

# Clinical Roundtable Monograph

Clinical Advances in Hematology & Oncology

June 2012

## Disease State Awareness in Gaucher Disease: A Q&A Expert Roundtable Discussion

### Discussants



**Pramod K. Mistry, MBBS, PhD, FRCP, MA**  
Professor of Pediatrics and Medicine  
Chief of Pediatric Gastroenterology and Hepatology  
Yale University School of Medicine  
New Haven, Connecticut



**Joel A. Weinthal, MD**  
Medical Director of Apheresis and Stem Cell Laboratory  
Texas Oncology Pediatrics  
Medical City Children's Hospital  
Dallas, Texas



**Neal J. Weinreb, MD, FACP**  
Director of the University Regional Gaucher Disease  
and Fabry Disease Treatment Center  
Coral Springs, Florida

**Abstract:** Gaucher disease is an inherited lysosomal storage disorder caused by mutations in the gene that encodes the lysosomal enzyme glucocerebrosidase. Inadequate enzymatic activity causes cells to become engorged due to an accumulation of glycolipids. Engorged cells then accumulate in various organs, resulting in a range of signs and symptoms. Gaucher disease occurs worldwide but is more common among individuals of Ashkenazi Jewish descent. Approximately 90% of patients with Gaucher disease have non-neuronopathic (type 1) disease, which is characterized by hematologic sequelae, potentially disabling skeletal complications, and late-onset neurologic complications. The other 2 subtypes of Gaucher disease cause neuronopathic disease, with early involvement of the central nervous system. Type 2 Gaucher disease results in death in infancy, while type 3 disease causes variable neurologic manifestations ranging from minimal ocular effects to seizures, ataxia, and cognitive regression. Because of its relative rarity, Gaucher disease often remains misdiagnosed or undiagnosed for some time. However, early diagnosis and appropriate treatment are essential for reducing the risk of complications, improving quality of life, and avoiding inappropriate procedures. Given the prevalence of hematologic manifestations associated with this condition, patients with undiagnosed Gaucher disease may seek treatment from hematologists or oncologists. Therefore, hematology and oncology clinicians need to be aware of the potential for Gaucher disease and consider it in their differential diagnosis.

## Table of Contents

Pathophysiology, Clinical Features, and Natural History of Gaucher Disease Neal J. Weinreb, MD, FACP	3
Genetics and Diagnosis of Gaucher Disease Pramod K. Mistry, MBBS, PhD, FRCP, MA	7
Prognosis of Patients with Gaucher Disease Joel A. Weinthal, MD	10
Discussion Awareness of Gaucher Disease	12
Slide Library	14

### **Disclaimer**

Funding for this clinical roundtable monograph has been provided through a grant from Shire Human Genetic Therapies. Support of this monograph does not imply the supporter's agreement with the views expressed herein. Every effort has been made to ensure that drug usage and other information are presented accurately; however, the ultimate responsibility rests with the prescribing physician. Millennium Medical Publishing, Inc., the supporter, and the participants shall not be held responsible for errors or for any consequences arising from the use of information contained herein. Readers are strongly urged to consult any relevant primary literature. No claims or endorsements are made for any drug or compound at present under clinical investigation.

©2012 Millennium Medical Publishing, Inc., 611 Broadway, Suite 310, New York, NY 10012. Printed in the USA. All rights reserved, including the right of reproduction, in whole or in part, in any form.

Publication for this supplement was made possible by Shire Human Genetic Therapies, who also funded medical writing support provided by Melinda Tanzola, PhD.

# Pathophysiology, Clinical Features, and Natural History of Gaucher Disease

Neal J. Weinreb, MD, FACP

**G**aucher disease is the most common of the lysosomal storage disorders, a group of more than 40 known genetic disorders caused by inborn errors of metabolism.<sup>1</sup> In the case of Gaucher disease, autosomal recessive inheritance of various gene defects results in a deficiency in the lysosomal hydrolase glucocerebrosidase (acid- $\beta$ -glucosidase). The lack of functional glucocerebrosidase causes an abnormal accumulation of the lipid glucocerebroside inside cells, primarily macrophages. The resulting engorged macrophages—referred to as Gaucher cells—accumulate in various organ systems and subsequently cause the signs and symptoms of Gaucher disease.

As a group, lysosomal storage disorders affect approximately 1 in 7,700 individuals, and Gaucher disease has an estimated prevalence of 1 in 40,000–60,000 worldwide.<sup>2</sup> Gaucher disease can affect persons of any ethnicity, and cases have been reported throughout the world, including Asia and Africa. However, the prevalence of Gaucher disease among individuals of Ashkenazi Jewish descent is particularly high—1 in 500–800—and even this high prevalence may be an underestimate, as up to half of the Ashkenazi Jewish individuals who are genetically affected by Gaucher disease have minimal or no clinical manifestations and therefore may remain undiagnosed.<sup>3</sup> Despite the high frequency of Gaucher disease among Ashkenazi Jewish individuals, the majority of Gaucher disease patients worldwide are not of Ashkenazi Jewish descent.

