WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 7.523
Volume 6, Issue 8, 563-584. Review Article ISSN 2277– 7105

OVERVIEW OF GAUCHER DISEASE AND ITS MANAGEMENT

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Article Received on
28 May 2017,
Revised on 18 June 2017,
Accepted on 08 July 2017
DOI: 10.20959/wjpr20178-9016

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ABSTRACT

Gaucher disease (GD) is an inherited, rare, lysosomal storage disorder caused by a genetic deficiency of glucocerebrosidase. enzyme replacement therapy has been the mainstay of treatment with its major disadvantage of long life dependency on biweekly IV therapy. It was more than a decade later when the substrate reduction therapy – an oral treatment – was approved for Gaucher disease. Future therapeutic modalities will include pharmacological chaperon and possibly gene therapy. The aim of this review is to high light the gaucher disease and its management.

KEYWORDS: Definition Epidemiology Classification Diagnosis management.

INTRODUCTION

Lysosomal storage disorders (LSDs) are inherited metabolic disorders and currently more than 45 LSDs are known. Gaucher disease (GD) is the most prevalent LSD world wide.[1,2]

It is a form of sphingolipidosis (a subgroup of lysosomal storage diseases), as it involves dysfunctional metabolism of sphingolipids[3], enzyme-degrading abilities of the metabolites which are essential components of cell membranes and regulators of various signaling pathways.[4] The disease is named after the French physician Philippe Gaucher, who originally described it in 1882.[5]

Definition

Gaucher disease (GD) is an inherited, rare, lysosomal storage disorder caused by a genetic deficiency of glucocerebrosidase. The result is the accumulation of the substrate,

glucosylceramide, in the lysosomes of macrophage cells in the liver, spleen, bones, lungs, and other vital tissues.[6]

Epidemiology

Gaucher disease is the commonest lysosomal storage disease seen in India and worldwide. It should be considered in any child or adult with an unexplained spleenohepatomegaly and cytopenia which are seen in the three types of Gaucher disease. The International Collaborative Gaucher Group(ICGC) (http://www.gauchercare.com/healthcare/registry.aspx) launched a registry in 1991 to document clinical, laboratory, demographic, genetic and therapeutic responses in patients with GD. Most of the published data and recommendations originate from this registry. The majority of patients have type 1 Gaucher disease(GD1), which is the non-neuronopathic form of GD. It is the main type seen in the Ashkenazi Jewish population. Type 2 Gaucher disease (GD2), is also called acute neuronopathic GD or infantile cerebral GD. It comprises about 1 percent of patients in the ICGC Registry.[7] Type 3 GD (GD3) is the chronic neuronopathic form and is seen in 5% of patients overall. GD3 is mainly seen in Northern Europe, Egypt and East Asia.[8] A high incidence of GD3 is found in the Swedish province of Norrbotten and is therefore also referred to as the Norrbottnian type of GD.[9,10]

Classification

- Gaucher disease type 1
- Gaucher disease type 2 (acute)
- Gaucher disease type 3 (subacute/chronic)
- Gaucher disease, perinatal-lethal form
- Gaucher disease, cardiovascular form

Diagnosis

Clinical Diagnosis

Gaucher disease (referred to as GD in this entry) is suspected in individuals with characteristic bone lesions, hepatosplenomegaly and hematologic changes, or signs of CNS involvement.[11-13] Clinical findings alone are not diagnostic.

Testing

1. Assay of glucocerebrosidase (glucosylceramidase) enzyme activity
2. Bone marrow examination.

3. Molecular Genetic Testing

Testing Strategy To confirm/establish the diagnosis in a proband

- Assay of glucocerebrosidase enzyme activity in leukocytes or other nucleated cells is the confirmatory diagnostic test.
- Molecular genetic testing (see **Molecular genetic testing strategy**) and the identification of two disease-causing alleles provide an alternative means of confirming the diagnosis. There is broad heterogeneity in causative variants; in individuals in whom genetic testing identifies a novel *GBA* variant, biochemical testing to confirm the diagnosis should be considered.
- As the diagnosis of GD can be confirmed through biochemical or molecular testing performed on peripheral blood leukocytes, it is not necessary to perform a bone marrow examination.

