



The Physician's Guide to **Gaucher Disease**

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Introduction

Welcome to the NORD Physician Guide to Gaucher disease. The NORD Online Physician Guides are written for physicians by physicians with expertise on specific rare disorders. This guide was written by Roscoe O. Brady, MD, National Institute of Neurological Disorders and Stroke (NINDS), National Institutes of Health (NIH) (see acknowledgements for additional information).

NORD is a nonprofit organization representing all patients and families affected by rare diseases. The information NORD provides to medical professionals is intended to facilitate timely diagnosis and treatment for patients.

Gaucher disease is a lipid storage disease caused by an enzyme deficiency that results in excess glycolipid glucocerebroside throughout the body especially in the spleen, liver and bone marrow, and is characterized by a wide range of severity.

The author and NORD appreciate your interest in this topic. There are opportunities for follow-up questions and/or discussion in the Clinician Comments section of the [online guide](#).

What is Gaucher Disease?

Gaucher disease is a rare, inherited metabolic disorder in which deficiency of the enzyme glucocerebrosidase results in the accumulation of harmful quantities of certain lipids, specifically the glycolipid glucocerebroside, throughout the body especially within the spleen, liver, and bone marrow. The symptoms and physical findings associated with Gaucher disease vary greatly from case to case. Some individuals develop few or no symptoms and others may have serious complications. Common manifestations of Gaucher disease include hepatosplenomegaly, anemia, thrombocytopenia, and skeletal abnormalities. Three clinical presentations of Gaucher disease

have been identified that are distinguished by the absence of, or the presence and extent of, neurological involvement. All three forms of Gaucher disease are inherited as autosomal recessive traits.

Gaucher disease is categorized as a lysosomal storage disorder. Lysosomes are the major digestive units in cells containing enzymes that breakdown carbohydrates, lipids (fatty materials) and proteins that arise from membranes and other components of cells undergoing turnover. In Gaucher disease, glycolipids accumulate in the body because of the lack of the enzyme, glucocerebrosidase, leading to the various symptoms and physical findings associated with a lysosomal storage disease. Gaucher disease is the most common type of lysosomal storage disorder.

Symptoms and Signs

There are three distinct forms of Gaucher disease classified by the absence (type 1) or presence and extent (type 2 or type 3) of neurological complications. The majority of affected individuals have Gaucher disease type 1. Approximately 5% of patients have type 2 and type 3 Gaucher disease. Type 2 patients have severe brain damage and die early in life. Type 3 patients live longer and have involuntary horizontal eye movement and often muscle contractions.

One of the earliest manifestations of Gaucher disease is enlargement of the spleen. It may be small and detectable just below the rib cage or huge extending down the left side of the abdomen and palpable from left to right across the lower pelvis. The liver also becomes enlarged but not to the magnitude exhibited by the spleen. The skeleton may also be involved. The long bones, pelvis and vertebrae become under-mineralized resulting in severe deformation and easy fracturing. A considerable percentage of patients experience painful bone crises. Major manifestations occur in the circulation including severe thrombocytopenia with easy bruising and hemorrhage and moderate to severe anemia. The lungs can become involved, and pronounced dyspnea occurs in a small number of patients. Respiratory gas exchange is compromised, and diffuse pulmonary infiltration is evident radiographically. The lymph nodes may be enlarged, and infiltration of pharyngeal tonsils and Peyer's patches in the intestine are common in children. Pericardial involvement has occasionally been noted. The kidneys are involved in some patients with Gaucher disease, but frank

renal failure is uncommon. There is a well-recognized increase in certain hematological malignancies including B-cell or plasma cell malignancies, multiple myeloma, chronic lymphocytic leukemia, acute myeloid leukemia, acute lymphoblastic leukemia, large B-cell lymphoma, Hodgkin lymphoma, as well as non-hematologic malignancies¹. Patients that survive to adulthood have a significantly increased chance of Parkinsonism⁽²⁾.

Gaucher disease type 2, also known as acute neuronopathic Gaucher disease, occurs in newborns and infants and is characterized by neurological complications due to the abnormal accumulation of glucocerebroside in the brain. Splenomegaly is often the first sign and may become apparent before six months of age. Hepatomegaly is not always present. Affected infants may lose previously acquired motor skills and exhibit hypotonia, spasticity, strabismus, rapid head thrusting and seizures. In addition, affected infants may experience dysphagia, resulting in feeding difficulties, retroflexion of the head, failure to thrive, and stridor due to laryngeal spasm. Anemia and thrombocytopenia may also occur. Gaucher disease type 2 often progresses to life-threatening complications such as respiratory distress or aspiration pneumonia. Severely affected newborns may show collodion skin or ichthyosiform changes and hydrops, with death in the first few weeks of life. Other children with type 2 Gaucher disease have greatly reduced lifespans, with death usually occurring between 1 and 3 years of life. It has been estimated that about 10 such infants are born in the U.S. each year.

