

Molecular basis and clinical management of Gaucher disease

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Abstract

Gaucher disease (GD) type I is an autosomal recessive disease caused by a genetic deficiency of lysosomal β -glucocerebrosidase that leads to accumulation of undergraded substrate glucocerebroside and other glycolipids, thus causing damage in different organs. *GBA* is the only gene in which mutations are known to cause GD. Nearly 300 mutations have been identified in GD patients, including frame-shift mutations, point mutations, deletions, insertions, splice site mutations and recombinants. The variety of phenotypes associated to GD shows imperfect correlation with mutations. GD encompasses a spectrum of clinical findings from a perinatal lethal form to an asymptomatic form. However the classification of GD by clinical subtype is still useful in describing the wide range of clinical findings and broad variability in presentation. Three major clinical types are delineated: type I (chronic non-neuropathic), type II (acute neuropathic), and type III (chronic neuropathic).

Patients with type I GD present with visceromegaly, hematological complications, and bone disease. Cardiac and pulmonary complications are rare. Type I GD adult patients have elevated risk of malignancies, Parkinson's disease or Parkinsonism. Neuropathic forms of GD are rare and clinically ranging from lethal perinatal form to very mild form limited to abnormalities of horizontal ocular saccades. Diagnosis of acid β -glucosylceramidase relies on enzyme activity in peripheral blood leukocytes or skin fibroblasts and/or identification of *GBA* mutations. Enzyme replacement therapy is an effective treatment for non-neuropathic GD. Substrate inhibitor is the alternative therapy for some patients with GD is miglustat, iminosugar inhibitor of glucocerebroside synthase.

Introduction

Gaucher disease (GD) is the first lysosomal storage disease described. In his 1882 doctoral

thesis, Gaucher provided the first clinical description of the disease, which was later named Gaucher disease. The systemic nature of this disease and its inheritance were described over the next century. The identification of the causal enzymatic genetic and molecular pathology provided insights into the phenotypic spectrum and the basis for developing specific treatment. Enzyme replacement therapy (ERT), available since the early '90s, is an effective treatment for Gaucher disease and the prototype for specific enzyme therapy in lysosomal storage diseases.

The point of view of molecular biologist

GD type I is a metabolic disorder caused by a genetic deficiency of lysosomal β -glucocerebrosidase that leads to accumulation of undergraded substrate glucocerebroside and other glycolipids, thus causing damage in different organ systems. *GBA* is the only gene in which mutations are known to cause GD. Nearly 300 mutations have been identified in GD patients, including frame-shift mutations, point mutations, deletions, insertions, splice site mutations. Furthermore, having *GBA* a closely related pseudogene (*GBAP*), with 96% homology between them and both occupying the same locus on chromosome 1q21, some mutated alleles have also arisen from homologous recombination between the active *GBA* gene and the *GBAP* gene.¹

Four mutations N370S (c.1226A>G), L444P (c.1448T>C), 84GG (-c.84dupG), and IVS2+1 (c.27+1G>A) account for approximately 90% of the disease causing alleles in the Ashkenazi Jewish population. In non-Jewish populations, the same four alleles account for approximately 50-60% of disease causing alleles. Non-Jewish individuals with GD tend to be compound heterozygotes with one common and one rare mutation. The variety of phenotypes associated to GD shows imperfect correlation with mutations and discordance in phenotype has been reported even among monozygotic twins.^{1,2} In general, individuals who are homozygous for the N370S mutation are said to have milder disease than those who are compound heterozygous. However data from GD registry show that patients with the N370S/N370S genotype exhibit a high degree of phenotypic heterogeneity and some may be at risk for early disease onset and severe clinical manifestations.³ Individuals who are homozygous for the L444P mutation tend to have severe disease, often with neurologic complications, although several individuals (including adults) with this genotype have had no overt neurologic problems.⁴ Concerning the very rare perinatal form,