## Classification of Gaucher Disease

A heterogeneous disorder, Gaucher disease causes a wide range of clinical sequelae and highly variable phenotypes, with outcomes ranging from minimal symptoms to death in early childhood. Gaucher disease is classified into 3 subtypes that vary in their pathology, clinical manifestations, and prognosis. The most prevalent subtype worldwide is type 1, which accounts for approximately 90% of cases of Gaucher disease. Type 1 is also referred to as non-neuronopathic Gaucher disease, as it is generally not associated with neurologic manifestations (at least not until later in the course of disease). Typical clinical manifestations among type 1 patients include anemia, thrombocytopenia, leucopenia, granulocytopenia, and hepatosplenomegaly. Enlarge-

ment of the spleen is a major contributor, but not the sole factor, in the development of hematologic cytopenias. Rarely, patients may have involvement of the lungs, either through infiltration of the lungs or development of pulmonary hypertension. Fortunately, these grave manifestations are uncommon. Nonetheless, the massive organomegaly, failure to thrive, severe anemia, and thrombocytopenia that are associated with Gaucher disease can cause significant morbidity, even in children. Before treatment for this condition became available, many of these patients died at a much younger age than would otherwise have been expected.

Gaucher disease is not solely a hematologic disease. In fact, the skeletal pathology associated with type 1 Gaucher disease is often patients' most debilitating symptom. Skeletal effects include necrosis of the bone, loss of mineralization, increased risk of fractures, and growth retardation in children. Patients with type 1 Gaucher disease can also develop late-onset neurologic manifestations, including Parkinsonism and peripheral neuropathy; in addition, recent evidence suggests that carriers of Gaucher disease can exhibit Parkinson-type symptoms. Given the presence of these neurologic features, type 1 Gaucher disease is not entirely non-neuronopathic; however, these neurologic features differ significantly from the neurologic manifestations seen in type 2 and 3 Gaucher disease.

Types 2 and 3 Gaucher disease are rare, occurring in 1 in every 100,000 to 200,000 births, and both subtypes are characterized primarily by central nervous system pathology.<sup>4</sup> Type 2 Gaucher disease, the acute neuronopathic variant, is the most severe form of the disease and causes death at an early age. In some cases, type 2 Gaucher disease can result in nonviable infants. In other cases, the disease progresses rapidly during the first 1–2 years of life, with infants showing neurologic manifestations such as bulbar involvement, stridor, dysphagia, head retroflexion, opisthotonos, spasticity, and cognitive impairment. The condition invariably causes death, typically before the age of 3 years, even with attentive supportive care.

Type 3 Gaucher disease, the subacute or chronic neuronopathic variant, is more clinically heterogeneous. Some individuals with type 3 Gaucher disease are fully functional and able to work, while others may have significant impairments. Mild manifestations include oculomotor apraxia, while more severe forms of type 3

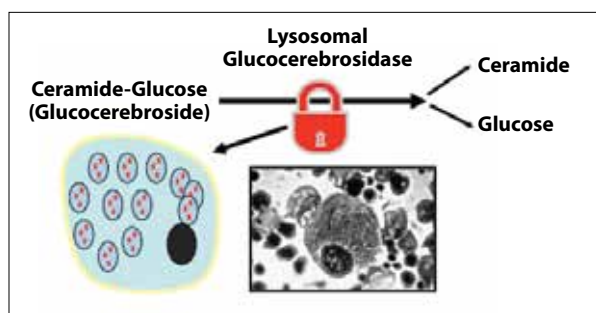
Gaucher disease are characterized by extrapyramidal manifestations such as myoclonic or generalized seizures, cerebellar ataxia, and intellectual regression.

Although neurologic pathology dominates the clinical presentation in patients with type 2 or type 3 Gaucher disease, many patients with these variants also have the systemic features found in type 1 disease, including hepatosplenomegaly, hematologic abnormalities, and skeletal complications. Patients with type 3 disease may also exhibit gibbus or humpback features.

