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Gaucher Disease

Synonyms: Glucocerebrosidase Deficiency, Glucosylceramidase Deficiency

Derralynn A Hughes, MA, DPhil, FRCP, FRCPath[1] and Gregory M Pastores, MD[2]

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Summary

Clinical characteristics

Gaucher disease (GD) encompasses a continuum of clinical findings from a perinatal-lethal disorder to an asymptomatic type. The characterization of three major clinical types (1, 2, and 3) and two clinical forms (perinatal-lethal and cardiovascular) is useful in determining prognosis and management. Cardiopulmonary complications have been described with all the clinical phenotypes, although varying in frequency and severity.

Type 1 GD is characterized by the presence of clinical or radiographic evidence of bone disease (osteopenia, focal lytic or sclerotic lesions, and osteonecrosis), hepatosplenomegaly, anemia, thrombocytopenia, lung disease, and the absence of primary central nervous system disease.

Type 2 GD is characterized by primary central nervous system disease with onset before age two years, limited psychomotor development, and a rapidly progressive course with death by age two to four years.

Type 3 GD is characterized by primary central nervous system disease with childhood onset, a more slowly progressive course, and survival into the third or fourth decade.

The *perinatal-lethal form* is associated with ichthyosiform or collodion skin abnormalities or with nonimmune hydrops fetalis.

The *cardiovascular form* is characterized by calcification of the aortic and mitral valves, mild splenomegaly, corneal opacities, and supranuclear ophthalmoplegia.

Diagnosis/testing

The diagnosis of GD relies on demonstration of deficient glucocerebrosidase (glucosylceramidase) enzyme activity in peripheral blood leukocytes or other nucleated cells, or by the identification of biallelic pathogenic variants in *GBA1* on molecular genetic testing.

Author Affiliations: 1 Professor of Experimental Haematology, Department of Academic Haematology, University College Medical School, London, United Kingdom; Email: derralynnhughes@nhs.net. 2 Clinical Professor, Medicine (Genetics), University College, Dublin, Ireland.

Management

Targeted therapy: Options include enzyme replacement therapy (ERT) or substrate reduction therapy (SRT; e.g., miglustat, eliglustat). Hematopoietic stem cell transplantation may be an option in individuals with severe GD, primarily those with chronic neurologic involvement (type 3 GD).

Supportive care: When possible, management by a multidisciplinary team at a GD Comprehensive Treatment Center. Symptomatic treatment includes partial or total splenectomy for those with massive splenomegaly, significant areas of splenic fibrosis, and persistent significant thrombocytopenia (platelets <30,000/mm^3) with a risk of bleeding; splenectomy may be needed even in those on targeted therapy. Supportive care for all affected individuals may include: orthopedic management of bone disease; analgesics for bone pain; joint replacement surgery for relief from chronic pain and restoration of function; anti-bone resorptive agents, calcium, and vitamin D for osteoporosis; transfusion of blood products for severe anemia and bleeding; the use of anticoagulants in individuals with severe thrombocytopenia and/or coagulopathy should be discussed with a hematologist to avoid the possibility of excessive bleeding; treatment of cholelithiasis, pulmonary disease, pulmonary hypertension, multiple myeloma, psychological manifestations, parkinsonism, and seizures according to the relevant specialist; social work support and care coordination as needed.

Surveillance: Clinical assessment of disease progression at least every six months to include hematologic, orthopedic, pulmonary, cardiac, psychiatric, and neurologic assessment; clinical assessment for abdominal pain, early satiety, evidence of bleeding diathesis, growth and weight gain, clinical disease markers, and liver enzymes; imaging for spleen and liver volumes at least every one to two years. Additional evaluations to be done as needed include radiographs, MRI, and dual-energy x-ray absorptiometry (DXA) scan; bone age in children with growth and pubertal delay; ultrasound for gallstones; serum iron, ferritin, and vitamin B_{12} in those with anemia; and EKG and echocardiography with Doppler in individuals after splenectomy and those with elevated pulmonary artery pressure.

Agents/circumstances to avoid: Nonsteroidal anti-inflammatory drugs in individuals with moderate-to-severe thrombocytopenia.

Evaluation of relatives at risk: It is appropriate to offer testing to asymptomatic at-risk relatives so that those with glucocerebrosidase enzyme deficiency or biallelic pathogenic variants can benefit from early diagnosis and treatment if indicated.

Pregnancy management: Pregnancy can exacerbate preexisting symptoms and trigger new features in affected women. Those with severe thrombocytopenia and/or clotting abnormalities are at increased risk for bleeding around the time of delivery. Evaluation by a hematologist prior to delivery is recommended. The lack of studies on the safety of eliglustat use during pregnancy and lactation has led to the recommendation that this medication be avoided during pregnancy, if possible.

Genetic counseling

GD is inherited in an autosomal recessive manner. The parents of an affected individual are typically heterozygous for a *GBA1* pathogenic variant; in some families, an asymptomatic parent may be found to be homozygous rather than heterozygous. If both parents are known to be heterozygous for a *GBA1* pathogenic variant, each sib of an affected individual has at conception a 25% chance of being affected, a 50% chance of being a heterozygote, and a 25% chance of inheriting neither of the familial *GBA1* pathogenic variants. Once the *GBA1* pathogenic variants have been identified in an affected family member, molecular genetic carrier testing for at-risk family members, preimplantation genetic testing, and prenatal testing for GD are possible. The identification of 0%-15% of normal glucocerebrosidase enzyme activity in fetal samples obtained by chorionic villus sampling (CVS) or amniocentesis – ideally complemented by molecular genetic testing – can also be used to establish affected status in a fetus.

GeneReview Scope

Gaucher Disease: Included Phenotypes	
Major clinical phenotypes	• Type 1 Gaucher disease • Type 2 Gaucher disease (acute; infantile [1]) • Type 3 Gaucher disease (subacute; juvenile)
Variant phenotypes	• Perinatal-lethal form • Cardiovascular form

1. Saposin C deficiency can be associated with features characteristic of severe neuropathic Gaucher disease; see Differential Diagnosis.

Diagnosis

Suggestive Findings

Scenario 1: Abnormal Newborn Screening (NBS) Result

NBS for Gaucher disease (GD) is primarily based on quantification of glucocerebrosidase enzyme activity on dried blood spots.

Glucocerebrosidase enzyme activity values below the cutoff reported by the screening laboratory are considered positive, and additional testing is required to establish the diagnosis (see Establishing the Diagnosis).

Scenario 2: Symptomatic Individual

GD encompasses a continuum of clinical findings from a perinatal-lethal disorder to type 1 GD with adult onset. GD **should be suspected** in individuals (by age) with the following combination of central nervous system, bony, hematologic, and other clinical and family history findings (see Table 1).

Table 1. Gaucher Disease: Clinical Phenotypes

Age of Onset	Phenotype	Primary CNS Involvement	Bone Disease [1]	Other
Adult	Type 1	No	Yes	• Splenomegaly • Hepatomegaly • Cytopenia [2] • Pulmonary disease
Infancy to early childhood	Type 2 (acute; infantile)	• Bulbar signs • Pyramidal signs • Cognitive impairment	No	• Hepatomegaly • Splenomegaly • Cytopenia [2] • Pulmonary disease • Dermatologic changes
Childhood	Type 3 (subacute; juvenile)	• Oculomotor apraxia • Seizures • Progressive myoclonic epilepsy	Yes	• Hepatomegaly • Splenomegaly • Cytopenia [2] • Pulmonary disease
Perinatal	Perinatal-lethal form	Pyramidal signs	No	• Ichthyosiform or collodion skin changes • Nonimmune hydrops fetalis

Table 1. continued from previous page.

Age of Onset	Phenotype	Primary CNS Involvement	Bone Disease [1]	Other
Childhood to early adolescence	Cardiovascular form	Oculomotor apraxia	Yes	• Calcification of mitral & aortic valves • Corneal opacity • Mild splenomegaly

CNS = central nervous system
1. Osteopenia, focal lytic or sclerotic lesions, and/or osteonecrosis
2. Anemia, leukopenia, and/or thrombocytopenia

Family history is consistent with autosomal recessive inheritance (e.g., affected sibs and/or parental consanguinity). Absence of a known family history does not preclude the diagnosis.

Establishing the Diagnosis

The diagnosis of GD **is established** in a proband by the finding of 0%-15% of normal glucocerebrosidase enzyme activity in peripheral blood leukocytes (or other nucleated cells), or by the identification of biallelic pathogenic (or likely pathogenic) variants in *GBA1* on molecular genetic testing (see Table 2). Note: Identification of deficient glucocerebrosidase enzyme activity is recommended in individuals with biallelic *GBA1* variants to confirm the diagnosis.