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homozygosity for recombinant *GBA* alleles, which are fundamentally null alleles, leads to early lethality, usually in utero or during the first few days of life, whereas genotypes involving a recombinant allele and a missense mutation may be less detrimental. Individuals homozygous for the D409H (c.1342G>C) allele have an atypical phenotype characterized by cardiovascular disease with calcification of the mitral and aortic valves as well as calcification of ascends aorta, corneal opacities, and hydrocephalus.⁵

Mutations of *GBA* are considered a well-established susceptibility factor for Parkinson's disease, Parkinsonism and other Lewy body disorders.⁶ Either homozygosity and heterozygosity for different *GBA* mutations are reported in patients with these neurological diseases. The mechanism underlying this association is unclear, but molecular interactions between glucocerebrosidase mutants and processing of α -synuclein are strongly implicated.⁷

At present the factors that influence disease severity or progression within particular genotypes are not completely known. Recently

CLN8 has been proposed as a candidate modifier gene that may function as a protective sphingolipid sensor and/or in glycosphingolipid trafficking⁸ and MSH6 as modifier gene that leads to constitutional mismatch repair deficiency syndrome and increased cancer risk in GD patients.⁹ Furthermore, as in other patient populations, vitamin D receptor polymorphic genotype may be an independently sorting modifier in the prediction of bone mineral density and bone involvement in Gaucher disease.¹⁰ Instead BMRP2 and ALK1 (supposed modifier genes for pulmonary hypertension/hepatopulmonary syndrome) are not mutated in patients with this rare complication of GD.¹¹

The point of view of clinical geneticist

GD is an autosomal recessive disease. The risk for family members is not different from the other autosomal recessive diseases. Concerning carrier detection, glucosylceramidase activity assay in peripheral blood leukocytes is unreliable for this purpose because of significant overlap in residual enzyme activity levels between obligate carriers and the general population.

Molecular genetic testing is used to identify carriers among at-risk family members once the disease-causing mutations have been identified in the family. Testing for the four common GBA alleles has been included in panels specifically designed for carrier screening in the Ashkenazi Jewish population.¹² Pre-conception testing of the partner of a known carrier or affected individual may be requested, especially in ethnic groups of high prevalence. In this instance targeted mutation analysis is insufficient and full sequence analysis should be undertaken. Prenatal testing in severe untreatable forms of Gaucher disease (types II and III) relies on analysis of glucosylceramidase enzymatic activity of fetal cells obtained by chorionic villus sampling or by amniocentesis. If GBA mutations have been identified in a previously affected sibling, prenatal testing could rely on mutation analysis of GBA performed on fetal DNA. Preimplantation genetic diagnosis may be available for families in which the disease-causing mutations have been identified. Individuals with acute neurologic disease (type II) tend to have a similar disease course. However GD patients with chronic neurologic involvement (type III) could show variable rates of disease progression, even when they are members of the same family. That could complicate genetic counseling. Requests for prenatal testing for treatable condition such as GD type I is not common.

The point of view of the clinician

GD is a pan-ethnic disorder affecting approximately 1:40,000 to 1:60,000 individuals globally. GD type I is prevalent in the Ashkenazi Jewish population, with a disease prevalence of 1:855 and an estimated carrier frequency of 1:18.¹³

The complex multisystemic phenotype of GD is attributed to widespread accumulation of glycolipid-engorged macrophages, which are named Gaucher cells (Figure 1).¹

However a number of manifestations of GD cannot be directly attributed to lysosomal accumulation of glycolipids, such as predilection to gallstones,¹⁴ cancers,¹⁵ pulmonary hypertension and hepatopulmonary syndrome.²

GD encompasses a spectrum of clinical findings from a perinatal lethal form to an asymptomatic form. However the classification of GD by clinical subtype is still useful in describing the wide range of clinical findings and broad

variability in presentation. Three major clinical types are delineated: type I (chronic non-neuropathic), type II (acute neuroathic), and type III (chronic neuropathic). The most prevalent form is GD type I, but in some countries (Egypt, Japan, Sweden, and Poland) the neuropathic forms can have a higher prevalence than GD type I.¹⁶

Gaucher disease type I

In the majority of patients with type I GD, the onset is reported in pediatric age even if diagnosis is delayed until the adult life. Usually, the patients present with visceromegaly, hematological complications, and bone disease (Table 1).