Analysis of the prevalence of the different Gaucher disease subtypes across different populations has revealed certain epidemiologic patterns. Although not a universal rule, persons of Ashkenazi Jewish ethnicity are much more likely to have non-neuronopathic disease compared to non-Jewish individuals. Additionally, although type 1 Gaucher disease is the most prevalent subtype worldwide, some countries have a disproportionate number of patients with the neuronopathic subtypes.<sup>5,6</sup>

### Pathophysiology of Gaucher Disease

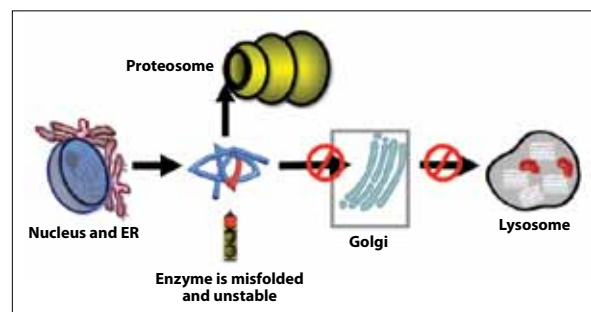
Although the clinical sequelae of Gaucher disease are heterogeneous, all variants of the disease share the same biochemical process, which stems from a defect in the enzymatic activity of the lysosomal enzyme glucocerebrosidase. Normally, glucocerebrosidase hydrolyzes the glucose component of glucocerebroside (glucosyl-ceramide), yielding ceramide and glucose. The ceramide moiety is then used to synthesize new glycosphingolipids or is further reduced to sphingosine and fatty acids. In patients with Gaucher disease, mutations in the gene encoding glucocerebrosidase cause a deficiency in its enzymatic activity, due to impaired catalytic function, intracellular stability, or subcellular trafficking.<sup>7</sup> The cell's inability to metabolize glucocerebroside, a fairly insoluble product, causes an accumulation of this and other glycosphingolipids (Figure 1).



**Figure 1.** Biochemical pathology: impaired hydrolysis of glucosyl-ceramide (glucocerebroside).

Recently, attention has focused on the possibility that the deficiency in glucocerebrosidase activity results

from misfolding of the enzyme during its formation. If an unstable misfolded protein lacks the proper 3-dimensional conformation required to exit from the endoplasmic reticulum (ER), it may be ubiquitinated and targeted for degradation by the proteasome rather than being routed to the lysosome (Figure 2). Recent thinking suggests that



**Figure 2.** Endoplasmic reticulum (ER) quality control: misfolded proteins.

the constant production of mutated glucocerebrosidase may overwhelm the ER's quality control mechanism, causing an accumulation of misfolded protein within the cell. This process may itself be responsible for some of the cellular pathology associated with Gaucher disease, particularly in patients with Parkinsonism. Not only does the misfolded-protein hypothesis provide a possible explanation for some manifestations of Gaucher disease, it may also identify a potential new target for therapy.

Deficiency in glucocerebrosidase activity results in accumulation of glycosphingolipids in all cell types, but macrophages are most prominently affected due to their heavy burden of substrate turnover. The storage and deposition of glucocerebroside within these cells results in the appearance of Gaucher cells, which are considered to be the hallmark of the disease. Although the degree of enzyme deficiency does not show an absolute correlation with the clinical manifestations of the disease, patients with severe enzymatic deficiency (resulting in minimal to no enzymatic activity) often have the most severe phenotypic manifestations.

While Gaucher cells are a hallmark of the disease, the appearance of Gaucher cells in the bone marrow or other tissues is not pathognomonic for Gaucher disease. Pseudo-Gaucher cells have been described in several other hematologic disorders, including acute lymphoblastic leukemia, Hodgkin disease, thalassemia, and multiple myeloma.<sup>8</sup> Although pseudo-Gaucher cells share many similarities with Gaucher cells, examination by electron microscopy reveals that pseudo-Gaucher cells lack the structural components of true Gaucher cells. Because the presence of pseudo-Gaucher cells can pose a diagnostic challenge, demonstration of

enzymatic deficiency is crucial in establishing the diagnosis of Gaucher disease.

### Clinical Features of Gaucher Disease

The accumulation of infiltrating Gaucher cells—plus, presumably, the release of cytokines and chemokines and the resulting inflammatory responses—invariably results in splenomegaly. The spleen can enlarge to massive proportions in patients with Gaucher disease, occasionally reaching 50 times its normal size or larger, which results in multiple physiologic problems. Hemodilution and anemia are caused by volume expansion, while the cytopenias associated with Gaucher disease result from pooling of platelets, accelerated destruction of platelets, and destruction of erythrocytes and leukocytes. Gaucher disease is also associated with enlargement of the liver, which causes pressure symptoms; if left untreated, hepatomegaly can lead to hepatic fibrosis, cirrhosis, portal hypertension, and end-stage liver disease.

Some degree of thrombocytopenia is also present in most patients with Gaucher disease. Occasionally, patients with Gaucher disease develop severe thrombocytopenia that causes spontaneous or even life-threatening bleeding, but in most cases, the thrombocytopenia associated with Gaucher disease does not cause spontaneous bleeding. In these latter patients, thrombocytopenia still poses challenges related to perioperative bleeding, post-traumatic bleeding, and dental bleeding. Concern about thrombocytopenia is a particular issue in pregnancy, as pregnant women are predisposed to thrombocytopenia irrespective of any coexisting condition.