Molecular genetic testing strategy

- Targeted analysis for pathogenic variants in a proband originally diagnosed by biochemical testing may be considered for genetic counseling purposes, primarily to identify the pathogenic variants and permit carrier detection among at-risk relatives.
- Sequence analysis of the *GBA* coding region may be used to detect pathogenic variants in affected individuals in whom targeted analysis has identified only a single pathogenic variant.
- If sequence analysis fails to detect the second pathogenic variant, deletion/duplication analysis may be appropriate.

Carrier testing for at-risk relatives requires prior identification of the pathogenic variants in the family.

Prenatal diagnosis and preimplantation genetic diagnosis (PGD) for at-risk pregnancies require prior identification of the pathogenic variants in the family.

Clinical Characteristics

Gaucher Disease: Clinical Subtypes

Subtype	Primary CNS Involvement	Bone Disease	Other
Type 1	No	Yes	• Splenomegaly • Hepatomegaly • Cytopenia • Pulmonary disease
Type 2 (acute or infantile)	• Bulbar signs • Pyramidal signs • Cognitive impairment	No	• Hepatomegaly • Splenomegaly • Cytopenia • Pulmonary disease • Dermatologic changes
Type 3 (subacute; juvenile)	• Oculomotor apraxia • Seizures • Progressive myoclonic epilepsy	Yes	• Hepatomegaly • Splenomegaly • Cytopenia • Pulmonary disease
Perinatal-lethal form	Pyramidal signs	No	• Ichthyosiform or collodion skin changes • Nonimmune hydrops fetalis
Cardiovascular form	Oculomotor apraxia	Yes	• Calcification of mitral and aortic valves • Corneal opacity • Mild splenomegaly

Genetically Related (Allelic) Disorders

Parkinsonian features have been reported in a few individuals with type 1 GD; although studies suggest a possible cause-and-effect relationship rather than mere coincidence, the underlying basis remains to be established.[16,17] The following findings suggest that mutation of *GBA* and/or alterations in glucosylceramide metabolism may be a risk factor for parkinsonism.[18]

Differential Diagnosis

Saposin C deficiency or prosaposin deficiency. Saposin C is a cofactor for glucocerebrosidase in the hydrolysis of GL1. Saposin C is derived from proteolytic cleavage of prosaposin, which is encoded by a gene on chromosome 10q21-q22. Individuals with saposin C deficiency or prosaposin deficiency may present with symptoms characteristic of severe neuropathic Gaucher disease (GD).

Lysosomal storage diseases (LSDs). Findings in GD may overlap with some lysosomal storage diseases; however, the distinctive clinical features associated with these lysosomal

storage diseases, the availability of biochemical testing in clinical laboratories and an understanding of their natural history should help distinguish between them.

Hepatosplenomegaly is observed in Niemann-Pick disease types A and Niemann-Pick disease type C, Wolman disease, the mucopolysaccharidoses (including mucopolysaccharidosis type I and mucopolysaccharidosis type II) and the oligosaccharidoses. The following features are not found in individuals with GD and should direct further investigations to these alternative diagnoses:

- Coarse facial features
- Dysostosis multiplex on skeletal radiographs
- Vacuolated lymphocytes on peripheral blood smear examination
- The presence of a cherry-red spot on fundoscopy
- White matter changes (leukodystrophy) on brain MRI

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.

Legg-Calvé-Perthes disease. Osteonecrosis may be a presenting feature of GD, which should be considered in the differential diagnosis of children with suspected Legg-Calvé-Perthes disease.[19]

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

Hydrops fetalis may be encountered in other LSDs, including GM1 gangliosidosis, sialidosis type 1, Wolman disease, mucopolysaccharidosis type VII (MPS VII), mucopolysaccharidosis type IV (MPS IV; see MPS IVA), galactosialidosis, Niemann-Pick disease type C, disseminated lipogranulomatosis (Farber disease), infantile free sialic acid storage disease (ISSD) and mucolipidosis II (I-cell disease).[20]

Myoclonic seizures are also observed in GM2 gangliosidosis, sialidosis type 1, alpha-N-acetylgalactosaminidase deficiency and fucosidosis. In addition to the LSDs, several genetic disorders are known to be associated with progressive myoclonic epilepsy.[21] The lysosomal

integral membrane protein-2 (LIMP-2) has been shown to facilitate lysosomal targeting for the nascent glucocerebrosidase.[22] Pathogenic variants in the gene encoding LIMP-2 have been associated with action myoclonus-renal failure.[23]

Management

Evaluations Following Initial Diagnosis

Baseline (pre-treatment) assessments may be useful in selecting treatment modality and regimen (i.e., enzyme dose and frequency of infusion).