The spleen is enlarged in almost all untreated patients with consequent hypersplenism associated with pancytopenia (*i.e.*, anemia, leukopenia, and thrombocytopenia). Complications of Gaucher's cell infiltration of the spleen include fibrotic scarring, risk of rupture, infarcts, nodules, so-called *Gaucheromas* and malignancies.

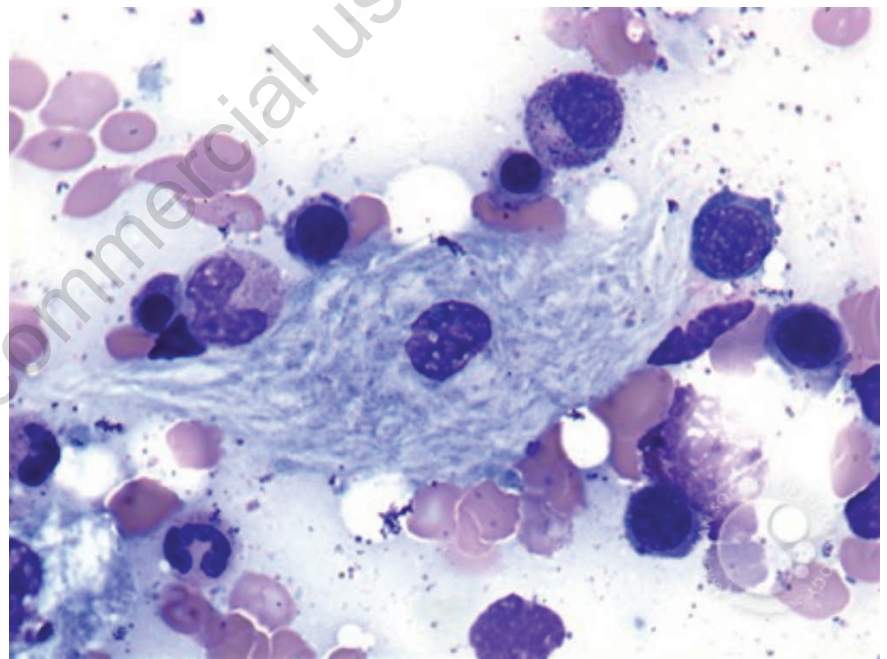


Figure 1. Bone marrow smear: Gaucher cell. The characteristic cytoplasm with striated pattern resembling wrinkled tissue paper or crumpled silk results from accumulation of glucocerebroside.

Table 1. Non-cardiac red flags.

Clinical spectrum from lethal perinatal form to adult asymptomatic form

Multisystemic disease

Visceromegaly

Hematologic abnormalities

Bone complications

Liver enlargement is common, although cirrhosis and hepatic failure are rare.

Cytopenia is almost universal in untreated GD patients. Anemia, thrombocytopenia and leukopenia may be present simultaneously or independently, secondary to hypersplenism or bone marrow failure from Gaucher cells infiltration. Immune thrombocytopenia has also been reported and it should be excluded in individuals with persistent thrombocytopenia despite GD-specific therapy. Acquired coagulation factor deficiencies including low-grade disseminated intravascular coagulation and specific inherited coagulation factor deficiencies have been reported. Abnormal platelet aggregation may contribute to bleeding diathesis in the presence of normal platelet counts.¹⁷

Clinical or radiographic evidence of bone disease occurs in 70-100% of individuals with type I GD. Bone disease ranges from asymptomatic osteopenia to focal lytic or sclerotic lesions and osteonecrosis. Bone involvement, which may lead to acute or chronic bone pain, pathologic fractures, and subchondral joint collapse with secondary degenerative arthritis, is often the most debilitating aspect of GD type I and may not correlate with the severity of hematologic or visceral problems.¹⁸ Untreated GD children show growth deficiency.