Note: (1) Molecular analysis of *GBA1* is complicated by the presence of a highly homologous pseudogene, *GBAP1*. (2) The amino acid numbering for glucocerebrosidase used in this *GeneReview* follows the HGVS-recommended nomenclature, which includes the first 39 amino acids, and differs from the traditional numbering system, which does not include the first 39 amino acids. Using the HGVS-recommended nomenclature, the pathogenic variant p.Asn370Ser is named p.Asn409Ser and the pathogenic variant p.Leu444Pro is named p.Leu483Pro. For a more complete list of pathogenic variants using traditional and standard nomenclature, see Montfort et al [2004]. (3) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variant" and "likely pathogenic variant" are synonymous in a clinical setting, meaning that both are considered diagnostic and can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this *GeneReview* is understood to include likely pathogenic variants. (4) Identification of biallelic *GBA1* variants of uncertain significance (or of one known *GBA1* pathogenic variant and one *GBA1* variant of uncertain significance) does not establish or rule out the diagnosis.

Molecular testing approaches can include **single-gene testing** or use of a **multigene panel**.

- **Single-gene testing.** Sequence analysis of *GBA1* is performed first to detect missense, nonsense, and splice site variants and small intragenic deletions/insertions. Note: Depending on the sequencing method used, single-exon, multiexon, or whole-gene deletions/duplications may not be detected. If only one or no variant is detected by the sequencing method used, the next step is to perform gene-targeted deletion/duplication analysis to detect exon and whole-gene deletions or duplications.
- **A multigene panel** that includes *GBA1* and other genes of interest (see Differential Diagnosis) may also be considered to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) Special consideration for the presence of the highly homologous pseudogene, *GBAP1*, must be taken into account. (2) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (3) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (4) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome

analysis that includes genes specified by the clinician. (5) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

Table 2. Molecular Genetic Testing Used in Gaucher Disease

Gene [1]	Method	Proportion of Pathogenic Variants [2] Detectable by Method
GBA1	Sequence analysis [3, 4]	~99% [5, 6]
	Gene-targeted deletion/duplication analysis [7]	<1% [5, 8]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include missense, nonsense, and splice site variants and small intragenic deletions/insertions; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. Due to the presence of a highly homologous pseudogene (*GBAP1*), PCR-based methods must be designed to differentiate *GBA1* from the pseudogene.
5. Data derived from the subscription-based professional view of Human Gene Mutation Database [Stenson et al 2020]
6. Complex disease-causing alleles derived from *GBA1-GBAP1* recombinant events, such as the common RecNciI allele, may be detected by sequence analysis.
7. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods that rely on hybridization, such as multiplex ligation-dependent probe amplification (MLPA) or gene-targeted microarray designed to detect single-exon deletions or duplications, may not detect deletions or duplications in regions of high homology between *GBA1* and *GBAP1*. Methods such as quantitative PCR, long-range PCR, and Southern blotting may be used to detect deletion/duplication of *GBA1*.
8. Deletions of 3,925 bp including exons 1-2 and the 5' UTR (a region unique to *GBA1*) and whole-gene deletions have been reported [Beutler & Gelbart 1994, Cozar et al 2011].

Clinical Characteristics

Clinical Description

Gaucher disease (GD) encompasses a spectrum of clinical findings from a perinatal-lethal form to an asymptomatic form. However, for the purposes of determining prognosis and management, the classification of GD by clinical type is still useful in describing the wide range of clinical findings and broad variability in presentation. Three major clinical types are delineated by the absence (type 1) or presence (types 2 and 3) of primary central nervous system (CNS) involvement (see Table 1).

Type 1 GD

Bone disease. Clinical or radiographic evidence of bone disease occurs in 70%-100% of individuals with type 1 GD. Bone disease ranges from asymptomatic osteopenia to focal lytic or sclerotic lesions and osteonecrosis [Hughes et al 2019]. 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 type 1 GD.

Acute bone pain manifests as "bone crises" or episodes of deep bone pain that are usually confined to one extremity or joint [Andrade-Campos et al 2018] and are often accompanied by fever, leukocytosis, and sterile blood culture. The affected region may be swollen and warm to touch; imaging studies may reveal signal abnormalities consistent with localized edema or hemorrhage; radiographs may show periosteal elevation ("pseudo-osteomyelitis").

Conventional radiographs may reveal undertubulation (Erlenmeyer flask configuration) in the distal femur and endosteal scalloping as a sign of bone marrow infiltration. MRI reveals the extent of marrow involvement and

the presence of fibrosis and/or infarction. In general, marrow infiltration extends from the axial to the appendicular skeleton, and greater involvement is often seen in the lower extremities and proximal sites of an affected bone. The epiphyses are usually spared, except in advanced disease. Bone densitometry studies enable quantitative assessment of the degree of osteopenia.

Bone disease in GD may not correlate with the severity of hematologic or visceral problems.

Secondary neurologic disease. Although individuals with type 1 GD do not have primary CNS disease, neurologic complications (spinal cord or nerve root compression) may occur secondary to bone disease (e.g., severe osteoporosis with vertebral compression; emboli following long bone fracture) or coagulopathy (e.g., hematomyelia) [Pastores et al 2003].

Peripheral neuropathy has been described in individuals with type 1 GD, when testing is performed; however, in most individuals this is a subclinical finding [Andréasson et al 2019]. Among symptomatic individuals, assessments should be undertaken to assess for an alternative explanation (e.g., vitamin B_{12} deficiency).

Splenic manifestations. The spleen size is enlarged to 1,500-3,000 cc in adults with GD, compared to a normal adult spleen size of 50-200 cc. Infarction of the spleen can result in acute abdominal pain. Rarely, acute surgical emergencies may arise because of splenic rupture [Stone et al 2000b].

Liver manifestations. Hepatomegaly is common, although cirrhosis and hepatic failure are rare [Ayto et al 2010].

Cytopenias are almost universal in untreated individuals with GD. Anemia, thrombocytopenia, and leukopenia may be present simultaneously or independently [Linari & Castaman 2016, Linari & Castaman 2022]. The pattern of cytopenia in GD is dependent on spleen status. Hypersplenism is associated with pancytopenia (i.e., anemia, leukopenia, and thrombocytopenia).

Thrombocytopenia may result from hypersplenism, splenic pooling of platelets, or marrow infiltration or infarction. Immune thrombocytopenia has also been reported and should be excluded in individuals with persistent thrombocytopenia despite GD-specific therapy. Thrombocytopenia may be associated with easy bruising or overt bleeding, particularly with trauma, surgery, or pregnancy. The risk for bleeding may be increased in the presence of clotting abnormalities.

Anemia may result from hypersplenism, hemodilution (e.g., pregnancy), iron deficiency, vitamin B_{12} deficiency, and, in advanced disease, decreased erythropoiesis as a result of bone marrow failure from Gaucher cell infiltration or medullary infarction.

Leukopenia is rarely severe enough to require intervention. Deficient neutrophil function has been reported.

Coagulation abnormalities. Acquired coagulation factor deficiencies include low-grade disseminated intravascular coagulation and specific inherited coagulation factor deficiencies (e.g., factor XI deficiency among Ashkenazi Jews). An investigation of Egyptian individuals with type 1 GD revealed a wide variety of coagulation factor abnormalities (fibrinogen, factors II, VII, VIII, X, and XII) [Deghady et al 2006]. Abnormal platelet aggregation may contribute to bleeding diathesis in the presence of normal platelet counts [Linari & Castaman 2016].

Cholelithiasis occurs in a significant proportion of adults with GD. In a cohort of 417 affected individuals, the prevalence of gallstones was 32%, and they were more common in women with GD. Those with gallstones were more likely to be asplenic and older; they were also more likely to have higher low-density lipoprotein concentrations, more severe GD, family history of gallstones, and higher body mass index values than those without gallstones [Taddei et al 2010, Zimmermann et al 2016].

Pulmonary involvement. Lung disease in individuals with type 1 GD is infrequent, and mainly observed among historical cases (i.e., individuals subjected to splenectomy) [Ramaswami et al 2021]. The following findings have been observed:

- Interstitial lung disease
- Alveolar/lobar consolidation
- Pulmonary arterial hypertension (PAH) is well documented in individuals with liver disease and is presumably the result of inability to detoxify gut-derived factors, which somehow adversely affect the pulmonary endothelium with resultant pulmonary hypertension. PAH can also occur in individuals with GD without liver disease, although in most individuals it is not clinically significant and is not progressive [Mistry et al 2002]. In a study of 14 individuals with PAH, median age at GD diagnosis was 36 years (range: 22-63). There was a female preponderance (ratio of 5:2), and all individuals in this report had undergone splenectomy (median age: 12 years) [Lo et al 2011].
- Dyspnea and cyanosis with digital clubbing attributed to hepatopulmonary syndrome have been described in individuals with liver dysfunction; this is often caused by an intercurrent disease (e.g., viral hepatitis).