Gaucher disease type 3, also known as chronic neuronopathic Gaucher disease, occurs during the first decade of life. Type 3 patients have a varying degree of early hepatosplenomegaly that may initially be moderate and in some may become extensive. In addition to the blood and bone abnormalities discussed above, affected individuals develop neurological complications that develop and progress slower than in Gaucher disease type 2. Associated neurological complications include mental deterioration, ataxia, and myoclonic seizures. Some individuals with type 3 Gaucher disease may have horizontal gaze palsy. Patients with Type 3 Gaucher disease can also have a vertical gaze palsy that usually occurs later than the horizontal gaze paresis. A significant proportion of patients also develop interstitial lung disease. There can be wide variability in presentation and clinical course among patients with type 3 Gaucher disease. Some affected patients may live into their teens and early 20's, while others have lived for much longer (30's and 40's). It is anticipated that the life span may be further extended

by effective treatment such as enzyme replacement therapy (vide infra).

Causes

Gaucher disease is an autosomal recessive genetic disorder caused by mutations in a gene on human chromosome 1 that codes for an enzyme that is important for lipid metabolism. Both parents must carry a mutation of the gene in order to produce a child that is affected with the disorder. Such parents are called carriers (heterozygotes). When two heterozygotes marry, there is a 1 in 4 chance with each pregnancy that the child will have the disorder. There is a 50-50 chance that the child will be a heterozygote carrying a mutation from one of its parents. Gaucher heterozygotes are generally asymptomatic. There is a 25% chance with each pregnancy that the offspring will be affected (have two mutations) or be completely unaffected (no mutations).

The cause of all three forms of Gaucher disease is the accumulation of a fatty material called glucocerebroside (also known as glucosylceramide) throughout the body and blood stream of patients. Glucocerebroside is a lipid consisting of three components. The first of these is a long chain alcohol called sphingosine (Fig 1). A long chain fatty acid is linked to the nitrogen atom (N) on carbon atom 2 of sphingosine creating a structure known as ceramide (Fig. 2). A molecule of glucose is linked to the oxygen atom on carbon 1 of the sphingosine moiety of ceramide forming glucocerebroside (Fig 3). Organs and cells in the body contain an enzyme called glucocerebrosidase that catalyzes the hydrolytic cleavage of glucose from glucocerebroside⁽³⁾ (Fig. 4). The activity of this enzyme is reduced in patients with Gaucher disease and is the metabolic defect in this disorder^(4,5). The reduction of glucocerebrosidase activity causes the accumulation of toxic amounts of glucocerebroside in organs, tissues and the blood of patients with Gaucher disease. The principal source of accumulating glucocerebroside in the spleen, liver and bone marrow are rapidly turning over cells such as white blood cells (Fig. 5). Glucocerebroside also arises from the biodegradation of ganglioside GM3 in platelets (Fig. 6) and from globoside, the principal sphingolipid in red blood cells (Fig. 7). The accumulation of glucosylsphingosine (Fig 8) in the brain is a major cause of the pathological changes that occur in the central nervous system of patients with types 2 and 3 Gaucher disease⁽⁶⁾.

Figure 1 Sphingosine

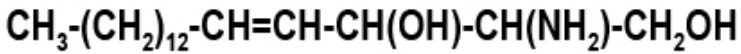


Figure 2. Ceramide. A long chain fatty acid is linked to the nitrogen atom on carbon atom 2 of sphingosine.



Figure 3. Glucocerebroside. A molecule of glucose is linked to the oxygen atom on carbon atom 1 of the sphingosine moiety of ceramide.

**PRINCIPAL ACCUMULATING MATERIAL IN
GAUCHER DISEASE IS GLUCOCEREBROSIDE**

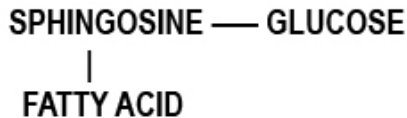


Figure 4. Site of action of glucocerebrosidase, the enzyme that catalyzes the hydrolytic cleavage of glucose from glucocerebroside.