Pulmonary involvement, rarely reported in GD patients, includes interstitial lung disease, alveolar/lobar consolidation, pulmonary hypertension and hepatopulmonary syndrome. The latter two pulmonary vascular manifestations result in life threatening disease. In series of GD/pulmonary hypertension-hepatopulmonary syndrome patients, there is preponderance of females and N370S heteroallelic GBA1 genotype. Splenectomy appears essential to develop pulmonary hypertension. Hepatopulmonary syndrome resulting from abnormal vascular shunting in the lungs mainly occurs in patients with severe liver disease or in whom the spleen has been removed and it may be associated with pulmonary hypertension.¹¹

Children or adults may have polyclonal gammopathy and an increased incidence of monoclonal gammopathy has been reported in adults.¹⁹ Affected individuals also exhibit altered cellular immune profiles with increased peripheral blood natural killer T lymphocytes and reduced numbers of functionally normal dendritic cells.²⁰ GD is also associated with elevated cytokine levels and increasing possibility to develop autoimmune disease.¹³

Adult GD patients have elevated risk of certain malignancies including multiple myeloma, hepatocellular carcinoma, non-Hodgkins lymphoma, malignant melanoma, and pancreatic cancer.^{15,21}

Adult patients with Gaucher disease also have a 7% higher risk of Parkinson's disease or Parkinsonism.^{22,23} Other neurologic complications (spinal cord or nerve root compression)

may occur secondary to bone disease (e.g., severe osteopenia with vertebral compression; emboli following long bone fracture).

The incidence of peripheral neuropathy has been reported in some casistic series and may be higher than previously recognized.^{24,25}

Gaucher disease types II and III

Neuropathic forms of GD are rare. It is estimated that approximately 6% of Gaucher patients have neuropathic GD; 5% have the chronic neuropathic form, and 1% have the acute form of the disease.²⁶

Clinically, neuropathic GD ranges from lethal perinatal form to very mild form limited to abnormalities of horizontal ocular saccades.

Perinatal lethal GD is characterized by non-immune hydrops fetalis, *in utero* fetal demise and neonatal distress. In some cases without hydrops, neurological signs occur in the first week of life and lead to death within 3 months. Less common signs of the disease are hepatosplenomegaly, ichthyosis, collodion-baby, arthrogyriposis and facial dysmorphism. Children with onset before the age of two years experience rapid disease progression and death by the age of 2-4 years. These are usually classified as having type II GD. They present with early onset of bulbar paresis, cranial nerve palsies, opisthotonus, spastic paresis, seizures, variable hepatosplenomegaly and usually mild hematological abnormalities and absent bone disease. Patients with type III GD may have onset before the age of 2 years or later, but they have a slowly course and death by the third to fourth decade of life. Type III GD represents a highly heterogeneous multisystem disorder including neurological deficits: it has been divided into 3 subtypes.

Type IIIA Gaucher disease is characterized by progressive neurological failure in children with cognitive impairment, myoclonic or tonic-clonic epilepsy, supranuclear gaze palsies, and ataxia; hepatosplenomegaly is usually mild, but the patients succumb to progressive brainstem degeneration or uncontrollable seizures. Patients with type IIIB Gaucher disease have static supranuclear gaze palsy, usually of horizontal but occasionally of vertical type and cog-

nitive impairment with severe hepatosplenomegaly, anemia, and extensive osseous manifestations including osteonecrosis and thoracic gibbus. Patients with type IIIC have stable oculomotor apraxia with moderate splenic and liver enlargement, while skeletal manifestations may not be prominent; typically they have involvement of the cardiac valves, corneal opacity and hydrocephalus. Heavy calcification of the valve leaflets, extensive calcification of the entire aortic arch, and involvement of the coronary arteries could occur. Sudden death due to cardiac tachyarrhythmia before surgery for aortic valve disease has been reported, and in some cases thickening and calcification has been noted within the myocardium and the descending aorta.¹³

The point of view of the cardiologist

Prevalence severity and time of onset

Cardiovascular involvement is generally rare in Gaucher disease. Although all the Gaucher subtypes may be interested, subtype IIIC is most frequently involved. The age of onset and severity of phenotype may vary.²⁷

Table 2 describes typical cardiac pictures of patients with Gaucher disease (*red flags*).²⁸⁻³⁷

The presence of one or more *red flags* could signal possible disease.

