variability among patients with the same genotype, indicating that environmental and epigenetic factors may influence the disease's course. However, it has been confirmed that the presence of at least one c.1226A>G (p.N370S) mutation prevents the development of severe neurological symptoms. Homozygosity for this allele is usually associated with mild forms of the disease, typically manifesting in adulthood. Conversely, homozygosity for c.1448T>C

(p.L444P) is most commonly described in neuronopathic forms of GD, and the p.L444P allele is also associated with severe GD progression [35]. Additionally, homozygosity for this allele leads to the development of kyphoscoliosis [16] and drug-resistant myoclonic epilepsy [32]. There are no individuals homozygous for the c.84_85insG or IVS2+1G>A alleles, suggesting that such genotypes are lethal. Heterozygotes for these alleles typically experience a progressive disease course, leading to death most often in the first or second decade of life [19, 10, 11, 6].

Gaucher disease is the most common sphingolipidosis. There are at least 60 other LSDs, including mucopolysaccharidoses, Tay-Sachs disease, Fabry disease, and Pompe disease [34]. All these diseases are characterized by a chronic course with progressive involvement of multiple organs. The characteristic involvement of macrophages in GD is associated with the presence of large quantities of lysosomes in these cells. In GD patients, lysosomes in macrophages gradually enlarge, filling with undigested glucocerebroside, leading to the failure of the monocyte-macrophage line and their accumulation in various organs, primarily the spleen and bone marrow.

Epidemiology

GD is considered a rare disease. In the general population, it occurs with a frequency of 1 in 20,000 to 1 in 75,000 live births, with a carrier frequency of 0.7% - 0.8%, and a prevalence between 1 in 40,000 and 1 in 200,000 inhabitants. The exception is the Ashkenazi Jewish population, among whom GD is the most common autosomal recessive disorder. The carrier frequency is estimated at 6%, with a prevalence of 1 in 850 individuals, and approximately 1 in 450 live-born newborns are affected [34, 14].

The most common type of GD is type 1 (GD1), which is non-neuronopathic [29]. In contrast, types 2 and 3 are rare and affect the central nervous system. These types are more severe, often leading to death in childhood.

Pathophysiology

The signs and symptoms of Gaucher disease can be divided into visceral, hematological, skeletal, and metabolic, and in types 2 and 3, also neurological. Visceral symptoms include hepatosplenomegaly and the resulting abdominal enlargement, discomfort, or pain. Without appropriate treatment, the accumulation of Gaucher cells in these organs can lead to an increase in liver size by 2 to 3 times and the spleen by up to 7.5 times their normal size.

Hematological symptoms of GD include thrombocytopenia, anemia, and leukopenia. Thrombocytopenia in these patients is caused by the accumulation of glucocerebroside in the bone marrow, leading to impaired platelet production. In the spleen, increased accumulation of glucocerebroside causes excessive breakdown of red and white blood cells, leading to anemia and leukopenia. These hematological complications result in a tendency to bruise, increased risk of bleeding, chronic fatigue and weakness [20], and more frequent infections.

Skeletal complications can include chronic or acute bone pain, bone crises (bone infarcts with subsequent osteosclerosis, manifesting as attacks of severe bone pain with fever and leukocytosis without an apparent infectious cause), avascular necrosis (most often of the femoral head), cortical bone abnormalities and pathological fractures, decreased bone density, osteolysis, bone cysts, and osteosclerotic lesions, impaired growth of long bones, loss of joint function, subchondral layer damage, secondary osteoarthritis, and the characteristic Erlenmeyer flask deformity of GD [23, 36, 12]. Many of these skeletal abnormalities are attributed to the accumulation of glucocerebroside-laden macrophages in the bone marrow, where they restrict blood flow and the delivery of nutrients and oxygen. Necrosis formation may also be associated with the formation of emboli in the bone microcirculation. Skeletal complications are chronic, progressive, and often unpredictable. Some may be irreversible despite treatment [39]. Radiological changes occur in about 90% of patients regardless of age and are not always associated with clinical symptoms [8].

Typical metabolic disturbances in GD patients include dyslipidemia and, as complications of enzyme replacement therapy, weight gain, insulin resistance, and an increased risk of type 2 diabetes [21].

Neurological symptoms result from damage to neurons in the central nervous system. This process is likely due to the action of toxins activated by the presence of glucosylceramide in CNS cells, although the exact mechanism is not yet known. Neurological symptoms in different types of Gaucher disease will be discussed in the section on the clinical classification of this disorder.