Note: Individuals with type 1 GD without evidence of pulmonary involvement who limit physical exertion because of easy fatigability may have impaired circulation [Miller et al 2003].

Pregnancy and childbirth. Except in women with significant PAH, pregnancy is not contraindicated in GD (see Pregnancy Management).

In some women the diagnosis of GD is first identified during pregnancy due to exacerbation of hematologic features.

Malignancy. Individuals with GD have an increased risk of multiple myeloma [Sudul et al 2023]. The increased risk for multiple myeloma has been attributed to chronic immune dysregulation secondary to antigenic properties of the incompletely metabolized substrate [Nair et al 2018].

Epidemiologic studies have also suggested an elevated risk of additional malignancies including hepatocellular carcinoma [de Fost et al 2006], non-Hodgkin lymphoma, malignant melanoma, and pancreatic cancer [Landgren et al 2007]. However, subsequent studies have failed to identify an increased risk of these additional malignancies [Cox et al 2015b].

Immunologic abnormalities. Children and adults with GD may have polyclonal gammopathy [Wine et al 2007]. An increased incidence of monoclonal gammopathy has been reported in adults [Brautbar et al 2004].

Psychological complications. Persons with GD exhibit moderate-to-severe psychological complications including somatic concerns and depressed mood [Packman et al 2006].

Parkinsonian features have been reported in a few individuals with type 1 GD and individuals heterozygous for a *GBA1* pathogenic variant. The following findings suggest that pathogenic variants in *GBA1* and/or alterations in glucosylceramide metabolism may be a risk factor for parkinsonism [Sidransky 2005]. Among those who developed PD, individuals with GD had a younger age at onset of PD than *GBA1* heterozygotes (mean: 54.2 vs 65.2 years, respectively; P=0.003). Estimated age-specific risk for PD at age 60 and 80 years was 4.7% and 9.1%, respectively, among individuals with GD. The risk for PD was higher in individuals with GD than non-carriers (P=0.008, log-rank test) and in *GBA1* heterozygotes than non-carriers (P=0.03, log-rank test), but it did not reach statistical significance between individuals with GD and *GBA1* heterozygotes (P=0.07, log-rank test) [Alcalay et al 2014].

Additional genetic risk factors may contribute to the risk of PD in those with type 1 GD. A recent study found that non-*GBA1* variants included in the PD genetic risk score were more frequent in individuals with type 1 GD who developed PD [Blauwendraat et al 2023].

Metabolic abnormalities. Serum concentrations of angiotensin-converting enzyme, tartrate-resistant acid phosphatase, ferritin, chitotriosidase, PARC/CCL18, and lyso-Gb1 (glucosylsphingosine) are usually elevated. Serum concentrations of total and high-density lipoprotein cholesterol are often low.

Type 2 GD / Type 3 GD (Primary Neurologic Disease)

Neurologic disease. Previously, affected individuals were classified into type 2 or type 3 GD based on the age of onset of neurologic signs and symptoms and the rate of disease progression. Children with onset before age two years with a rapidly progressive course, limited psychomotor development, and death by age two to four years were classified as having type 2 GD. Individuals with type 3 GD may have onset before age two years but often have a more slowly progressive course, with life span extending into the third or fourth decade in some individuals. However, these distinctions are not absolute, and it is increasingly recognized that neuropathic GD represents a phenotypic continuum, ranging from abnormalities of horizontal ocular saccades at the mild end to hydrops fetalis at the severe end [Daykin et al 2021].

Bulbar signs (i.e., stridor, squint, and swallowing difficulty) and pyramidal signs (i.e., opisthotonos, head retroflexion, spasticity, and trismus) in infancy are characteristic of type 2 GD.

Oculomotor apraxia, saccadic initiation failure, and opticokinetic nystagmus are common in type 3 GD [Nagappa et al 2015]. Oculomotor involvement may be found as an isolated sign of neurologic disease in individuals with a chronic progressive course and severe systemic involvement (e.g., massive hepatosplenomegaly).

Generalized tonic-clonic seizures and progressive myoclonic epilepsy have been observed in some individuals [Roshan Lal & Sidransky 2017]. In a study of 122 affected individuals, seizures and myoclonic seizures were reported in 19 (16%) and three (2%) persons, respectively [Tylki-Szymańska et al 2010].

Dementia and ataxia have been observed in the later stages of chronic neurologic disease.

Brain stem auditory evoked response (BAER) testing may reveal abnormal wave forms (III and IV) [Okubo et al 2014]. MRI of the brain may show mild cerebral atrophy. (A normal EEG, BAER, or brain MRI does not exclude neurologic involvement.)

Perinatal-Lethal Form

The perinatal-lethal form of GD is associated with hepatosplenomegaly, pancytopenia, and microscopic skin changes (i.e., abnormalities in the stratum corneum attributed to altered glucosylceramide-to-ceramide ratio) and may present clinically with ichthyosiform or collodion skin abnormalities or as nonimmune hydrops fetalis [Orvisky et al 2002]. Arthrogryposis and dysmorphic facial features are seen in 35%-43% of affected individuals [Mignot et al 2003]. These infants are usually stillborn or die shortly after birth.

Another rare severe variant of GD is associated with hydrocephalus, corneal opacities, deformed toes, gastroesophageal reflux, and fibrous thickening of splenic and hepatic capsules [Stone et al 2000b, Inui et al 2001].

Cardiovascular Form

Individuals homozygous for *GBA1* pathogenic variant p.Asp448His present with an atypical phenotype dominated by cardiovascular disease with calcification of the mitral and aortic valves that develops around puberty [Altunbas et al 2015]. Additional findings, which develop earlier but may be missed unless specifically searched for, include mild splenomegaly, corneal opacities, and supranuclear ophthalmoplegia [George et al 2001].

Heterozygotes

Family studies suggest that the incidence of parkinsonism is higher in obligate heterozygotes for a *GBA1* pathogenic variant. Estimated age-specific risk for PD at age 60 and 80 years was 1.5% and 7.7% among heterozygotes and 0.7% and 2.1% among non-carriers, respectively [Alcalay et al 2014].

Genotype-Phenotype Correlations

The level of residual glucocerebrosidase enzyme activity as measured in vitro from extracts of nucleated cells does not correlate with disease type or severity.

Genotype-phenotype correlations in GD are imperfect. Significant overlap in the clinical manifestations found between individuals with the various genotypes precludes specific counseling about prognosis in individual cases [Lepe-Balsalobre et al 2020]. At present the factors that influence disease severity or progression within particular genotypes are not known. Discordance in phenotype has been reported even among monozygotic twins [Lachmann et al 2004, Biegstraaten et al 2011].

Type 1 GD

- Individuals with at least one p.Asn409Ser variant do not develop primary neurologic disease [Koprivica et al 2000]. However, the presence of a p.Asn409Ser allele does not eliminate the risk for PD among individuals with GD.
- In general, individuals who are homozygous for the p.Asn409Ser or p.Arg535His variant tend to have milder disease than those with other genotypes. It is suspected that a significant proportion of Ashkenazi Jewish individuals with this genotype may be asymptomatic and thus do not come to the attention of medical professionals [Bronstein et al 2014]. However, surveillance is critical, as a proportion of these individuals develop progressive disease [Taddei et al 2009].

Primary neurologic disease (type 2 and type 3 GD)

- Individuals who are homozygous for *GBA1* pathogenic variant p.Leu483Pro tend to have severe disease, often with neurologic complications (i.e., types 2 and 3 GD), although several individuals (including adults) with this genotype have had no overt neurologic problems. This variant results in an unstable enzyme with little or no residual activity.
  - In a study of 31 individuals with type 2 GD, p.Leu483Pro accounted for 25 alleles (40%) [Stone et al 2000c]. The p.Leu483Pro variant occurred alone (nine alleles), with the p.Glu365Lys polymorphism (one allele), and as part of a recombinant allele (15 alleles).
  - In another study, homozygosity for p.Leu483Pro was the most common genotype among individuals with type 3 GD (10/24 individuals, or 42%) [Koprivica et al 2000].
  - In a study of affected individuals of Japanese and Korean ancestry with GD including type 1, p.Leu483Pro accounted for 41% and 20.8% of alleles, respectively. The second most common allele among Japanese individuals was p.Phe252Ile (14%); among Korean individuals, p.Gly85Glu (13.9%). The absence of p.Asn409Ser among those examined accounted for the higher frequency of the neuropathic subtype when compared to that seen in Western countries [Eto & Ida 1999, Jeong et al 2011].
- In individuals with GD and myoclonic epilepsy, Park et al [2003] identified 14 genotypes (including the variants p.Val433Leu, p.Gly416Ser, and p.Asn227Ser) previously associated with non-neuronopathic GD, in combination with the variant p.Leu483Pro and recombinant alleles that have been previously associated with neuropathic GD.
- A second variant, p.His294Gln, occurring in *cis* with the p.Asp448His variant has been identified among Greek and Albanian individuals. Homozygosity for the p.[Asp448His;His294Gln] allele has been associated with type 2 GD [Michelakakis et al 2006].