In addition to hematologic symptoms, Gaucher disease also causes skeletal problems. Most patients with Gaucher disease have some discomfort due to bone pain, and skeletal involvement results in varying degrees of disability. Patients may have episodes of acute, severe, potentially disabling bone pain—called bone crises—as well as more chronic, unremitting bone pain. In some Gaucher disease patients, skeletal manifestations are the most troubling and disabling aspect of their condition. According to data from the Gaucher Registry—which is an international, observational, longitudinal registry—skeletal aspects of Gaucher disease have a greater negative impact on quality of life than hematologic or visceral manifestations.<sup>9</sup>

Skeletal manifestations of Gaucher disease stem from the infiltration of Gaucher cells into the bone and bone marrow, a process that occurs in more than 90% of Gaucher disease patients. In about one third of patients, this infiltration leads to avascular necrosis of the bone, which can eventually result in irreversible bone destruction. Potential complications include sclerosis, joint collapse, pathologic fracture, and need for joint replace-

ment. Patients' mobility can eventually become extremely limited, with some patients being confined to wheelchairs or requiring the use of orthopedic devices.

Another skeletal aspect of Gaucher disease is generalized osteopenia, which is thought to result from an increase in bone resorption and a decrease in bone formation. In many patients with Gaucher disease, osteopenia starts early in life; low bone mineral density can be detected in children younger than 10 years of age. Low bone mineral density then continues during adolescence and into adulthood. Because many patients do not reach normal peak bone mass early in life, they are at a disadvantage when normal aging processes accelerate and thus are more likely to develop severe osteoporosis.<sup>10</sup> Overall, the incidence of osteopenia and osteoporosis in individuals with Gaucher disease likely exceeds 60%.

Finally, fatigue is a common feature of Gaucher disease. Although fatigue can be due to anemia, fatigue is an independent feature of Gaucher disease that occurs regardless of the degree of anemia. Cytokines may play a role in the development of fatigue in Gaucher disease.

### Natural History of Gaucher Disease

Gaucher disease is quite variable in its clinical presentation and disease progression. In many cases, disease progression is sporadic and unpredictable. The disease may be relatively silent for long periods of time, with these quiescent periods punctuated by episodes of acute crises or evidence of disease advancement.

The interval between onset of symptoms and diagnosis of Gaucher disease is also quite variable. Patients are often symptomatic for some time, even years, prior to being correctly diagnosed; this delay in diagnosis is due to the relative rarity of the disease and physicians' lack of familiarity with the full spectrum of abnormalities associated with Gaucher disease.<sup>11</sup> Unfortunately, this delay in diagnosis can lead to severe and potentially life-threatening complications, including avascular necrosis, severe bleeding, chronic bone pain, sepsis, pathologic fractures, growth abnormalities, and liver disease. Delay in diagnosis also causes tremendous psychologic stress for patients, as they often move from one physician to another seeking an explanation for their symptoms. Thus, patients with undiagnosed or misdiagnosed Gaucher disease are at a significantly increased risk for habitual drug use or even suicide.

While some Gaucher disease patients have symptoms but remain undiagnosed, others are diagnosed despite being asymptomatic. Genetic screening for Gaucher disease is growing increasingly popular, particularly in the Ashkenazi Jewish population, resulting in diagnosis among patients who may have few or no symptoms. This

increase in the detection of Gaucher disease is introducing new opportunities for intervention but also presents new challenges. Given the variable natural history of the disease, a substantial proportion of individuals may have relatively indolent or nonprogressive disease, rendering treatment unnecessary. On the other hand, starting treatment early in patients with a more aggressive disease could allow clinicians to preempt the onset of complications.

### Historical Perspective and Future Directions

Tremendous advances have been made in the understanding of Gaucher disease since 1882, when Philippe Gaucher first described a woman whose enlarged spleen contained unusual engorged cells that he believed were due to a malignant lymphoepithelioma. In the 1960s, understanding of the biology of Gaucher disease grew tremendously, largely due to research by Roscoe Brady at the National Institutes of Health. Although previous researchers had already determined that glucocerebroside was the accumulating lipid product, Brady and colleagues determined that the condition was caused by a deficiency of glucocerebrosidase, rather than a synthetic abnormality causing the excess glucosyl-ceramide. During this period, studies by Brady and myself identified glucocerebrosidase as a lysosomal enzyme.<sup>12</sup> The subsequent years have continued to bring additional advances in the understanding of Gaucher disease pathophysiology, culminating with the development of active therapy for some types of Gaucher disease.