Myocardial involvement

Gaucher disease is part of inherited infiltrative disorders causing restrictive cardiomyopathy. It is secondary to the accumulation of the lipid-laden macrophages with possible consequent inflammatory and hyperplastic cellular response.³⁸ Emblematic cases, such as a 17-year old girl with pseudo-hypertrophy and calcification of both left and right ventricles²⁸ and a patients with adult type I Gaucher with left ventricular thickening and an extended area of apical akinesis have been described.²⁹ A dilated/hypokinetic

Table 2. Cardiac red flags.

Heart valve disease: valvular fibrosis and calcification
Restrictive cardiomyopathy
Dilated/hypokinetic cardiomyopathy
Calcification of aortic artery
Constrictive pericarditis
Pulmonary hypertension

phenotype represents probably the evolution of the pseudo hypertrophy or the initial inflammatory response to Gaucher's cells infiltration. The enzyme replacement therapy has been reported to be beneficial for the recovery of left ventricular function.³⁹ Myocardial involvement is often sub-clinical (preclinical phase of the cardiac phenotype), and circumstances such as pregnancy may favor the clinical onset of the cardiac phenotype.⁴⁰

Pulmonary hypertension

Considering that severe pulmonary involvement is reported mainly in types II and III Gaucher's disease, these forms are at mayor risk to develop pulmonary hypertension and *cor pulmonale*. Several patho-physiological mechanisms can contribute to this condition, including the infiltration of Gaucher's cells that lead to hypoxemia and consequent pulmonary vasoconstriction and the extensive infiltration of the alveolar capillaries with Gaucher cells. Pulmonary hypertension is well documented also in individuals with liver disease and it is presumably the result of inability to detoxify gut-derived factors, which somehow adversely affect the pulmonary endothelium with consequent pulmonary hypertension.³⁰

Valvular involvement

Valvular involvement may be present in both pediatric and adult age. Valvular fibrosis and calcifications interest mitral or aortic valves or both with possible various degree of regurgitation or stenosis. They increase with age and in some cases is necessary valve replacement.³¹⁻³³

Since the risk of perioperative bleeding is high in patients with type IIIC GD, it is important to exclude this type of disease in adolescent or young adults with severe mitral and or aortic valve disease.⁴¹

The valvular involvement is mainly reported in patients with D409H homozygosis.³⁰ However, it has been reported in association with other gene defects. A 60-year old woman, known to have aortic valve pathology since the age of 30, presented with heart failure. Echocardiography showed severe aortic stenosis. Bone marrow aspiration revealed typical Gaucher cells and DNA investigation showed homozygous for G377S mutation.⁴²

Nevertheless, pathogenesis of valve disease is poorly understood, so far. Veinot *et al.*⁴³ first documented the presence of Gaucher cells in the heart valve tissue and proposed a cell-mediated mechanism involving bone matrix proteins and integrins in the pathogenesis of the valvular injury. It has been suggested that calcifications may be the results of recurrent valvulitis attacks triggered by the deposition of Gaucher cells or by the release of excessive cytokines.³²

Pericardial involvement

Pericardial calcification and pericardial effusion have been reported.^{34,35} An hypothesis claims that calcification may be secondary to the organization of unrecognized pericardial hemorrhage. This hypothesis was supported by the evidence of extensive hemosiderosis in the pericardium.³⁴ In cases of constrictive pericarditis and pericardiectomy, the removed fibrotic tissue consisted of collagen fibres, scattered macrophages containing hemosiderin pigment, without Gaucher cells.³⁵

Aortic and other vascular sites involvement

Calcification of the aortic artery has been described in literature. As reported by Leslie *et al.*³⁶ an 18-year old patient affected by Gaucher type IIIC had a relative hypoplasia of the entire thoracic aorta with wall thickening and calcification from the aortic root to the proximal descending aorta. She needed an intervention of replacement of the ascending aorta and proximal aortic arch.