**THE ENZYMIC DEFECT IN GAUCHER DISEASE
IS A DEFICIENCY OF GLUCOCEREBROSIDASE**

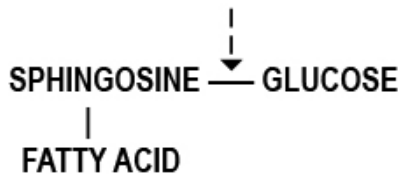


Figure 5. Structure of the principal sphingolipid of white blood cells.

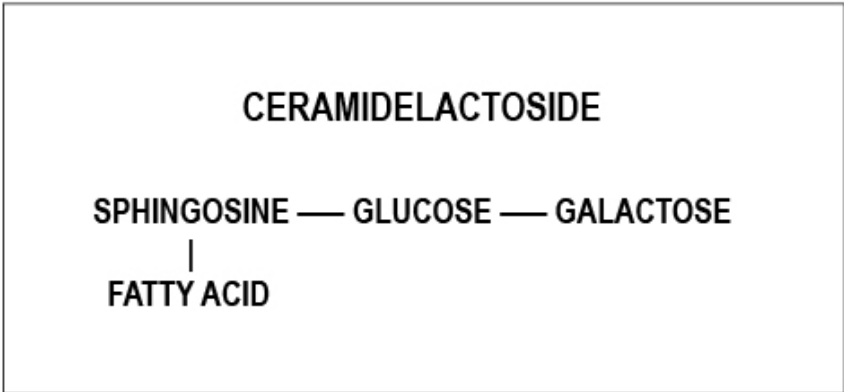


Figure 6. Major sphingolipid of blood platelets.

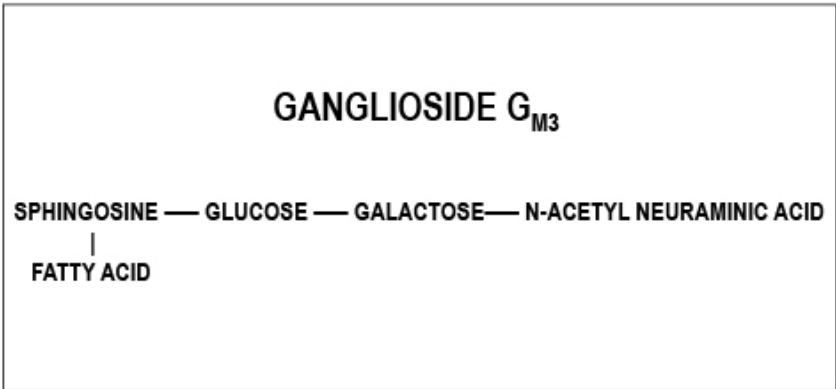


Figure 7. Major sphingolipid of red blood cells.

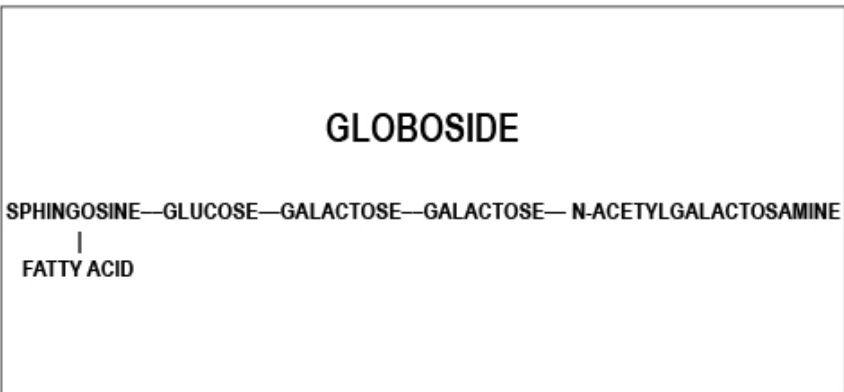
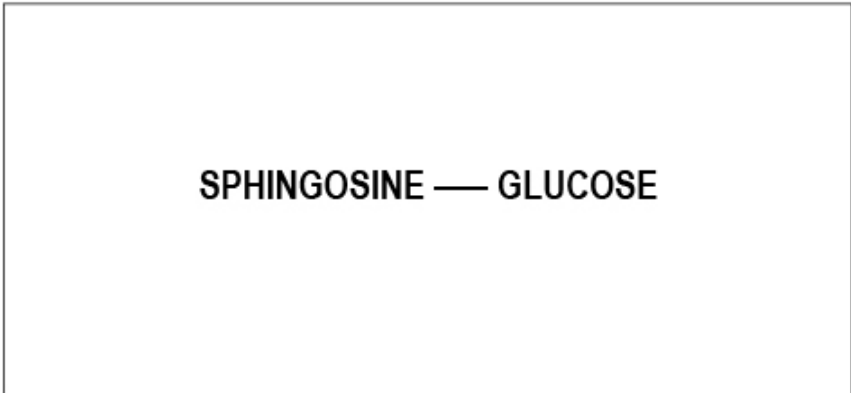