Today, researchers are continuing to investigate the pathophysiology of Gaucher disease. Evidence suggests that this condition is not simply a disorder of macrophages, but rather is associated with abnormalities in immune regulation, mesenchymal cell function, and osteoblast function.<sup>13</sup> Studies are also investigating the relationship between Gaucher disease and other disease

processes—including oncogenesis, metabolic effects, and late neurologic effects—which could help to further improve outcomes for patients with Gaucher disease.

### Acknowledgment

*Neal J. Weinreb, MD, FACP has received honoraria and expense reimbursement for serving on the Board of Advisors of the ICGG Gaucher Registry, as well as travel reimbursements and/or honoraria and/or research support from Genzyme (a Sanofi Corporation), Shire HGT, Amicus Therapeutics, and Actelion Corporation.*

### References

1. Meikle PJ, Hopwood JJ, Clague AE, Carey WF. Prevalence of lysosomal storage disorders. *JAMA*. 1999;281:249-254.
2. Cox TM, Schofield JP. Gaucher's disease: clinical features and natural history. *Baillieres Clin Haematol*. 1997;10:657-689.
3. Grabowski GA. Gaucher disease: gene frequencies and genotype/phenotype correlations. *Genet Test*. 1997;1:5-12.
4. Beutler E, Grabowski GA. Gaucher disease. In: Scriver CR, Beaudet AL, Sly WS, Valle D, eds. *Metabolic and Molecular Bases of Inherited Disease*. New York: McGraw-Hill; 2001:3635-3668.
5. El-Beshlawy A, Ragab L, Youssry I, et al. Enzyme replacement therapy and bony changes in Egyptian paediatric Gaucher disease patients. *J Inher Metab Dis*. 2006;29:92-98.
6. Lee JY, Lee BH, Kim GH, et al. Clinical and genetic characteristics of Gaucher disease according to phenotypic subgroups. *Korean J Pediatr*. 2012;55:48-53.
7. Grabowski GA. Phenotype, diagnosis, and treatment of Gaucher's disease. *Lancet*. 2008;372:1263-1271.
8. Saroha V, Gupta P, Singh M, Singh T. Pseudogaucher cells obscuring multiple myeloma: a case report. *Cases J*. 2009;2:9147.
9. Wenstrup RJ, Roca-Espiau M, Weinreb NJ, Bembli B. Skeletal aspects of Gaucher disease: a review. *Br J Radiol*. 2002;75 Suppl 1:A2-A12.
10. Mistry PK, Weinreb N, Kaplan P, Cole JA, Gwosdow AR, Hangartner T. Osteopenia in Gaucher disease develops early in life: response to imiglucerase enzyme therapy in children, adolescents and adults. *Blood Cells Mol Dis*. 2011;46:66-72.
11. Mistry PK, Sadan S, Yang R, Yee J, Yang M. Consequences of diagnostic delays in type 1 Gaucher disease: the need for greater awareness among hematologists-oncologists and an opportunity for early diagnosis and intervention. *Am J Hematol*. 2007;82:697-701.
12. Weinreb NJ, Brady RO, Tappel AL. The lysosomal localization of sphingolipid hydrolases. *Biochim Biophys Acta*. 1968;159:141-146.
13. Mistry PK, Liu J, Yang M, et al. Glucocerebrosidase gene-deficient mouse recapitulates Gaucher disease displaying cellular and molecular dysregulation beyond the macrophage. *Proc Natl Acad Sci U S A*. 2010;107:19473-19478.

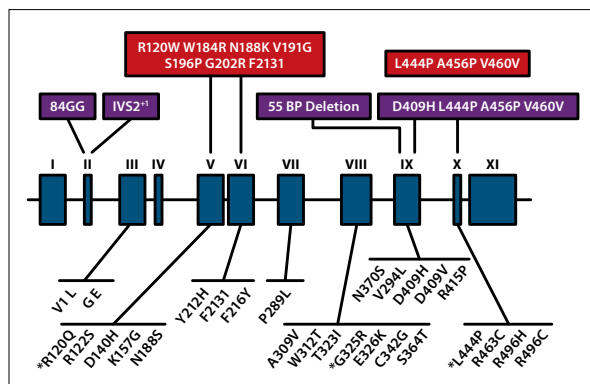


# Genetics and Diagnosis of Gaucher Disease

Pramod K. Mistry, MBBS, PhD, FRCP, MA

**G**aucher disease results from biallelic mutations in the glucocerebrosidase gene (*GBA*), which is assigned to a gene-dense region of chromosome 1q. Molecular analysis of the *GBA1* gene is complex, as this gene is linked with an actively transcribed, highly homologous pseudogene that also harbors several mutations. However, only mutations in the active gene lead to Gaucher disease.