Perinatal-lethal form. Genotypic heterogeneity is significant in this rare subset of individuals. The following have been observed:

- Homozygosity for recombinant alleles [Stone et al 2000a]
- *GBA1* pathogenic variants p.Ser235Pro, p.Arg170Leu, p.Arg159Trp, and p.Arg296Gln [Stone et al 2000a]
- Compound heterozygosity for an insertion-type pathogenic variant and the pathogenic missense variant p.Arg159Gln, previously reported in an individual with type 1 GD [Felderhoff-Mueser et al 2004]

Cardiovascular form. This phenotype has been described only in individuals who are homozygous for *GBA1* pathogenic variant p.Asp448His. The biochemical basis for the unique clinical features associated with this form is not fully delineated. It should be noted that homozygosity for the p.[Asp448His;His294Gln] allele is associated with neuropathic type 2 GD and not the cardiovascular form (see **Primary neurologic disease** above).

c.84dupG and c.115+1G>A. Despite the observed allele frequencies for the pathogenic variants c.84dupG and c.115+1G>A, no live-born homozygote for either variant has been identified. Thus, it is presumed that these genotypes are lethal.

Prevalence

Incidence and prevalence estimates for GD are scarce, except for reports regarding specific populations. Prevalence estimates are also variable, with higher prevalence in populations or regions with known founder variants (e.g., Ashkenazi Jews). A recent review, based on a targeted literature search conducted from January 2011 to September 2020, revealed incidence estimates including all GD subtypes ranging from 0.45-25.0:100,000 live births (16 studies); incidence was lowest for Asia-Pacific populations. The incidence of type 1 GD was estimated at 0.45-22.9:100,000 live births (Europe and North America) and type 3 GD at 1.36:100,000 live births (Asia-Pacific only). GD type-specific prevalence estimates per 100,000 population were type 1 GD: 0.26-0.63; type 2 GD and type 3 GD: 0.02-0.08 (Europe only). Estimates for GD type unspecified or overall ranged from 0.11-139.0:100,000 inhabitants (17 studies); the highest prevalence was in North America [Castillon et al 2022].

A founder effect for specific alleles underlies the observed occurrence of GD in specific populations:

- Ashkenazi Jewish, Spanish, and Portuguese (p.Asn409Ser)
- Swedish (p.Leu483Pro)
- Jenin Arab, Greek, and Albanian (p.Asp448His). Among Greeks and Albanians, p.Asp448His has been found in *cis* with p.His294Gln.

Type 1 GD (non-neuropathic) is prevalent in the Ashkenazi Jewish population, with a disease prevalence of 1:855 and an estimated carrier frequency of 1/18.

As noted, the prevalence of types 2 and 3 GD (neuropathic) varies across ethnic groups but appears to be higher among those who are not of European origin.

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *GBA1*.

Differential Diagnosis

Lysosomal Storage Disorders

Findings in Gaucher disease (GD) may overlap with some lysosomal storage diseases (see Table 3); however, the distinctive clinical features associated with these lysosomal storage disorders, biochemical testing, and an understanding of their natural history should help distinguish between them.

Table 3. Genes of Interest in the Differential Diagnosis of Gaucher Disease

Gene	Disorder	Key Feature(s) of Disorder Overlapping w/GD	Comment / Distinguishing Features
Lysosomal storage disorders [1]			
PSAP	Saposin C deficiency or prosaposin deficiency [2] (OMIM 610539)	Affected persons may present w/features characteristic of severe neuropathic GD (i.e., progressive horizontal ophthalmoplegia, pyramidal & cerebellar signs, myoclonic jerks, & generalized seizures) or non-neuronopathic disease.	Persons w/saposin C deficiency demonstrate GL1 accumulation & visceromegaly but have normal glucocerebrosidase enzyme activity measured in vitro.
ASAH1	Farber disease (FD) (See *ASAH1*-Related Disorders.)	Hepatosplenomegaly (in type 4 FD [neonatal-visceral FD]), hydrops fetalis	The following features are not found in persons w/GD & should direct further investigations to these alternative diagnoses: • Coarse facial features • Dysostosis multiplex on skeletal radiographs • Vacuolated lymphocytes on peripheral blood smear • Presence of a cherry-red spot on fundoscopy • White matter changes (leukodystrophy) on brain MRI
CTSA	Galactosialidosis (OMIM 256540)	Hepatosplenomegaly, hydrops fetalis	
GALNS	MPS IV (See MPS IVA.)	Hepatomegaly, hydrops fetalis	
GLB1	GM1 gangliosidosis (See *GLB1*-Related Disorders.)	Hepatosplenomegaly, hydrops fetalis	
GUSB	MPS VII		
IDS	MPS II	Hepatosplenomegaly	
IDUA	MPS I		
LIPA	Wolman disease (See Lysosomal Acid Lipase Deficiency.)	Hepatosplenomegaly, hydrops fetalis	
MAN2B1	Alpha-mannosidosis	Hepatosplenomegaly	
NEU1	Sialidosis types I & II (OMIM 256550)	Hepatosplenomegaly, hydrops fetalis, myoclonic seizures	
NPC1 *NPC2*	Niemann-Pick disease type C	Hepatosplenomegaly, hydrops fetalis	
SLC17A5	Infantile free sialic acid storage disease		
SMPD1	Niemann-Pick disease types A & B (See Acid Sphingomyelinase Deficiency.)	Hepatosplenomegaly	

Table 3. continued from previous page.

Gene	Disorder	Key Feature(s) of Disorder Overlapping w/GD	Comment / Distinguishing Features
GNPTAB	Mucolipidosis II (See *GNPTAB*-Related Disorders.)	Hydrops fetalis	Coarse facial features evident at birth, gingival hyperplasia
FUCA1	Fucosidosis (OMIM 230000)	Myoclonic seizures	Angiokeratomas
HEXA	*HEXA* disorders		Cherry-red spot on eye exam
NAGA	Schindler disease (OMIM 609241)		

GD = Gaucher disease; GL1 = glucosylceramide; MPS = mucopolysaccharidoses
1. Lysosomal storage disorders are typically inherited in an autosomal recessive manner. An exception is mucopolysaccharidosis type II, which is inherited in an X-linked manner.
2. Saposin C is a cofactor for glucocerebrosidase in the hydrolysis of GL1.

Gaucher cells. The characteristic storage cells of GD should be distinguished from those found in other storage disorders such as Niemann-Pick disease type C. "Pseudo-Gaucher cells," which resemble Gaucher storage cells at the light microscopic but not ultrastructural level, occur in a number of hematologic conditions including myeloproliferative and myelodysplastic disorders.

Other Disorders

Osteonecrosis may be a presenting feature of GD, which should be considered in the differential diagnosis of children with suspected Legg-Calvé-Perthes disease [Kenet et al 2003]. A heterozygous pathogenic variant in *COL2A1* causes a subset of cases of Legg-Calvé-Perthes disease inherited in an autosomal dominant manner (OMIM 150600).

Congenital ichthyoses and collodion skin changes are observed in autosomal recessive congenital ichthyosis.

Myoclonic seizures. In addition to the lysosomal storage disorders noted in Table 3, several genetic disorders are known to be associated with progressive myoclonic epilepsy (see *SCARB2*-Related Action Myoclonus – Renal Failure Syndrome and OMIM Phenotypic Series: Progressive myoclonic epilepsy).

Management

Clinical management guidelines for Gaucher disease (GD) have been published [Biegstraaten et al 2018]. Management by a multidisciplinary team with expertise in treating GD is available at Comprehensive Treatment Centers (see National Gaucher Foundation).

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with GD, the evaluations summarized in Table 4a or Table 4b (if not performed as part of the evaluation that led to the diagnosis) are recommended. Recommended evaluations following initial diagnosis can vary based on age at diagnosis, mode of ascertainment (e.g., asymptomatic vs symptomatic individual), and presence or absence of primary neurologic involvement. Baseline (pre-treatment) assessments may be useful in selecting treatment modality and regimen (e.g., enzyme dose, frequency of infusion).