There is a known association between Gaucher disease and an increased risk of certain cancers. The mechanisms behind this association have not yet been determined. The most commonly described cancers in GD patients involve the hematopoietic and lymphatic systems - multiple myeloma, ALL, CLL, AML, CML, Hodgkin's lymphoma, and non-Hodgkin's lymphomas, as well as mono-, oligo-, and polyclonal gammopathies [26, 2].

Among solid tumors, the highest incidence rates are for primary bone, liver, kidney, breast, lung, CNS, testicular, prostate, colorectal cancers, and melanoma [31].

Clinical Division

The most important criteria for dividing GD are the presence of CNS involvement and the disease's progression rate. Based on this, three main types of the disease have been identified: non-neuronopathic GD1 and neuronopathic types 2 and 3.

GD1 (non-neuronopathic type, so-called adult type) is the most common form of the disease. It is characterized by the mildest course; symptoms may appear in childhood or adulthood, and an asymptomatic course is also possible. It typically manifests with splenomegaly and hepatomegaly [13], usually mild anemia and thrombocytopenia, and bone symptoms [8], which can manifest as growth retardation in children, especially during puberty. Despite the absence of CNS involvement characteristic of the other GD types, there is an increased incidence of Parkinson's disease [4, 3, 27] and peripheral neuropathy in GD1. Life expectancy does not significantly differ from the general population, ranging from 60 to 80 years.

GD2 (acute neuronopathic type, so-called infantile type) is characterized by a severe course, with a maximum survival period of 3 years. Typical GD visceral and hematological symptoms are present, but bone complications seen in GD1 and GD3 usually do not develop due to the early death of children with GD2.

Two subtypes of GD2 have been identified [17]:

- Perinatal
- Classic

In the perinatal form, symptoms are evident during fetal development. Prenatal ultrasound may show hepatosplenomegaly, fetal edema with decreased motor activity, and growth disturbances. Due to these abnormalities, fetal demise or premature birth often occurs. After birth, characteristic symptoms of arthrogryposis, involving congenital joint contractures, may appear, leading to neonatal death.

In the classic form, symptoms appear in the first months of life. Progressive brain damage is observed, manifesting as developmental delays, weakened sucking and swallowing reflexes, seizures, abnormal horizontal and vertical eye movements, muscle tone abnormalities with exaggerated tendon reflexes and spasticity, and brainstem damage with bulbar palsy, apnea, and laryngeal spasm. Forty percent of children have congenital ichthyosis due to abnormal

ceramide-to-glucosylceramide ratios in the skin. Facial dysmorphism, likely due to microcephaly and reduced skin elasticity, is also observed. The progressive nature of thrombocytopenia and anemia, common to other types, and hepatosplenomegaly are less frequent in GD2. The disease progresses rapidly, with death usually occurring due to respiratory failure between 2 and 3 years of age.

GD3 (subacute neuronopathic type, juvenile type) accounts for only 3-5% of Gaucher disease cases. Visceral, hematological, neurological, and skeletal symptoms typically appear in early childhood. Horizontal saccadic eye movement impairment is characteristic of GD3.

Three subtypes of GD3 have been identified:

- 3a, characterized by myoclonic epilepsy, with patients also experiencing mobility issues and dysphagia due to progressive CNS involvement. This subtype has the poorest prognosis among GD3 subtypes, with death usually occurring before the age of 20.
- 3b, also known as the Norrbottnian type [24], resembles severe GD1 with pronounced hematological, visceral, and skeletal symptoms. Neurological symptoms are usually less severe. Life expectancy ranges from 30 to 60 years, making this subtype the most favorable prognostically.
- 3c, associated with the homozygous D409H genotype, is characterized by aortic and heart valve calcifications, coronary insufficiency, corneal clouding, hydrocephalus, and skeletal abnormalities. Death usually occurs before the age of 20, typically due to cardiovascular causes.