Factors that may influence the extent of clinical testing at the time of diagnosis:

- Age
- Mode of ascertainment (e.g., family screening vs disease signs and symptoms)
- Presence/absence of primary neurologic involvement

Treatment of Manifestations

Management by a multidisciplinary team with expertise in treating GD is available at Comprehensive Gaucher Centers (see National Gaucher Foundation).

Although enzyme replacement therapy (ERT) has changed the natural history of GD and eliminated the need for splenectomy in individuals with hypersplenism, persons not receiving ERT and certain other individuals may require symptomatic treatment, including the following:

- **Partial or total splenectomy** for individuals with massive splenomegaly with significant areas of infarction and persistent severe thrombocytopenia with high risk of bleeding
- **Transfusion of blood products** for severe anemia and bleeding. Anemia and clotting problems unresponsive to ERT should prompt investigations for an intercurrent disease process. Evaluation by a hematologist is recommended prior to any major surgical or dental procedures or parturition.[22]
- **Analgesics for bone pain.** Persistent bone pain in individuals receiving ERT should prompt evaluations to exclude the possibility of a mechanical problem (e.g., pathologic fracture or joint collapse secondary to osteonecrosis, degenerative arthritis).
- **Joint replacement surgery** for relief from chronic pain and restoration of function (i.e., improved joint range of motion). Bone pain in individuals who have undergone joint replacement may indicate a problem with the prosthesis and the need for surgical revision.

- **Supplemental treatment.** Oral bisphosphonates and calcium/vitamin D may benefit individuals with GD and low bone density.[14]

Persons with GD with findings suggestive of multiple myeloma and parkinsonism should be referred to the appropriate specialists.

Prevention of Primary Manifestations

Bone marrow transplantation (BMT)

- Bone marrow transplantation (BMT) has been undertaken in individuals with severe GD, primarily those with chronic neurologic involvement (type 3 GD). Successful engraftment can correct the metabolic defect, improve blood counts and reduce increased liver volume. In a few individuals, stabilization of neurologic and bone disease has occurred. However, the morbidity and mortality associated with BMT limit its use in individuals with type 1 and type 3 GD. Therefore, this procedure has been largely superseded by enzyme replacement therapy (see **ERT**).
- Individuals with chronic neurologic GD and progressive disease despite ERT may be candidates for BMT or a multi-modal approach (i.e., combined ERT and BMT).

Enzyme replacement therapy (ERT).

Macrophage-targeted enzyme replacement therapy (ERT) has long been the standard of care. It is not a cure for GD, i.e.: it does not repair the underlying genetic defect but it can reverse and prevent numerous manifestations of GD type 1.[24-26]

The goal of ERT is to provide sufficient amount of enzyme to allow processing of accumulated material for patients including children with GD who manifest signs and symptoms.[27] ERT is well established as being effective in reducing hematologic, visceral and bone symptoms. Early treatment may prevent development of irreversible pathology. Treatment also improves growth and reduce the impact of disease on physical and psychological development However, it comes with a therapeutic burden due to the need for regular lifelong IV therapy as well as high cost.[28]

In order to establish the severity of disease and to tailor the initial and maintenance ERT dose, a classification in high- and low-risk type 1 GD patients has been suggested by a panel of experts.[29]

Response to ERT was documented by international collaborative Gaucher group (ICGG) registry with decreased liver and spleen volumes and increase in hemoglobin levels and platelet counts within 6 months of therapy.[30,31] However, GD I involvement beyond the monocyte/macrophage system may underlie unmet treatment needs with respect to skeletal, pulmonary, and immune manifestations.[32] Likewise, the CNS manifestations of type II and III GD do not respond well to ERT due to the inability of exogenous enzyme to cross the BBB.[33]