Table 4a. Gaucher Disease: Recommended Evaluations Following Initial Diagnosis in Adults or Those with Type 1 Gaucher Disease

System/Concern	Evaluation	Comment
General	Referral to GD treatment center	
Musculoskeletal	Assess for clinical manifestations of bone disease.	
	Radiographs, incl: • AP femora & lateral spine • Any symptomatic extremities (w/pain, swelling, or warmth to touch) • Bone age (left hand & wrist) in children w/growth & pubertal delay	
	Bone density assessment by DXA scan	Osteoporosis should prompt referral to skeletal health specialist to assess for additional complications of osteoporosis.
Hepatosplenomegaly	Assessment of spleen & liver volume by MRI or ultrasound	Liver dysfunction should prompt referral to gastroenterologist, to assess for alternative cause.
Hematologic	Hemoglobin concentration & platelet count; platelet function if bleeding/bruising w/normal platelet count	Referral to hematologist to assess bleeding risk prior to surgical intervention
Biliary disease	• Assess for clinical manifestations of gallstones: acute severe abdominal pain w/liver dysfunction (e.g., conjugated hyperbilirubinemia) • Ultrasound of gallbladder	Referral to gastroenterologist or abdominal surgeon if gallstones are detected
Pulmonary	• Assess for clinical manifestations of pulmonary disease • EKG & echocardiogram to identify ↑ pulmonary artery pressure	
Psychiatric	Assess for depression &/or other mood disorder.	
Genetic counseling	By genetics professionals [1]	To inform affected persons & their families re nature, MOI, & implications of GD to facilitate medical & personal decision making

AP = anterior posterior; DXA = dual-energy x-ray absorptiometry; GD = Gaucher disease; MOI = mode of inheritance
1. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Table 4b. Type 2 and Type 3 Gaucher Disease: Recommended Evaluations Following Initial Diagnosis in Neonates and Children

System/Concern	Evaluation	Comment
Gastrointestinal/ Feeding	Gastroenterology / nutrition / feeding team eval	• To incl eval of aspiration risk & nutritional status • Consider eval for gastrostomy tube placement in persons w/dysphagia &/or aspiration risk.
Development	Developmental assessment	• To incl motor, adaptive, cognitive, & speech-language eval • Eval for early intervention / special education
Neurologic	• Assess for seizures. • Consider EEG if seizures are a concern. • Assess for bulbar involvement & abnormal ocular movements.	Brain stem auditory evoked potential testing; abnormal findings confirm presence of neuronopathic form of GD.
Musculoskeletal	Radiograph & MRI of symptomatic areas as indicated to assess for bone disease progression	In persons w/type 3 GD only

Table 4b. continued from previous page.

System/Concern	Evaluation	Comment
Family support & resources	By clinicians, wider care team, & family support organizations	Assessment of family & social structure to determine need for: • Community or online resources such as Parent to Parent • Social work involvement for parental support • Home nursing referral

GD = Gaucher disease

Treatment of Manifestations

Targeted Therapy

In GeneReviews, a targeted therapy is one that addresses the specific underlying mechanism of disease causation (regardless of whether the therapy is significantly efficacious for one or more manifestation of the genetic condition); would otherwise not be considered without knowledge of the underlying genetic cause of the condition; or could lead to a cure. —ED

Targeted therapy includes enzyme replacement therapy (ERT), substrate reduction therapy (SRT), and hematopoietic stem cell transplantation (HSCT). Note: Individuals with type 2 GD and those with hydrops fetalis are not appropriate candidates for ERT, SRT, or HSCT; although life may be prolonged by these therapeutic options, severe neurologic manifestations are not altered [Roshan Lal et al 2020].

ERT is based on the provision of sufficient exogenous enzyme to overcome the block in the catabolic pathway and effect the clearance of the stored substrate, glucosylceramide (GL1). There are three recombinant glucocerebrosidase enzyme preparations currently available: imiglucerase (Cerezyme®); velalglucerase alfa (VPRIV®); and taliglucerase alfa (Elelyso®). Consensus recommendations exist for ERT and monitoring of children with type 1 GD [Baldellou et al 2004, Charrow et al 2004, Grabowski et al 2004] (see Published Guidelines / Consensus Statements).

- The optimal dose and frequency of ERT is not certain, mostly due to limited information regarding tissue half-life, distribution, and clinical disease markers. Intravenously infused enzyme may not reach adequate concentrations in certain body sites (e.g., brain, bones, and lungs). In the majority of individuals, treatment is initiated with a dose of 15-60 units of enzyme per kg of body weight administered intravenously every two weeks. The enzyme dose may be increased or decreased after initiation of treatment and during the maintenance phase, based on response (e.g., hematopoietic reconstitution, reduction of liver and spleen volumes, and stabilization or improvement of skeletal findings). Long-term data from the ICGG Registry have been published [El-Beshlawy et al 2017].
- ERT has been demonstrated to be safe and effective in reversing features resulting from hematologic and visceral (liver/spleen) involvement. After prolonged treatment, ERT reduces the rate of bone loss in a dose-dependent manner [Wenstrup et al 2007], improves bone pain, and reduces bone crises [Charrow et al 2007]. Individuals with type 1 GD report improved health-related quality of life after 24-48 months of ERT [Damiano et al 1998, Masek et al 1999, Weinreb et al 2007].
- It is likely that end-stage histologic changes (e.g., fibrosis, infarction) influence the response to ERT. Thrombocytopenia may persist in individuals with residual splenomegaly and/or the presence of splenic nodules [Stein et al 2010].

ERT is well tolerated. Approximately 10%-15% of individuals develop antibodies to infused imiglucerase, whereas antibody formation has been reported in 1% of persons receiving velaglucerase. Four of 18 (22%) individuals in the taliglucerase trials developed anti-drug antibodies [Pastores et al 2016]. Most individuals with

antibodies remain asymptomatic [Starzyk et al 2007]. Adverse effects (e.g., pruritus, hives) are relatively well controlled with premedication using antihistamines.

- **Individuals with type 2 GD** and pyramidal tract signs are not likely to respond to ERT, perhaps because the underlying neuropathology is cell death rather than lysosomal storage of GL1 [Takahashi et al 1998], and the blood-brain barrier prevents drug access to the brain.
- **Individuals with type 3 GD** appear to derive some benefit from ERT, although long-term prognosis remains to be defined for this heterogeneous group [Lee et al 2014, Cappellini et al 2023].
- ERT does not alter the ultimate prognosis of neurologic disease in GD, although treatment can lead to significant improvement in systemic manifestations and quality of life [Sechi et al 2014, Charrow & Scott 2015]. Onset of progressive myoclonic seizures while on ERT appears to indicate a poor prognosis [Frei & Schiffmann 2002]. Brain stem auditory evoked responses have deteriorated in individuals with type 3 GD on ERT [Campbell et al 2003].

Note: Affected individuals may require assistance with insurance-related issues and reimbursement because of the high cost of ERT.

SRT aims to restore metabolic homeostasis by limiting the amount of substrate precursor synthesized (and eventually subject to catabolism) to a level that can be effectively cleared by the mutated enzyme with residual hydrolytic activity [Coutinho et al 2016].

- **Miglustat** is an oral medication for individuals with mild-to-moderate GD for whom ERT is not a therapeutic option (e.g., because of constraints such as allergy, hypersensitivity, or poor venous access). In at least three studies, including more than 30 individuals with type 1 GD, miglustat treatment resulted in a significant decrease in liver and spleen volume after six to 18 months, with clinical improvement noted over 24 months. Bone involvement and platelet and hemoglobin values remained stable or were modestly improved [Cox et al 2000, Elstein et al 2004, Pastores et al 2005]. An increase in bone density at the lumbar spine and femoral neck was reported to occur as early as six months after the initiation of miglustat monotherapy [Pastores et al 2007]. The most common adverse reactions noted in the clinical trials were weight loss (60% of individuals) and bloating, flatulence, and diarrhea (80%), which resolved or diminished with continued treatment with miglustat.

- **Eliglustat,** an alternative inhibitor of glucosylceramide synthetase, has been shown in clinical trials to be a safe and effective treatment for individuals with type 1 GD who are not on any therapy as well as those previously treated with ERT [Kamath et al 2014, Cox et al 2015a, Mistry et al 2015, Cox et al 2017]. Longer-term studies provide further support to conclusions derived from the pivotal trials [Cox et al 2015a, Mistry et al 2017]. The experience with once-daily and twice-daily dosing in affected individuals has been found to maintain mean values for hematologic and visceral measures within established therapeutic goals during the double-blind treatment and long-term extension periods. Individuals on twice-daily eliglustat showed more stability overall [Charrow et al 2018]. Skeletal improvement was also noted in individuals treated with eliglustat [Kamath et al 2014, Cox et al 2023].