Table 1 - Clinical division and symptoms characteristic of Gaucher disease

	Type 1	Type 2	Type 3
General information	GD1 (non-neuronopathic type, so-called adult type) is the most common form of the disease. It is characterized by the mildest course; symptoms may appear	GD2 (acute neuronopathic type, so-called infantile type) is characterized by a severe course, with a maximum survival period of 3 years.	GD3 (subacute neuronopathic type, juvenile type) accounts for only 3-5% of Gaucher disease cases. Visceral, hematological, neurological, and

	in childhood or adulthood, and an asymptomatic course is also possible.		skeletal symptoms typically appear in early childhood.
Symptoms of internal organs	Splenomegaly, hepatomegaly, rarely interstitial lung disease	Splenomegaly, hepatomegaly less frequently than in other GD types, generalized edema, rarely interstitial lung disease	Splenomegaly, hepatomegaly, rarely interstitial lung disease
Hematological and skeletal symptoms	anemia and thrombocytopenia chronic or acute bone pain, bone crises, avascular necrosis, cortical bone abnormalities and pathological fractures, decreased bone density, osteolysis, bone cysts, and osteosclerotic lesions, impaired growth of long bones	anemia and thrombocytopenia In severe cases, symptoms resembling arthrogryposis.	anemia and thrombocytopenia chronic or acute bone pain, decreased bone density, bone crises, abnormalities and pathological fractures, kyphoscoliosis
Neurological symptoms	absence of neurological symptoms typical for other GD types, increased incidence of	psychomotor developmental delay, abnormal horizontal and vertical eye	Horizontal saccadic eye movement impairment, cognitive impairment, tonic-clonic seizures,

	Parkinson's disease and peripheral neuropathy	movements, increased muscle tone, bulbar palsy	myoclonic epilepsy

Diagnosis

Symptoms that suggest a need for expanding diagnostics towards Gaucher disease (GD) include:

- hepatosplenomegaly

- symptoms related to the skeletal system, such as bone pain, pathological fractures, long bone deformities

- abnormal growth

- symptoms of thrombocytopenic bleeding disorder

- chronic fatigue

- susceptibility to infections

- neurological disorders: delayed psychomotor development, early childhood epilepsy; impairment of eye movement and positioning

- anemia, thrombocytopenia, and/or leukopenia detected in routine check-ups, especially in conjunction with hepatosplenomegaly, can be the first diagnostic indicator.

Unfortunately, delays in diagnosing the disease and initiating treatment are not uncommon, and the possible asymptomatic course does not rule out the development of hidden and sometimes irreversible complications.

To establish a diagnosis, a detailed medical history including family history and the patient's ethnic background should be considered. Additionally, appropriate imaging studies and laboratory tests (complete blood count with smear, lipid profile, liver function tests, LDH, total bilirubin, urinalysis, creatinine, urea, APTT, INR, CRP, fasting glucose, serum ferritin concentration, iron studies, TIBC, TRF, serum protein electrophoresis) are necessary. The final diagnosis is made based on enzymatic testing results confirming reduced glucocerebrosidase activity and genetic testing showing a mutation in the GBA1 gene.

Glucocerebrosidase activity can range from near zero in children with GD2 and 3 to

approximately 10-30% in adults with GD1. Measurement is performed in leukocytes, and in case of leukopenia, fibroblasts obtained during skin biopsy or dried blood spot testing using capillary blood (DBS). Besides glucocerebrosidase activity measurements, there are other parameters applicable to the diagnosis and monitoring of Gaucher disease (measurement of chitotriosidase activity, CCL18 chemokine levels, Lyso-Gb1 levels [38, 1, 33]). In Poland, in addition to glucocerebrosidase enzyme activity measurement, chitotriosidase activity in serum is also determined, which correlates well with the disease severity. Unfortunately, high enzyme activity is not specific to GD since elevated levels are also found in sarcoidosis, thalassemia, arthritis, multiple sclerosis, COPD, malaria, atherosclerosis, and other LSDs like Niemann-Pick disease type A and B. Additionally, about 6-8% of patients have reduced enzyme activity due to mutations in the chitotriosidase gene, and in such cases, CCL18 cytokine levels can be measured. However, this test is not available in Poland. Other biochemical abnormalities observed in GD patients include low vitamin B12 and D levels, low lipoproteins (LDL and HDL), and hyperferritinemia.

In diagnosing and monitoring bone involvement, periodic monitoring of serum calcium, phosphorus, vitamin D3 levels, and alkaline phosphatase isoform is recommended. Bone marrow examination is a significant test that can steer towards diagnosing and treating GD as it can reveal the presence of Gaucher cells. However, due to the frequent difficulty in obtaining reliable material for marrow assessment, negative results do not exclude GD. Moreover, the presence of Gaucher cells in the material does not confirm the diagnosis due to the pseudo-Gaucher cells present in other conditions associated with increased cellular turnover, such as hematologic malignancies or certain infections. These cells are indistinguishable under an optical microscope. Thus, the key to diagnosis remains enzymatic testing for glucocerebrosidase activity and the confirmation of GBA1 gene mutations through genetic testing.