Figure 8. Glucosylsphingosine. A highly cytotoxic substance that also accumulates in organs and tissues of patients with Gaucher disease but to a much lesser extent than glucocerebroside.



Prognosis

With the exception of patients with Type 2 Gaucher disease with severe central nervous system involvement and death in infancy, the rapidity and extent of the severity of the signs and symptoms in patients with Gaucher disease is remarkably variable. The life span of patients with Type 3 Gaucher disease has been mentioned previously in the section on Symptoms and Signs. The prognosis in patients with Type 1 Gaucher disease is quite variable. Many patients develop hepatosplenomegaly as early as four years of age while in others, this manifestation may not become apparent until the mid or late thirties. Generally, the earlier the onset of prominent signs that often include anemia and thrombocytopenia, the more rapidly the pathological manifestations of the disorder proceed.

Affected Populations

All forms of Gaucher disease affect males and females in equal numbers. Gaucher disease type 1 is the most common type, accounting for more than 90 percent of cases. Individuals with Gaucher disease type 1 usually exhibit symptoms during adolescence, but the age of onset ranges from childhood to adulthood. The age of onset for Gaucher disease type 2 is during early infancy. The age of onset of Gaucher disease type 3 varies, but the disorder generally begins during childhood or adolescence.

There are approximately 6,000 individuals with Gaucher disease in the U.S. Gaucher disease is the most common genetic disorder of persons of

Ashkenazic Jewish ancestry, where the incidence may be as high as 1 in 600 births. There is no ethnic prevalence associated with Gaucher disease types 2 or 3. However, there is a subtype of Gaucher disease type 3 that occurs with greater frequency in the Norrbotten region of Sweden (Norrbottnian Gaucher disease). The estimated prevalence in the Swedish Norrbotten population is 1 in 50,000.

Diagnosis

Gaucher disease should be considered in persons with enlargement of the spleen and liver. Additional major signs include anemia, easy bruising, episodes of bone pain and fractures of the femur and pelvis. The diagnosis can be readily confirmed by measuring the activity of glucocerebrosidase in white blood cells⁽⁷⁾ or cultures of skin fibroblasts⁽⁸⁾. A fluorogenic mimic of glucocerebroside was employed as substrate in the investigation with skin fibroblasts. This substrate is widely used for the diagnosis of Gaucher disease at the present time. The diagnosis may be confirmed by DNA analysis for mutations in the causal genes. The identification of heterozygous carriers of Gaucher disease⁽⁹⁾ and the prenatal diagnosis of Gaucher disease by genetic analysis are established procedures⁽¹⁰⁾.

Treatment

Enzyme replacement therapy (ERT) has proven highly effective for patients with type 1 Gaucher disease. Anemia and low platelet counts have improved with ERT, enlargement of the liver and spleen have been greatly reduced, and skeletal findings have improved⁽¹¹⁻¹⁵⁾. These systemic manifestations also improve in individuals with type 3 Gaucher disease who receive ERT^(16,17). However, ERT has not been effective in reducing or reversing neurological signs associated with types 2 and 3 Gaucher disease.

ERT is the standard of care for patients with Gaucher disease. Many patients have been successfully treated with purified human placental glucocerebrosidase⁽¹¹⁾. The sugar side chains of the enzyme were shortened so that it is primarily taken up by macrophages. The use of this product has been superseded by the administration of recombinant glucocerebrosidase. The first preparation was produced in Chinese hamster ovary cells⁽¹²⁾. This preparation is called Cerezyme (imiglucerase). It is marketed by Genzyme, a Sanofi Company.