  Note: (1) Reported side effects of eliglustat were generally mild. (2) The use of eliglustat requires cytochrome P450 2D6 genotyping and avoidance of drugs that may interact through this metabolic pathway [Balwani et al 2016]. (3) Drug distribution studies indicate that eliglustat, a P-glycoprotein ligand, is not transported across the blood-brain barrier and, thus, not indicated for neuronopathic forms of GD.

Individuals with type 2 GD and pyramidal tract signs are not likely to respond to SRT, perhaps because the underlying neuropathology is cell death rather than lysosomal storage of GL1 [Takahashi et al 1998], and the blood-brain barrier prevents drug access to the brain.

Note: SRT used in combination with ERT for type 3 GD with progressive neurologic disease does not appear to alter ultimate prognosis. Moreover, residual somatic symptoms, including kyphosis and lymphadenopathy, may also be observed [Lee et al 2014].

HSCT. Individuals with chronic neurologic GD and progressive disease despite ERT or SRT may be candidates for HSCT or a multimodal approach (e.g., combined ERT and HSCT or SRT).

Supportive Care

Supportive care to improve quality of life, maximize function, and reduce complications is recommended. This ideally involves multidisciplinary care by specialists in relevant fields through a Comprehensive Gaucher Center (see Table 5).

Table 5. Gaucher Disease: Treatment of Manifestations

Manifestation/ Concern	Treatment	Considerations/Other
Bone pain	• Referral to orthopedist to eval for mechanical problem (e.g., pathologic fracture or joint collapse secondary to osteonecrosis, degenerative arthritis) • Analgesics • Joint replacement surgery as needed	Bone pain in persons who have undergone joint replacement may indicate a problem w/the prosthesis & need for surgical revision.
Low bone density	• Referral to metabolic bone specialist • Calcium & vitamin D • Anti-bone-resorbing agents may be indicated.	Wenstrup et al [2004], Masi & Brandi [2015]
Splenomegaly	Partial or total splenectomy as needed for persons w/: • Massive splenomegaly • Significant areas of splenic fibrosis • Persistent severe thrombocytopenia w/high risk of bleeding	• Partial or toral splenectomy may be needed in those w/massive spleen, areas of fibrosis, & persistent significant thrombocytopenia (platelets <30,000/mm^3) & risk of bleeding, whether on therapy or not. • Splenectomy is not recommended where ERT/SRT is available, & there is no emergency bleeding, as it is assoc w/↑ bone disease.
Severe anemia / Bleeding	• Transfusion of blood products as needed for severe anemia &/or bleeding diathesis • Eval by hematologist prior to any major surgery, dental procedure, or parturition.	Anemia & bleeding unresponsive to ERT or SRT should prompt investigations for intercurrent disease process.
Cholelithiasis	Treatment per gastroenterologist or abdominal surgeon in those w/gallstones	
Pulmonary disease / Pulmonary hypertension	Treatment per pulmonologist &/or cardiologist	
Multiple myeloma	Treatment per oncologist	
Psychological manifestations	Treatment per psychiatrist &/or clinical psychologist	
Parkinsonism	Treatment per neurologist	
Seizures	Treatment per neurologist	In persons w/type 3 GD

Table 5. continued from previous page.

Manifestation/ Concern	Treatment	Considerations/Other
Family/Community	• Ensure appropriate social work involvement to connect families w/local resources, respite, & support. • Coordinate care to manage multiple subspecialty appointments, equipment, medications, & supplies.	• Ongoing assessment of need for palliative care involvement &/or home nursing • Consider involvement in adaptive sports or Special Olympics in older persons w/ neurologic involvement.

GD = Gaucher disease; ERT = enzyme replacement therapy; SRT = substrate reduction therapy

Surveillance

Physicians who are the US regional coordinators for the International Collaborative Gaucher Group Registry (ICGG) and other groups have published recommendations for comprehensive serial monitoring of the severity and rate of disease progression [Baldellou et al 2004, Charrow et al 2004, Grabowski et al 2004, Vom Dahl et al 2006]. A European working group has also published a consensus document relating to management goals for individuals with type 1 GD [Biegstraaten et al 2018]. To monitor existing manifestations, the individual's response to supportive care, and the emergence of new manifestations, the evaluations summarized in Table 6 are recommended.

Table 6. Gaucher Disease: Recommended Surveillance

System/Concern	Evaluation	Frequency
General	Clinical assessment of disease progression using disease severity scoring system (DS3) [1]	At least every 12 mos
	Clinical disease markers: [2] • Lyso-Gb1 • Plasma activity of chitotriosidase (a macrophage-derived chitin-fragmenting hydrolase) • Plasma PARC/CCL18 Note: Lyso-Gb1 is preferred, if available, obviating the need to monitor w/non-specific biomarker.	At least every 6-12 mos
Musculoskeletal	Assess for joint pain, ↓ range of movement, & bone pain	
	Radiograph of femur (AP view), spine (lateral view), & any symptomatic sites	For emergent complaints, or just before treatment modality or dose change
	Coronal T_1- & T_2-weighted MRI of hips to distal femur • T_1-weighted MRI to monitor bone marrow infiltration • T_2-weighted MRI to detect bone infarcts, osteonecrosis, & osteomyelitis	
	DXA scan to identify osteoporosis	• In those w/suspected osteoporosis • At least every 2 yrs, in persons w/ osteoporosis identified on previous DXA scan
	Bone age radiograph	In children w/growth & pubertal delay

Table 6. continued from previous page.

System/Concern	Evaluation	Frequency
Liver / Spleen manifestations / Biliary disease	Assess for abdominal pain & early satiety due to abdominal pressure.	At least every 6-12 mos
	• Assessment of spleen & liver volumes (& parenchymal abnl) by abdominal MRI or ultrasound (if MRI is not available) • Assessment for gallstones [3]	• At least every 1-2 yrs • Persons w/gallstones may need more frequent follow up by ultrasound.
	Serum iron, ferritin, & vitamin B_{12}	In persons whose blood counts indicate anemia
	Liver enzymes (aspartate aminotransferase or alanine amino transferase)	• At least every 6-12 mos • If abnormal results are obtained, consider referral to gastroenterologist.
Hematologic	Assess for bleeding from nose or gums, menorrhagia, bruises, petechiae	At least every 6-12 mos
	• Hemoglobin • Platelet count • Coagulation indices	• Prior to surgical or dental procedures • Additional testing based on symptoms & treatment status
Pulmonary	• Assessment for shortness of breath • Pulmonary exam	At least every 6-12 mos
	EKG & echocardiography w/Doppler to identify ↑ pulmonary artery pressure	In those who have had splenectomy, ≥ every 6-12 mos if initial reading has indicated ↑ PA pressures; or as indicated, per cardiologist
Cardiac	• Assessment for fatigue • Clinical cardiac exam	In adults, at least every 6-12 mos
Nutrition	Assessment of growth (height, weight, & head circumference using standardized growth charts)	In children, at least every 6-12 mos
	Assessment for weight loss	In adults, at least every 6-12 mos
	Vitamin D	In those taking vitamin D, every 6-12 mos
Psychiatric	Assessment for depression, change in social, domestic, or school- or work-related activities	In adults, at least every 6-12 mos
Endocrine	Assessment of pubertal changes (using Tanner staging system)	In prepubertal patients, at least every 6-12 mos
Neurologic	Assessment of gait & for neurologic manifestations A severity scoring tool has been developed to evaluate neurologic features of type 2 & 3 GD. [4]	At least every 6-12 mos
	Assessment for parkinsonian manifestations	Per neurologist

DXA = dual-energy x-ray absorptiometry; lyso-Gb1 = glucosylsphingosine

1. Ganz et al [2017]

2. Levels are typically elevated and are felt to correlate with body-wide burden of disease. An enzyme dose-dependent decrease in plasma chitotriosidase activity has been observed in affected individuals on ERT or SRT; however, up to 40% of affected individuals of European origin are homozygous or heterozygous for a common null variant, confounding interpretation of test results [Grace et al 2007]. The latter is not an issue when lyso-Gb1 is monitored, and its increased sensitivity and specificity has made it the preferred biomarker for monitoring patients [Giuffrida et al 2023].