To date, more than 300 mutations in the *GBA* gene are known that cause defects in the glucocerebrosidase enzyme (Figure 3). The vast majority of these mutations



**Figure 3.** Glucocerebrosidase gene mutations.

are missense mutations, and most of the less common mutations are restricted to single families.<sup>1-4</sup> In the Ashkenazi Jewish population, approximately 1 in every 12–15 individuals is a carrier of a *GBA1* mutation, which suggests that these mutations may have a possible selective advantage; however, the nature of any potential advantage remains under debate. Of the approximately 300 mutations associated with Gaucher disease, 4 account for the majority of mutations seen in Ashkenazi Jewish patients: N370S, L444P, 84GG, and IVS2+1. These 4 mutations also account for approximately half of the mutations seen in non-Jewish white patients.

The N370S mutation in the *GBA* gene is the most frequently observed mutation among Ashkenazi Jewish patients. Homozygosity for the N370S mutation occurs in 29% of individuals with Gaucher disease, nearly all of whom are of Ashkenazi Jewish descent.<sup>4</sup> Specifically, this genotype is found in 41% of Ashkenazi Jewish patients and 9% of non-Jewish patients.<sup>5</sup>

The most common *GBA* disease allele worldwide is the missense mutation L444P.<sup>6</sup> The presence of L444P in diverse populations throughout the world indicates that this muta-

tion likely arises on a recurrent basis. The L444P/L444P genotype carries a high risk for the development of neuronopathic forms of Gaucher disease. Interestingly, the L444P mutation normally exists in the pseudogene sequence, suggesting that gene conversion events between the pseudogene and the active gene underlie this mutation. Complex alleles have also been identified in which the *GBA1* gene is formed as a hybrid of the active gene and the pseudogene, causing a transfer of mutations from the pseudogene to the active gene. These types of complex alleles are more often associated with the type 2 form of Gaucher disease.<sup>7</sup>

The third most frequent mutation in individuals with Gaucher disease is the insertion mutation 84GG, which leads to a frame shift and premature termination. This rare allele is found exclusively in persons of Ashkenazi Jewish descent. The 84GG/84GG genotype is believed to be incompatible with life, and 1 fetal death associated with this genotype has been described in the literature. The 84GG/N370S genotype is typically associated with more severe disease compared to N370S/N370S and N370S/L444P.<sup>8</sup>

The fourth most common mutation in Gaucher disease is IVS2+1, an RNA processing mutation that causes deletion of the second exon of the *GBA* gene.<sup>2</sup> This mutation is associated with greater enzyme impairment than the N370S mutation; accordingly, the N370S/IVS2+1 genotype is associated with more severe disease.

Together, these 4 mutations—N370S, L444P, 84GG, and IVS2+1—account for 80–90% of all mutations detected in Ashkenazi Jewish individuals with Gaucher disease and 50–60% of all mutations in the non-Jewish patient population.<sup>2</sup> Genetic screening for these 4 mutations in Ashkenazi Jewish patients has identified N370S/N370S as the most common genotype, affecting 29% of patients, following by the N370S mutation in combination with an unidentified allele (20%), then the L370S/L444P mutation (16%), and finally the N370S/84GG mutation (12%). All other combinations are present in fewer than 10% of patients.<sup>9</sup>

In the non-Jewish patient population, these common mutations account for only 50–60% of disease alleles, indicating greater heterogeneity in this group. Comparison of *GBA* genotypes among Ashkenazi Jewish patients and non-Jewish individuals has also found notable genetic differences in the Ashkenazi Jewish population; for example, the N370S mutation is present in more than 80% of Ashkenazi Jewish patients but occurs in only 34% of non-Jewish patients.<sup>5</sup>

## Correlation Between Genotype and Phenotype in Gaucher Disease

Genetic studies in Gaucher disease indicate a broad correlation between genotype and phenotype. In general, the N370S/N370S genotype, which is the most frequently occurring genotype among Ashkenazi Jewish patients, results in a milder form of the disease compared to the N370S/84GG or N370S/L444P genotype. In fact, the presence of at least 1 N370S allele absolutely precludes the development of neuronopathic Gaucher disease. Analysis of splenomegaly among patients with at least 1 N370 allele illustrates this trend towards less severe disease among patients with the N370S/N370S phenotype. The average spleen size in patients with the N370S/N370S genotype is 7 times larger than normal, while patients with the N370S/L444P and N370S/84GG genotypes show 13-fold and 16-fold enlargement, respectively ( $P < .0001$  and  $P = .001$ , respectively, compared with N370S/N370S).<sup>8</sup>

Despite these general trends, phenotypes can vary between individuals in a genotype group. For example, some patients with the more severe genotypes have no splenomegaly, and significant enlargement of the spleen (to nearly 75 times normal) has been observed in patients with the N370S/N370S genotype.<sup>10</sup> This variability is also observed among different members of the same family, indicating that factors other than genetics contribute to disease severity.<sup>11</sup>