At the present time there are two additional sources of glucocerebrosidase. One of them called VPRIV (velaglucerase alfa) is produced from a

fibrosarcoma cell line by Shire Pharmaceuticals. The other called taliglucerase alfa is from carrot root cells produced by Protalix Biotherapeutics, an Israeli company and distributed by Pfizer, Inc. under the trade name ELELYSO™ (UPLYSO™).

Administration of the enzyme causes reduction in the size of the spleen and liver and improvement of the skeleton, anemia and thrombocytopenia. Severely ill patients with type 1 Gaucher disease are generally started with a dose of 60 Units (U) of enzyme per kg of body weight every other week. As patients improve, the dose may be reduced to 30 U per kg of body weight, and in many cases to 20 U per kg of body weight every other week. The frequency of administration of enzyme has been extended to every 3 weeks in a number of patients who have been maintained in good condition with this regimen. Long term benefit of ERT in patients with type 1 Gaucher has been clearly documented ⁽¹³⁻¹⁵⁾. Hepatosplenomegaly and hematological manifestations can be improved by ERT in patients with type 3 Gaucher disease but neurological and other complications of the condition have not responded to this therapy ^(16,17).

Another approach to the treatment of patients with Gaucher disease is to try to block the formation of glucocerebroside with compounds that inhibit the addition of glucose to ceramide (Fig.2). A product of this type called Miglustat (Zavesca) is marketed by Actelion. It is approved by the U.S. Food and Drug Administration for the treatment of patients with Gaucher disease "for whom enzyme replacement therapy is not an option".

Investigative Therapies

Oral delivery of plant Glucocerebrosidase (prGCD) ERT as a carrot cell suspension, (expressed) is under development. Additionally, a number of investigations are directed toward reducing the formation of glucocerebroside ⁽¹⁸⁻²⁰⁾. Molecular chaperone therapy that prevents intracellular mis-folding and subsequent destruction of mutant forms of glucocerebrosidase is also under active investigation ⁽²¹⁾. Blocking the activity of histone deacetylases may be a promising strategy to restore reduced mutant glucocerebrosidase activity ⁽²²⁾. Future investigations may include the use of viral vectors to increase the expression of the gene for glucocerebrosidase ⁽²³⁾.

Information on current clinical trials is posted at www.clinicaltrials.gov.

NORD does not endorse or recommend any particular studies.

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Clinical Centers and Medical Experts

The following link is to a page on the National Gaucher Foundation website that lists physicians and treatment centers.

http://www.gaucherdisease.org/gaucher_treatment_locations.php

Acknowledgements



NORD is grateful to Roscoe O. Brady, MD, National Institute of Neurological Disorders and Stroke (NINDS), National Institutes of Health (NIH), for writing this guide.

Dr. Brady's accomplishments include the identification of the metabolic defects in hereditary lipid storage disorders including Gaucher disease, Niemann-Pick disease, Fabry disease, and Tay-Sachs disease.

A brief history of Dr. Brady's pioneering role in promoting better understanding of Gaucher disease may be found at the following location on the website of the National Institutes of Health (NIH): http://history.nih.gov/exhibits/gaucher/docs/page_05.html

Roscoe Brady was born in Philadelphia, PA. He attended the Pennsylvania State University and obtained his M.D. degree from Harvard Medical School in 1947. He interned at the Hospital of the University of Pennsylvania. From 1948 to 1952 he was a post-doctoral fellow in the Department of Physiological Chemistry at the University of Pennsylvania School of Medicine and fellow in clinical medicine in the Department of Medicine. After two and one-half years on active duty in the U.S. Naval Medical Corps, he joined the National Institutes of Health in 1954. He was Chief of the Developmental and Metabolic Neurology Branch in the National Institute of Neurological Disorders and Stroke from 1972 to 2006. Dr. Brady received the Lasker Foundation Award in 1982; the Kovalenko Medal from the National Academy of Sciences USA in 1991; the Alpert Foundation Prize from Harvard Medical School in 1992 and the National Medal of Technology and Innovation in 2008. He is a member of the National Academy of Sciences, USA and the Institute of Medicine of the National Academy of Sciences. Dr. Brady and his colleagues identified the enzymatic defects in Gaucher disease, Niemann-Pick disease, Fabry disease and the specific metabolic abnormality in Tay-Sachs disease. He and his associates developed diagnostic, carrier detection and prenatal tests for these conditions. He developed effective enzyme replacement therapy for patients with Gaucher disease and Fabry disease. He is currently investigating substrate depletion, molecular chaperone therapy and gene therapy for patients with metabolic storage disorders.

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