Stone and co-authors³⁷ described another case of a 6-year old child diagnosed when he was 6-month old; he died six months later after pulmonary edema. Necroscopy showed ventricular hypertrophy, intimal fibrosis of the coronary arteries and aorta and a grey fibrotic thickening of the intimal surface of the root of the aorta. Gaucher cells were scattered along the intimal and media of the aorta in the area of fibrosis.

Figure 2 reports a case of a young male with both calcification and slight dilatation of the ascending aorta.

Also coronary and carotid arteries can have severe stenosis as documented from Mireles *et al.*⁴¹ in a 13-year old girl.

Diagnosis

The most efficient and reliable method of establishing the diagnosis of GD is the assay of acid β -glucosylceramidase enzyme activity in peripheral blood leukocytes or in skin fibroblasts. Molecular genetic testing gives confirmation of the diagnosis and may be considered for genetic counseling purpose. It could be used for diagnosis of homozygous relatives only when disease-causing mutations have been identified in the propositus or in specific ethnic groups (*e.g.* in the Ashkenazi Jewish population).

Therapy

Enzyme replacement therapy, available since the early 1990s, is an effective treatment for Gaucher disease, and today imiglucerase is the acknowledged standard of care for the treatment of patients with GD. Enzyme replacement therapy does not cross blood brain barrier and therefore is not indicated for neuropathic forms. Recently two other biosimilar agents have been developed. One of these, velaglucerase alfa, has received international marketing authorization, and another, taliglucerase alfa, is in late stage development. Substrate reduction therapy (miglustat) has also been approved for the treat-

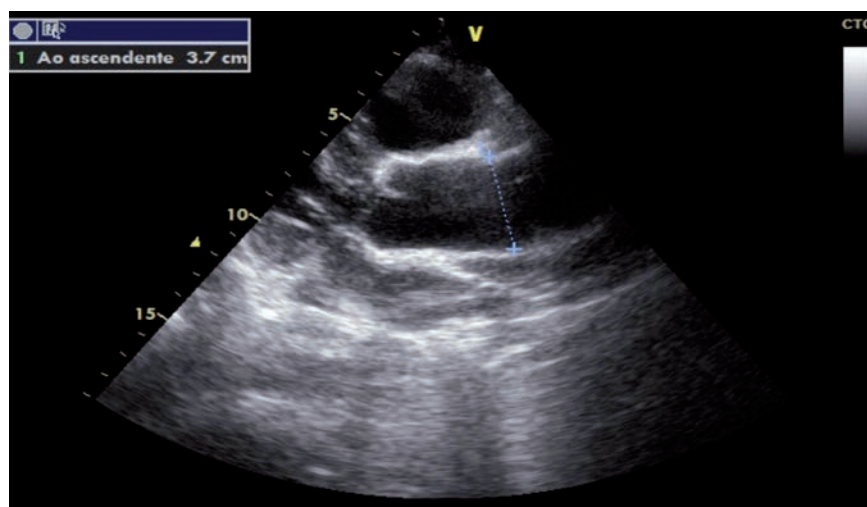


Figure 2. Personal experience (Adult and Pediatric Cardiology Division and Unit of Metabolic Disease St. Gerardo Hospital, Monza, Italy). Fifteen-year old boy (from Kosovo) with type I Gaucher disease and a slight dilatation and calcification of the ascending aorta.

ment of symptomatic type I patients with mild to moderate disease for whom ERT is unsuitable or not a therapeutic option. Another substrate reduction therapy (eliglustat) is in late stage development.⁴⁴

Future perspectives

Being GD the most frequent lysosomal disease with more than 6000 patients reported in the International Collaborative Gaucher disease Group database, many data are available to understand the determinants of heterogeneity or biologic features that influence clinical manifestations. However little has been understood of the cardiovascular complication.

Improved understanding of physiopathogenic mechanisms of this complication will allow rational assessment and treatment of patients.

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