The standard dose is 60 units/kg every two weeks and can be individualized according to response and requirements. Higher doses may be needed in the initial stage of GD type III and lower doses may be given as a maintenance dose in GD type I.[34]

ERT includes imiglucerase (Cerezyme), velaglucerase alfa (VPRIV), and taliglucerase alfa (Elelyso). Historically, most patients received the recombinant enzyme imiglucerase.[35] All are recombinant GC enzyme preparations based on the human gene sequence but differ in the cell type involved in their production: Imiglucerase is generated from Chinese Hamster ovary cells, velaglucerase alfa is generated from human fibroblast-like cell line and taliglucerase alfa is generated from a carrot cell line. Each formulation is modified to expose the alpha-mannosyl (carbohydrate) residues for enhanced uptake by the macrophage:

Imiglucerase and velaglucerase alfa Imiglucerase and velaglucerase alfa are produced in different mammalian cell system and require production glycosylation modifications to expose terminal alpha-mannose residues, which are needed for mannose receptor-mediated uptake by target macrophages: such modifications add to production costs.[36] Side effects are few including pruritis which can be controlled by antihistaminics. Antibody formation has been reported in imiglucerase more than velaglucerase (10–15% versus 1%) but in most cases the patient is asymptomatic.[37]

Taliglucerase (Elelyso) It is a plant cell expressed enzyme using carrot root cell cultures using recombinant DNA technology. It is approved by FDA on May 1st, 2012 for ERT in adults with symptomatic GD. It does not require additional processing for post-production glycosidic modifications.[36] It is a safe and efficacious initial therapy in adults and pediatric patients with symptomatic GD as well as for those previously treated with Imiglucerase. It can be used also for treatment of hematological manifestations of GD type III.[38] It is administered in a dose of either 30 units/kg or 60 units/kg in type I GD. It reduces the spleen and liver volumes by 29–40% and improves platelet counts and hemoglobin levels. It is also

effective in maintaining spleen and liver volumes, platelet counts, hemoglobin levels as well as biomarker levels over a 6–9 month evaluation period in type I GD switched from imiglucerase.[36,38]

The most common side effects reported were transient and included infusion reactions, allergic reactions and anaphylaxis. Infusion reactions occur within 24 h of infusion in 44–46% of treated cases.[39] These include headache, chest pain or discomfort, weakness, fatigue, skin redness, increased blood pressure, back pain, joint pain and flushing. Allergic reactions includes angioedema, wheezing and hypotension. Anaphylaxis has been observed in some patients during infusion. In 10% of cases urinary tract infection, common clod like symptoms, arthralgia, headache were also observed. Hypersensitivity reaction occurred and included swelling under the skin, flushing, redness, rash, nausea, vomiting and chest tightness.[38,39]

Alglucerase (Ceredase) This is a placental derived macrophage-targeted GC first introduced in 1991. It leads to reduction in hepatosplenomegaly, improvement of hypersplenism, decreased biomarkers and amelioration of bone pain, it has a reliable safety profile. The original dosage used was 60 units/kg of body weight (BW) every other week (the high-dose regime), which is still the most frequently used in clinical trials and accordingly highly promoted by the manufacturers.[40–43]

- **Individuals with type 1 GD** report improved health-related quality of life after 24-48 months of ERT.[44,45]

After prolonged treatment, ERT reduces the rate of bone loss in a dose-dependent manner [15], improves bone pain and reduces bone crises.[45]

The effectiveness of ERT for the treatment of neurologic disease remains to be established, although a few reports have suggested some benefit.[46]

- **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.[47] These individuals and those with hydrops fetalis are not appropriate candidates for BMT, ERT, or substrate reduction therapy (SRT).[48,49]

- **Individuals with type 3 GD** appear to derive some benefit from ERT, although long-term prognosis remains to be defined for this heterogeneous group.[50] Onset of

progressive myoclonic seizures while on ERT appears to indicate a poor prognosis.[51] Brain stem auditory evoked responses have deteriorated in individuals with type 3 GD on ERT.[48] SRT used in combination with ERT for type 3 GD with progressive neurologic disease does not appear to alter ultimate prognosis.