The clinical course of Gaucher disease can also vary substantially among patients within genetic groups, particularly among patients with the N370S/N370S genotype. Patients who develop symptomatic disease earlier in life tend to have florid visceral and hematologic disease, whereas those who become symptomatic later in life primarily develop skeletal manifestations, including osteoporosis, avascular necrosis, and fractures. Persons developing disease later in life also appear to have a higher risk of malignancy. Finally, splenectomy correlates significantly with disease severity; within each genotype group, patients who have previously undergone splenectomy generally have more severe disease manifestations in the liver and bone compared to patients with an intact spleen.

While genetic studies have yielded considerable insight into Gaucher disease, more detailed genetic studies are currently under way, which should help to more fully determine the influence of modifier genes on the disease course.<sup>12</sup> Researchers are using whole exome sequencing and genome-wide association studies to discover modifier genes for protean phenotypes of Gaucher disease.<sup>13,14</sup>

## Diagnosis of Gaucher Disease

The gold standard for the diagnosis of Gaucher disease is demonstration of low acid- $\beta$ -glucosidase activity in peripheral blood leukocytes. (Measurement of acid- $\beta$ -

glucosidase activity can also be performed on cultured fibroblasts, which may be useful for prenatal diagnosis, but typically peripheral blood leukocytes are used for this test.) Compared to a healthy person, glucocerebrosidase activity is reduced 70–90% in a typical adult patient with Gaucher disease and more than 90% in children with more severe forms of the disease.

Other laboratory findings can aid in the diagnosis of Gaucher disease, including low levels of high-density lipoprotein and total cholesterol; elevated levels of angiotensin converting enzyme, tartrate-resistant acid phosphatase, and/or ferritin; and elevated levels of biomarkers, including chitotriosidase and CCL18.<sup>15</sup> However, these ancillary tests cannot replace the need for measurement of glucocerebrosidase activity.

Finally, genetic testing can be useful for family screening or detection of carriers after a family member has been diagnosed. Genetic testing is of great utility for prenatal diagnosis in families with a history of neuronopathic disease, particularly for those with type 2 disease. However, research from multiple groups has shown an imperfect correlation between genotype and phenotype in type 1 disease.<sup>1,9,10</sup> Genetic testing can also identify patients with variants that put them at high risk of neuronopathic disease, such as homozygous mutations for L444P or D409H.

## Clinical Evaluation of Patients with Suspected Gaucher Disease

Gaucher disease is associated with a variety of phenotypes that encompass severe visceral involvement, cytopenia, and complex bone disease. These classic features are particularly seen in patients with younger age at disease onset. In an International Collaborative Gaucher Group (ICGG) analysis of 1,474 children with non-neuronopathic Gaucher disease, the most common clinical features were moderate-to-severe splenomegaly (97%), thrombocytopenia (91%), and hepatomegaly (89%).<sup>16</sup> The majority of patients also had some bone involvement. Radiologic evidence of bone involvement—including Erlenmeyer flask deformity, marrow infiltration, osteopenia, avascular necrosis, and/or new fractures—was present in 79% of patients; 29% had bone pain, and 11% had bone crises. Other common symptoms in this cohort included anemia (37%) and growth retardation (31%).

The splenomegaly associated with Gaucher disease is often massive, with the spleen enlarging below the level of the umbilicus and often impacting into the pelvic brim. In addition to occurring in Gaucher disease, this degree of massive splenomegaly can also be caused by chronic myelogenous leukemia, myelofibrosis, lymphoma, visceral leishmaniasis, hyperreactive malarial splenomegaly, thalassemia major, and AIDS with *Mycobacterium avium* complex.<sup>8</sup>

When a patient presents with an enlarged spleen, clinicians should consider Gaucher disease as part of the



differential diagnosis, which includes sequestration of red blood cells, in conditions such as congenital spherocytosis; proliferation secondary to chronic inflammation or infection (ie, systemic lupus erythematosus, rheumatoid arthritis, infective endocarditis, or chronic malaria); lipid deposition disorders such as Gaucher disease; endowment (ie, congenital causes, including splenic hemangioma, hamartoma, or cysts); engorgement caused by splenic trauma with intracapsular hematoma formation; sequestration crises, as occur in sickle cell disease, chronic congestive heart failure, or portal hypertension; or invasion (with granulomatous or malignant hematologic disease).

To help clinicians distinguish among these causes of splenomegaly, an international group of Gaucher disease experts recently published diagnostic algorithms that incorporate the frequencies of disorders associated with splenomegaly; these algorithms were published in the *American Journal of Hematology* in 2010.<sup>17</sup> Depending on whether the patient is of Ashkenazi Jewish heritage, 1 of 2 different algorithms should be used.