3. Patlas et al [2002]

4. Davies et al [2007]

Agents/Circumstances to Avoid

Nonsteroidal anti-inflammatory drugs should be avoided in individuals with moderate-to-severe thrombocytopenia. The use of anticoagulants in individuals with severe thrombocytopenia and/or coagulopathy should be discussed with a hematologist to avoid the possibility of excessive bleeding.

Evaluation of Relatives at Risk

It is appropriate to evaluate asymptomatic at-risk relatives of an affected individual in order to identify as early as possible those who would benefit from early diagnosis and targeted therapy to reduce morbidity. Evaluations can include:

- Assay of glucocerebrosidase enzyme activity in peripheral blood leukocytes or other nucleated cells;
- Molecular genetic testing if the pathogenic variants in the family are known.

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Pregnancy Management

Pregnancy may affect the course of GD both by exacerbating preexisting symptoms and by triggering new features such as bone pain. Women with severe thrombocytopenia and/or clotting abnormalities may be at an increased risk for bleeding around the time of delivery; therefore, evaluation by a hematologist prior to delivery is recommended [Hughes et al 2007, Rosenbaum 2015]. In symptomatic women, treatment should ideally be started prior to conception [Granovsky-Grisaru et al 2011].

Although eliglustat use is not contraindicated during pregnancy and breastfeeding, the lack of controlled studies demonstrating the safety of eliglustat during human pregnancy and lactation has led to a recommendation to avoid this treatment during pregnancy, if possible [Balwani et al 2016, Belmatoug et al 2017].

See MotherToBaby for further information on medication use during pregnancy.

Therapies Under Investigation

Substrate reduction therapy. Venglustat, an investigational, brain-penetrant glucosylceramide synthase inhibitor, has been administered to adults with type 3 GD receiving imiglucerase. In an early phase clinical trial, addition of once-daily venglustat showed acceptable safety and tolerability and preliminary evidence of clinical stability but inconsistent changes in selected biomarkers [Schiffmann et al 2023]. These findings need to be validated and confirmed in future research.

Chaperone-mediated enzyme enhancement therapy. Pharmacologic chaperones (PCs), competitive reversible active site inhibitors, serve as a folding template for the defective enzyme during its transit to the endoplasmic reticulum. Such agents may restore enzyme activity within the lysosome and clear stored substrate. The drug isofagamine, which exhibited these properties in studies of cultured fibroblasts in vitro, was evaluated in clinical trials to establish its safety and efficacy in adults with type 1 GD [Steet et al 2007, Mena-Barragán et al 2018]. To date, no PCs have been approved for treatment of GD.

Ambroxol, a mucolytic agent, is also a potential pharmacologic glucocerebrosidase chaperone. An open-label pilot study of high-dose oral ambroxol in combination with ERT in five affected individuals found that ambroxol had a good safety and tolerability profile. Significantly increased lymphocyte glucocerebrosidase activity and decreased glucosylsphingosine levels in the cerebrospinal fluid were also noted. Myoclonus, seizures, and pupillary light reflex dysfunction markedly improved in all affected individuals. Relief from myoclonus led to impressive recovery of gross motor function in two individuals, allowing them to walk again [Narita et al 2016].

The beneficial effects of treatment with high-dose ambroxol has also been described in a more recent report [Istaiti et al 2023].

Gene therapy. Ex vivo gene therapy involves the introduction of *GBA1* into hematopoietic stem cells. In limited trials, some enzyme has been produced by transduced cells, but enzyme production does not appear to be sustained and therefore does not result in a permanent cure. In vivo gene therapy involves a *GBA1* transgene delivered using an adeno-associated virus vector resulting in liver expression of glucocerebrosidase and release of the enzyme into the circulation.

AVROBIO, a clinical-stage biotechnology company, initiated a lentiviral-based gene therapy trial in GD, but this study has been discontinued. A new in vivo gene therapy trial (GALILEO-1) is recruiting adults with type 1 GD (NCT05324943).

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for information on clinical studies for a wide range of diseases and conditions.

Other

The elevation of the serum concentration of several serologic markers (e.g., CCL18/PARC, chitotriosidase) in individuals with GD is considered a possible surrogate indicator of disease burden that could be used in monitoring treatment response [Smid et al 2016]. However, the prognostic value of these markers, their role in stratification according to clinical disease severity, and determination of the optimum time to initiate therapy are unknown.

Glucosylsphingosine (lyso-Gb1), a deacylated lysolipid, has been found to be massively elevated in the plasma of individuals with type 1 GD (n=169), with marked reduction observed following treatment with ERT or SRT [Murugesan et al 2016]. Lyso-Gb1 levels correlated significantly with plasma chitotriosidase and CCL18/PARC levels, hepatomegaly, splenomegaly, splenectomy, and treatment mode [Giuffrida et al 2023].

Elevation of the protein glycoprotein non-metastatic B, found in brain samples from individuals with type 2 and 3 GD, may be used as a marker to quantify neuropathology in those with GD and as a marker of treatment efficacy once suitable treatments are initiated [Zigdon et al 2015].

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

Gaucher disease (GD) is inherited in an autosomal recessive manner.

Risk to Family Members

Parents of a proband

- The parents of an affected individual are typically heterozygous for a *GBA1* pathogenic variant. In some families, an asymptomatic parent may be found to be homozygous rather than heterozygous (it is suspected that a significant proportion of Ashkenazi Jewish individuals who are homozygous for the p.Asn409Ser or p.Arg535His variant may be asymptomatic [see Genotype-Phenotype Correlations]).

- If a molecular diagnosis has been established in the proband, molecular genetic testing is recommended for the parents of the proband to confirm that both parents are heterozygous for a *GBA1* pathogenic variant and to allow reliable recurrence risk assessment. If a pathogenic variant is detected in only one parent and parental identity testing has confirmed biological maternity and paternity, the following possibilities should be considered:
  - One of the pathogenic variants identified in the proband occurred as a *de novo* event in the proband or as a postzygotic *de novo* event in a mosaic parent [Jónsson et al 2017].
  - Uniparental isodisomy for the parental chromosome with the pathogenic variant resulted in homozygosity for the pathogenic variant in the proband.
- Heterozygotes are not at risk of developing GD. However, family studies suggest that the incidence of parkinsonism may be higher in obligate heterozygotes for GD (see Clinical Description, Heterozygotes).

Sibs of a proband

- If both parents are known to be heterozygous for a *GBA1* pathogenic variant, each sib of an affected individual has at conception a 25% chance of being affected, a 50% chance of being a heterozygote, and a 25% chance of inheriting neither of the familial *GBA1* pathogenic variants.
- If one parent has biallelic *GBA1* pathogenic variants (e.g., p.[Asn409Ser];[Asn409Ser]) and the other parent is heterozygous for a *GBA1* pathogenic variant, each sib of an individual with GD has a 50% chance of inheriting biallelic *GBA1* pathogenic variants and being affected and a 50% chance of inheriting one *GBA1* pathogenic variant and being heterozygous.
- Heterozygotes are not at risk of developing GD. However, family studies suggest that the incidence of parkinsonism may be higher in obligate heterozygotes for GD (see Clinical Description, Heterozygotes).

Offspring of a proband

- Unless an affected individual's reproductive partner also has GD or is a carrier (see **Family planning**), offspring will be obligate heterozygotes (carriers) for a pathogenic variant in *GBA1*.
- A higher carrier rate for GD exists in populations or regions with known founder variants (see Prevalence), increasing the risk that an affected individual may have a reproductive partner who is heterozygous. In the Ashkenazi Jewish population, for example, one in 18 individuals is a carrier for GD; the offspring of such an individual and a proband are at 50% risk of being affected and 50% risk of being heterozygous.

Other family members. Each sib of an obligate heterozygote is at a 50% risk of being a carrier of a *GBA1* pathogenic variant.

Carrier Detection

Molecular genetic carrier testing for at-risk relatives requires prior identification of the *GBA1* pathogenic variants in the family.

Note: Measurement of glucocerebrosidase enzyme activity in peripheral blood leukocytes is unreliable for carrier determination because of significant overlap in residual enzyme activity levels between obligate carriers and the general (non-carrier) population.

Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk relatives for the purpose of early diagnosis and treatment.

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected, are carriers, or are at risk of being carriers.
- The American Academy of Medical Genetics includes GD among those disorders for which expanded carrier screening should be offered to all pregnant individuals and individuals planning a pregnancy [Gregg et al 2021]. Of note, because of the inherent detection limitations of ancestry-based targeted variant testing, sequence analysis (rather than targeted variant analysis) is recommended in the National Society of Genetic Counselors practice guidelines for expanded carrier screening [Sagaser et al 2023].