The optimal dose and frequency of recombinant enzyme administration is not certain, mostly because of limited information regarding tissue half-life and distribution and the limitations associated with the modalities used for assessing clinical disease course. 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 – i.e., hematopoietic reconstitution, reduction of liver and spleen volumes and stabilization or improvement in skeletal findings.[27]

Substrate reduction therapy (SRT). 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 mutant enzyme with residual hydrolytic activity.[52] A potential concern regarding the use of SRT is its nonspecificity; i.e., the substrate whose production is blocked or limited is a precursor in the formation of other glycosphingolipids (ganglio- and lacto- series).

Miglustat, the first oral agent for the treatment of individuals with mild to moderate Gaucher disease for whom ERT is not a therapeutic option (e.g., because of constraints such as allergy, hypersensitivity, or poor venous access). 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 longer use of the product.

Eliglustat, an alternative inhibitor of glucosylceramide synthetase recently approved by the FDA, has been shown in clinical trials to be a safe and effective treatment for individuals with Gaucher disease type 1 who are not on any therapy as well as those previously treated with ERT.

Pharmacological chaperon therapy (PCT)

Pharmacological chaperon therapy (PCT) are competitive reversible active site inhibitors that selectively bind and stabilize the mutant misfolded GC enzyme, thus prevent endoplasmic reticulum (ER), associated degradation in proteosome, restore enzymatic activity and clear stored substrate.[53] It also facilitates trafficking of the enzyme to the lysosomes and have the potential to attenuate the unfolded protein response and prevent ER stress that can lead to apoptosis and inflammatory response.[54] This approach is especially applicable in GD because only a modest increase in residual GC should be sufficient to ameliorate the phenotype. Another advantage is that PCT can cross the BBB and can be orally available. Combination of ERT and PCT should enhance the effect of ERT, since PCT assists in trafficking of the endogenous mutant GC out of the ER to lysosomes where they may have some residual activity. PCT can also stabilize the recombinant enzyme and increase its half-life in the circulation.[55] The fact that PCs are less expensive, can be given orally and usually cross the BBB, opens up the possibility of treating Type II and Type III GD patients with neurological involvement that are not responsive to ERT.

Isofagamine (IFG) The pharmacological chaperon iminosugar isofagamine (IFG), have shown these properties in cultured fibroblasts in vivo. This iminosugar can bind, stabilize and promote lysosomal trafficking and increase activity of N370S mutant form of the enzyme GC in cultured fibroblasts in vivo as well as in mice for GCase mutations: V394L, D409H, or D409V.[53,56]

IFG can also increase the lysosomal activity of L444p mutant form of GC enzyme in cells and tissues. IFG has also a broad tissue distribution including access to the CNS and multiple tissues thus merit therapeutic option for patients with neuropathic and non-neuropathic GD.[57]

Ambroxol Ambroxol, a mucolytic agent, is also a potential pharmacologic GBA chaperone.[58] It has an advantage of its long history use in humans and its very low level of toxicity. **Bicyclic L-idonojirimycin** Bicyclic L-idonojirimycin derivative has been suggested as a potential therapeutic option acting as PCT for patients with homozygous L444P mutations[59] Reduced activity of glucocerebrosidase enzyme has been associated with mitochondrial dysfunction. Supplementation of Coenzyme Q10 (CoQ), together with PCT have resulted in restoring enzyme folding and trafficking in fibroblasts. It also improved mitochondrial function and the associated pathophysiological alterations.[60]

Prevention of Secondary Complications

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.

- **Medical history** (at least every 6-12 months) including weight loss, fatigue, depression, change in social, domestic, or school- or work-related activities, bleeding from the nose or gums, menorrhagia, shortness of breath, abdominal pain, early satiety as a result of abdominal pressure, joint aches or reduced range of movement, and bone pain.

- **Physical examination** (at least every 6-12 months) including: heart and lungs, joint range of motion, gait, neurologic status, evidence of bleeding (bruises, petechiae). In children, attention should be given to growth (height, weight and head circumference using standardized growth charts) and pubertal changes (using the Tanner staging system). Neurologic evaluation is particularly important in the early detection of type 2 and type 3 disease in children. A severity scoring tool has been developed to evaluate neurologic features of neuronopathic GD.[61]

- **Assessment of hemoglobin concentration and platelet count** (with frequency based on symptoms and treatment status). Hemoglobin, platelet count and coagulation indices should also be assessed prior to surgical or dental procedures.