Imaging studies allow the assessment of organ involvement, disease progression, and treatment effectiveness. According to current recommendations, MRI is the preferred method for assessing internal organ size, especially when a more precise evaluation is required. However, routine MRI imaging has limitations due to the need for sedation in children and the costliness of the procedure. Therefore, abdominal ultrasound is commonly used for disease monitoring. Computed tomography can also provide a detailed assessment of internal organs but is not routinely used due to children's radiation exposure.

The most comprehensive assessment of bone morphology, osteonecrotic changes, and bone marrow can also be performed using MRI. Interpreting bone marrow changes involves comparing marrow images with T1/T2 sequences in healthy bones as Gaucher cell infiltration reduces signal intensity. Various methods such as BMB (bone marrow burden), VDR (vertebra disc ratio), S-MRI (Spanish-MRI), Rosenthal scale, Dusseldorf classification, and Terk classification are used for assessing affected areas. BMB is the most commonly used method, evaluating the lumbar spine and femurs. However, since bone changes often occur in other locations, an initial overall bone assessment with MRI is suggested, followed by specific area evaluation through imaging studies.

When suspecting interstitial lung disease in GD patients, high-resolution computed tomography (HRCT) is the most precise diagnostic tool. Chest X-rays can also reveal reticulonodular changes in these patients. In case of complications like respiratory impairment or pulmonary hypertension, additional tests like spirometry, arterial blood gas analysis, echocardiography, ECG, and the mentioned imaging studies are recommended.

For neurologic types of GD, MRI of the head/CNS, EEG, evoked potentials, electroneurography, electrooculography, and extensive psychometric tests are suggested.