DNA banking. Because it is likely that testing methodology and our understanding of genes, pathogenic mechanisms, and diseases will improve in the future, consideration should be given to banking DNA from probands in whom a molecular diagnosis has not been confirmed (i.e., the causative pathogenic mechanism is unknown). For more information, see Huang et al [2022].

Prenatal Testing and Preimplantation Genetic Testing

Molecular genetic testing. Once the *GBA1* pathogenic variants have been identified in an affected family member, molecular genetic prenatal and preimplantation genetic testing for GD are possible.

Biochemical testing. The identification of 0%-15% of normal glucocerebrosidase enzyme activity in fetal samples obtained by chorionic villus sampling (CVS) or amniocentesis – ideally complemented by molecular genetic testing – establishes affected status in a fetus. Enzyme activity testing does not reliably detect fetal carrier status.

With the exception of families in which a previously affected sib had neurologic disease (i.e., types 2 or 3), it is not possible to be certain of the phenotypic severity in a pregnancy at risk. Individuals with GD with acute neurologic disease (i.e., type 2) tend to have a similar disease course. However, it should be noted that individuals with GD and chronic neurologic involvement (i.e., type 3) could show variable rates of disease progression, even when they are members of the same family.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **Gauchers Association**

  United Kingdom

  Phone: 01453 549231

  Email: ga@gaucher.org.uk

  www.gaucher.org.uk

- **Medline Plus**

  Gaucher Disease

- **National Gaucher Foundation**

www.gaucherdisease.org

- **NCBI Genes and Disease**
  Gaucher disease
- **Canadian MPS Society for Mucopolysaccharidoses and Related Diseases**
  Canada
  Phone: 800-667-1846
  Email: info@mpssociety.ca
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Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. Gaucher Disease: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
GBA1	1q22	Lysosomal acid glucosylceramidase	CCHMC - Human Genetics Mutation Database (GBA)	GBA1	GBA1

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for Gaucher Disease (View All in OMIM)

168600	PARKINSON DISEASE, LATE-ONSET; PD
230800	GAUCHER DISEASE, TYPE I; GD1
230900	GAUCHER DISEASE, TYPE II; GD2
231000	GAUCHER DISEASE, TYPE III; GD3
231005	GAUCHER DISEASE, TYPE IIIC; GD3C
606463	GLUCOSIDASE, BETA, ACID; GBA
608013	GAUCHER DISEASE, PERINATAL LETHAL

Molecular Pathogenesis

GBA1 encodes glucocerebrosidase (also known as glucosylceramidase), a lysosomal membrane-associated glycoprotein. The mature protein is composed of 497 amino acids, with four oligosaccharide chains coupled to specific asparagine residues [van Weely & Aerts 2000]. The three-dimensional conformation of the enzyme is stabilized by the formation of three disulfide bonds. The enzyme is responsible for hydrolyzing glucosylceramide (GL1) into glucose and ceramide.

Glucocerebrosidase enzyme activity is stimulated by interaction with the lipid phosphatidylserine and the protein saposin C. Structural predictions (based on hydrophobic cluster analysis) indicate that the glutamine residues 235 and 340 play key roles in the active site of human glucocerebrosidase [Fabrega et al 2002]. The nascent glucocerebrosidase polypeptide is composed of 536 amino acids, including 39 that encode a signal sequence that is later cleaved after it directs the polypeptide to transit the endoplasmic reticulum. Two different upstream ATG codons are utilized as translation initiation sites; use of the second ATG translation start leaves a functional signal sequence of 19 amino acid residues. The 497-amino-acid sequence of the mature protein is the same regardless of the translation start codon.

Gaucher disease (GD) is caused by deficient glucocerebrosidase activity and the resultant accumulation of its undegraded substrate, GL1, and other glycolipids. The major peripheral substrate source is the breakdown of senescent blood cells and tissue debris; the incompletely metabolized GL1 substrate is stored in cells of monocyte/macrophage lineage of the reticuloendothelial system. In the central nervous system, GL1 is believed to originate from the turnover of membrane gangliosides, although neuronal cell death may be the basis of neuropathic involvement [Aerts et al 2003].

Mechanism of disease causation. *GBA1* pathogenic variants result in mRNA instability and/or loss of protein, or in an enzyme with altered activity and/or conformation [Grabowski & Horowitz 1997].

GBA-specific laboratory technical considerations

- Two different upstream ATG codons are utilized as translation initiation sites.
- A highly homologous (96% identity) pseudogene, *GBAP1*, is located 16 kb downstream. Approximately 12% of disease-causing alleles are formed by recombination between *GBA1* and *GBAP1* [Tayebi et al 2003]. The most common recombinant allele, termed RecNciI, is defined by the creation of an *NciI* restriction site [Zimran et al 1990, Tayebi et al 2003].

Table 7. *GBA1* Pathogenic Variants Referenced in This *GeneReview*

Reference Sequences	DNA Nucleotide Change (Alias [1])	Predicted Protein Change (Alias [1, 2])	Comment [Reference]
NM_001005741.3 NP_001005741.1	c.84dupG [3] (84GG; 84-85insG)	p.Leu29AlafsTer18	Common variant in Ashkenazi Jewish persons w/ type 1 GD [4]
NM_001005741.3	c.115+1G>A [3] (IVS2+1G>A)	--	
NM_001005741.3 NP_001005741.1	c.254G>A	p.Gly85Glu (Gly46Glu)	See Genotype-Phenotype Correlations.
	c.476G>A	p.Arg159Gln (Arg120Gln)	
	c.475C>T	p.Arg159Trp (Arg120Trp)	
	c.509G>T	p.Arg170Leu (Arg131Leu)	

Table 7. continued from previous page.

Reference Sequences	DNA Nucleotide Change (Alias [1])	Predicted Protein Change (Alias [1, 2])	Comment [Reference]
	c.680A>G	p.Asn227Ser (Asn188Ser)	
	c.703T>C	p.Ser235Pro (Ser196Pro)	
	c.754T>A	p.Phe252Ile (Phe213Ile)	• See Genotype-Phenotype Correlations. • Accounts for 14% of pathogenic variants among Japanese persons w/GD [Wan et al 2006]
	c.882T>G	p.His294Gln (His255Gln)	See Genotype-Phenotype Correlations.
	c.887G>A	p.Arg296Gln (Arg257Gln)	
	c.1093G>A	p.Glu365Lys (Glu326Lys)	
	c.1226A>G	p.Asn409Ser (Asn370Ser)	Accounts for 61% of pathogenic variants in Ashkenazi Jewish persons, [4] 63% of Portuguese persons, & 46% of Spanish persons [Giraldo et al 2000, Alfonso et al 2007]
	c.1246G>A	p.Gly416Ser (Gly377Ser)	See Genotype-Phenotype Correlations.
	c.1297G>T	p.Val433Leu (Val394Leu)	
	c.1342G>C	p.Asp448His (Asp409His)	
	c.1448T>C	p.Leu483Pro (Leu444Pro)	• Common variant in Ashkenazi Jewish persons w/type 1 GD [4] • Accounts for 41% of pathogenic variants among Japanese persons & 54% of Chinese persons w/GD [Wan et al 2006]
	c.1604G>A	p.Arg535His (Arg486His)	See Genotype-Phenotype Correlations.
NG_009783.1	(Complex allele involving several changes at a specific location) [5]	(RecNciI) [5]	Accounts for 25% of pathogenic variants in Chinese persons w/GD [Wan et al 2006]

GD = Gaucher disease

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.

GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.

1. Variant designation that does not conform to current naming conventions

2. In the common variant names, amino acid number 1 is the first residue (Ala) of the mature protein. In contrast, the standard naming convention designates amino acid number 1 as the first residue (Met) of the signal sequence.

3. Variants in the signal sequence

4. The variants p.Asn409Ser, c.84dupG, c.115+1G>A, and p.Leu483Pro account for 90% of pathogenic variants in Ashkenazi Jewish individuals with type 1 GD and 50%-60% of pathogenic variants in non-Ashkenazi Jewish individuals with type 1 GD.

5. Recombinant allele derived from a recombination between functional *GBA1* and pseudogene *GBAP1*; see also Table 3 [Eyal et al 1990, Tayebi et al 2003].

Chapter Notes

Revision History

- 7 December 2023 (sw) Comprehensive update posted live
- 21 June 2018 (ma) Comprehensive update posted live
- 19 September 2013 (me) Comprehensive update posted live
- 1 February 2011 (me) Comprehensive update posted live
- 13 March 2008 (me) Comprehensive update posted live
- 2 June 2005 (me) Comprehensive update posted live
- 8 April 2003 (me) Comprehensive update posted live
- 27 July 2000 (me) Review posted live
- 23 March 2000 (gp) Original submission

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