- **Other blood tests** at the physician's discretion may include measurement of the following:
  - Serum concentrations of tartrate-resistant acid phosphatase, liver enzymes (aspartate aminotransferanse or alanine amino transferase), iron, ferritin and vitamins B_{12} and D.
  - Plasma activity of chitotriosidase, a macrophage-derived chitin-fragmenting hydrolase, and plasma concentration of PARC/CCL18. 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; however, up to 40% of affected individuals of European origin are homozygous or heterozygous for a common null variant, confounding interpretation of test results.[62]

- **Assessment of spleen and liver volumes** by MRI or volumetric computed tomography (CT). Parenchymal abnormalities can be identified as well. In situations in which access to an MRI or CT is problematic, abdominal ultrasonography (US) may be performed.

Abdominal US may provide information on organ volume and parenchymal abnormalities and also call attention to the presence of gallstones.[63] MRI or US are the preferred modalities in the pediatric population.

- **Screening for pulmonary hypertension.** EKG and echocardiography with Doppler studies to identify elevated pulmonary artery pressure
- **Skeletal assessment**
  - **Plain radiographs**
  - **Coronal T_1- and T_2-weighted MR images of the hips to the distal femur.**
- **Assessment of disease severity.** Two recent reports have delineated a means for scoring disease severity, incorporating standard assessments of disease severity.[64,65] With increasing therapeutic options, the ability to benchmark response may inform the modality of choice and selected regimen.[66]

Agents/Circumstances to Avoid

Nonsteroidal anti-inflammatory drugs (NSAIDs) should be avoided 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 two disease-causing alleles can benefit from early diagnosis and treatment to reduce morbidity.

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 have an increased risk of bleeding around the time of delivery.[67]

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, 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. This

section is not meant to address all personal, cultural, or ethical issues that individuals may face 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

- In most instances, the parents of a proband are heterozygotes and thus carry a single copy of a pathogenic variant in *GBA*.
- Heterozygotes are asymptomatic.
- Because the carrier frequency for GD in certain populations is high (e.g., 1:18 in individuals of Ashkenazi Jewish heritage) and the N370S/N370S phenotype is variable, it is possible that a parent may be found to be homozygous rather than heterozygous.

Sibs of a proband

- At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier and a 25% chance of being unaffected and not a carrier.
- Once an at-risk sib is known to be unaffected, the chance of his/her being a carrier is 2/3.
- Heterozygotes are asymptomatic.

Offspring of a proband

- The offspring of a proband are obligate heterozygotes.
- A high carrier rate for GD exists in certain populations, 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 obligate heterozygotes.

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

Carrier (Heterozygote) Detection

Biochemical genetic testing. 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.

Molecular genetic testing can be used to identify carriers among at-risk family members once the pathogenic variants have been identified in the family.

Testing for the four common *GBA* alleles (N370S, L444P, 84GG, IVS2+1) has been included in panels specifically designed for carrier screening in the Ashkenazi Jewish population.[68]

Because the frequency for GD in certain populations is high (e.g., individuals of Ashkenazi Jewish heritage) and the N370S/N370S phenotype is variable, individuals who undergo carrier testing may be identified as being homozygous.

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 analysis for pathogenic variants is insufficient and full sequence analysis should be undertaken.

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, clarification of carrier status, and discussion of the availability of prenatal 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.

DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, allelic variants, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals.

Prenatal Testing

If the pathogenic variants have been identified in a family member, prenatal testing for pregnancies at increased risk is possible either through a clinical laboratory or a laboratory offering custom prenatal testing.

Except in families in which a previously affected sibling 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.

Requests for prenatal testing for treatable conditions such as GD type 1 are not common. Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing, particularly if the testing is being considered for the purpose of pregnancy termination rather than early diagnosis. Although most centers would consider decisions about prenatal testing to be the choice of the parents, discussion of these issues is appropriate.[17-21]

Preimplantation genetic diagnosis (PGD) may be an option for some families in which the pathogenic variants have been identified.

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