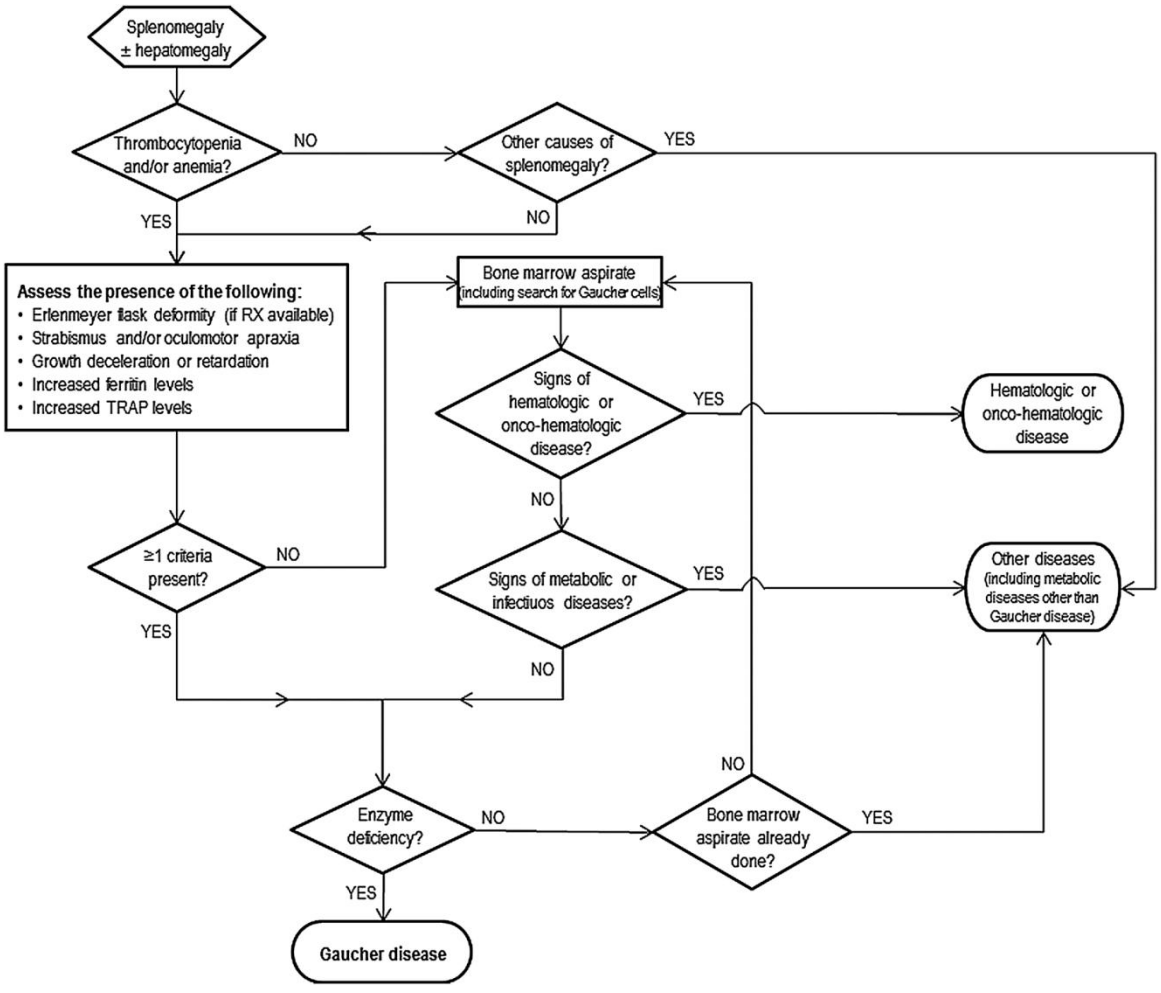

Fig. 1. A proposed algorithm for early diagnosis of GD in the pediatric age group [9].

Treatment

The current basic therapeutic methods include enzyme replacement therapy (ERT) involving intravenous administration of synthetic glucocerebrosidase and, for milder cases, substrate reduction therapy (SRT) inhibiting glucosylceramide production.

ERT is the main treatment method used for GD, recommended for all children with GD1 and GD3 and adults meeting treatment criteria. Notably, drugs used in therapy do not cross the blood-brain barrier and are thus ineffective in treating neurological symptoms [22].

Currently registered ERT preparations include:

- Imiglucerase

- Velaglucerase alfa

- Taliglucerase alfa

In Poland, imiglucerase and velaglucerase alfa are reimbursed for GD1 patients, with imiglucerase being the only effective drug for GD3 , also reimbursed for this form of the disease. ERT drugs are administered intravenously every two weeks at doses of 15-60 IU/kg, adjusted for the patient's age, disease severity, and treatment response [15]. Most patients show improvements within 6 months, with benefits including improved blood morphology, reduced liver and spleen size, and decreased bone-related symptoms [40].

Substrate reduction therapy serves as an alternative treatment for patients with mild or moderate GD1 forms [25].

There are currently two substrate reduction therapy inhibitors:

- Miglustat, recommended for adults with mild to moderate GD1 who cannot or don't want to undergo ERT. It is taken orally at a dose of 100mg three times daily. Miglustat may cause bothersome side effects primarily affecting the gastrointestinal system (diarrhea, bloating, abdominal pain), metabolism and nutrition (loss of appetite, weight loss), and neurological disorders (tremors, peripheral neuropathy, ataxia, memory impairment, paresthesia).

- Eliglustat, reimbursed in Poland for adult GD1 patients with poor, intermediate, or extensive

metabolizers involving the CYP2D6 isoenzyme (not recommended for ultra-rapid metabolizers). Compared to miglustat, eliglustat has less severe side effects and is more effective. Significant reductions in spleen and liver volumes and hematological improvements were observed in ENGAGE studies [30]. The recommended dose for moderate and fast metabolizers is 84mg twice daily, whereas slow metabolizers should take 84mg once daily.

Supportive therapy also plays a crucial role for GD patients. The decision to use symptom-mitigating medications should be individualized based on patient needs. Pain management is essential due to frequently reported bone pain in GD. Nonsteroidal anti-inflammatory drugs are typically used for mild to moderate pain, while opioid therapy may be necessary for bone fractures. Supplementing vitamin D3 and calcium is recommended for patients with reduced bone mineral density. Also, orthopedic interventions may be required for bone complications, alongside tailored rehabilitation.

Supportive therapy is particularly significant for managing neurological complications in GD due to the ineffectiveness of ERT drugs in neurological symptom treatment. For GD3a patients, antiepileptic therapy significantly reduces symptoms and enhances patient quality of life.

Previously used treatment methods for hematologic disorders have become less relevant following the introduction of ERT. Allogeneic hematopoietic stem cell transplantation or blood component transfusions are only recommended for severe GD cases. Routine splenectomy is not preferred for treating thrombocytopenia, with selective splenectomy considered only in rare cases of platelet issues resistant to causal therapy [7].

Summary

Gaucher disease (GD) is a genetically determined lysosomal storage disorder inherited in an autosomal recessive manner. It is caused by a mutation in the gene encoding glucocerebrosidase (GBA1), an enzyme responsible for breaking down glucocerebrosides. This mutation leads to the accumulation of glucocerebroside in cells, particularly in the monocyte-macrophage system, known as Gaucher cells. These cells primarily accumulate in the bone marrow, spleen, and liver, causing an inflammatory response in these organs and manifesting in a range of clinical symptoms.

The primary cause of all forms of GD is a mutation in the GBA1 gene, located on

chromosome 1. Over 600 alleles have been identified, with four specific mutations (p.N370S, c.84_85insG, p.L444P, and IVS2+1G>A) accounting for 50-60% of cases. Among Ashkenazi Jews, these mutations are present in up to 90% of affected individuals. Despite a thorough understanding of the genetic basis of the disease, significant phenotypic variability exists among patients with the same genotype, indicating that environmental and epigenetic factors may influence the disease's course.

GD is considered a rare disease, occurring with a frequency of 1 in 20,000 to 1 in 75,000 live births in the general population. The carrier frequency is 0.7% - 0.8%, with a prevalence between 1 in 40,000 and 1 in 200,000 inhabitants. In the Ashkenazi Jewish population, GD is the most common autosomal recessive disorder, with a carrier frequency estimated at 6% and a prevalence of 1 in 850 individuals. Approximately 1 in 450 live-born newborns are affected.

The signs and symptoms of Gaucher disease can be divided into visceral, hematological, skeletal, and metabolic categories, with types 2 and 3 also exhibiting neurological symptoms. Visceral symptoms include hepatosplenomegaly and abdominal discomfort or pain. Hematological symptoms include thrombocytopenia, anemia, and leukopenia, leading to bruising, bleeding, fatigue, weakness, and increased infection risk. Skeletal complications can include chronic bone pain, bone crises, avascular necrosis, cortical bone abnormalities, pathological fractures, decreased bone density, osteolysis, bone cysts, osteosclerotic lesions, impaired growth, loss of joint function, secondary osteoarthritis, and Erlenmeyer flask deformity. Neurological symptoms in types 2 and 3 are due to neuron damage, likely caused by toxins activated by glucosylceramide in CNS cells.

There is an increased risk of certain cancers in GD patients, particularly hematopoietic and lymphatic system cancers. The most commonly reported cancers involve multiple myeloma, ALL, CLL, AML, CML, Hodgkin's lymphoma, and non-Hodgkin's lymphomas. Among solid tumors, the highest incidence rates are for primary bone, liver, kidney, breast, lung, CNS, testicular, prostate, colorectal cancers, and melanoma.

GD is divided into three main types based on CNS involvement and disease progression rate: non-neuronopathic GD1 and neuronopathic types 2 and 3. GD1 is the most common and mildest form, typically manifesting with splenomegaly, hepatomegaly, anemia, thrombocytopenia, and bone symptoms. GD2 is severe, with symptoms appearing in infancy and a maximum survival period of 3 years. GD3 is rare, with symptoms appearing in early childhood and a life expectancy ranging from 20 to 60 years, depending on the subtype.

Diagnosis involves a detailed medical history, imaging studies, and laboratory tests, with confirmation based on enzymatic testing showing reduced glucocerebrosidase activity and genetic testing for GBA1 mutations. Treatment includes enzyme replacement therapy (ERT) and substrate reduction therapy (SRT), with supportive therapy playing a crucial role. ERT is recommended for all children with GD1 and GD3 and adults meeting treatment criteria, while SRT serves as an alternative for patients with mild or moderate GD1 forms.

Author's contribution:

Conceptualization: Alicja Kotula, Natalia Kucy ;

methodology: Adrianna Czachor, Olga Grelewicz;

software: Paula Kula;

check: Elwira Servaas, Mateusz Haber;

formal analysis: Alicja Pilcicka;

investigation: Elwira Servaas;
resources: Paula Kula, Adam Juśkiewicz;
data curation: Natalia Kucy;
writing - rough preparation: Olga Grelewicz;
writing - review and editing: Adam Juśkiewicz, Alicja Pilcicka;
visualization: Mateusz Haber;
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