For patients of Ashkenazi Jewish ancestry, the frequency of Gaucher disease is much higher than the frequency of hematologic malignancies. Therefore, patients of Ashkenazi Jewish descent who present with splenomegaly should be immediately evaluated for Gaucher disease using the peripheral blood acid- $\beta$ -glucosidase assay. In patients of non-Ashkenazi Jewish ancestry, malignancy is more likely to cause splenomegaly. In these patients, portal hypertension must first be excluded, after which a bone marrow biopsy is a reasonable initial investigation. If Gaucher cells are detected in the bone marrow, this finding would suggest the possibility of Gaucher disease and would warrant measurement of peripheral blood leukocyte acid- $\beta$ -glucosidase activity. Certainly, Gaucher disease and malignancy are not mutually exclusive. Moreover, pseudo-Gaucher cells have been observed in some non-Gaucher disease patients with malignant conditions.<sup>17</sup>

## Conclusion

Significant advances in clinicians' understanding of the genetics of Gaucher disease have occurred in recent years. In Ashkenazi Jewish patients, most cases of Gaucher disease can be traced to a small number of mutations. Other populations show more genetic variability in the mutations in the glucocerebrosidase gene that lead to Gaucher disease. Correlative studies have revealed some association between genotype and phenotype in individuals with Gaucher disease; for example, some mutations and types of mutations are associated with a higher risk of neuropathic disease, while other mutations are found more often in type 1 disease. However, patients within the same genotype group still show phenotypic variability in regards to symptomatology and clinical course.

Additional studies are under way that may help clinicians better understand the role of genetics in Gaucher disease.

Although genetic testing for mutations associated with Gaucher disease is useful in some clinical scenarios, demonstration of low acid- $\beta$ -glucosidase activity in peripheral blood leukocytes is still necessary for diagnosis of Gaucher disease. Given the prevalence of significant splenomegaly among individuals with Gaucher disease, clinicians should consider Gaucher disease in the differential diagnosis when patients presents with an enlarged spleen. A timely diagnosis of Gaucher disease ensures the greatest benefit from available therapies and maximizes patients' long-term outcomes and quality of life.

## Acknowledgment

Pramod K. Mistry, MBBS, PhD, FRCP, MA, has received research grants from Genzyme Corporation and Shire Human Genetic Therapies.

## References

- Grabowski GA. Phenotype, diagnosis, and treatment of Gaucher's disease. *Lancet*. 2008;372:1263-1271.
- Hruska KS, LaMarca ME, Scott CR, Sidransky E. Gaucher disease: mutation and polymorphism spectrum in the glucocerebrosidase gene (GBA). *Hum Mutat*. 2008;29:567-583.
- Gelb MH, Turecek F, Scott CR, Chamoles NA. Direct multiplex assay of enzymes in dried blood spots by tandem mass spectrometry for the newborn screening of lysosomal storage disorders. *J Inherit Metab Dis*. 2006;29:397-404.
- Grabowski GA, Petsko GA, Kolodny EH. Gaucher disease. In: Valle D, Beaudet AL, Vogelstein B, Kinzler KW, Antonarakis SE, Ballabio A, eds. *The Online Metabolic & Molecular Bases of Inherited Disease*. www.ommbid.com/. Chapter 146.
- Horowitz M, Tzuri G, Eyal N, et al. Prevalence of nine mutations among Jewish and non-Jewish Gaucher disease patients. *Am J Hum Genet*. 1993;53:921-930.
- Koprivica V, Stone DL, Park JK, et al. Analysis and classification of 304 mutant alleles in patients with type 1 and type 3 Gaucher disease. *Am J Hum Genet*. 2000;66:1777-1786.
- Stone DL, Tayebi N, Orvisky E, Stubblefield B, Madike V, Sidransky E. Glucocerebrosidase gene mutations in patients with type 2 Gaucher disease. *Hum Mutat*. 2000;15:181-188.
- Mistry PK, Cappellini MD, Lukina E, et al. A reappraisal of Gaucher disease-diagnosis and disease management algorithms. *Am J Hematol*. 2011;86:110-115.
- Charrow J, Andersson HC, Kaplan P, et al. The Gaucher registry: demographics and disease characteristics of 1698 patients with Gaucher disease. *Arch Intern Med*. 2000;160:2835-2843.
- Fairley C, Zimran A, Phillips M, et al. Phenotypic heterogeneity of N370S homozygotes with type I Gaucher disease: an analysis of 798 patients from the ICGG Gaucher Registry. *J Inherit Metab Dis*. 2008;31:738-744.
- Amato D, Stachiw T, Clarke JT, Rivard GE. Gaucher disease: variability in phenotype among siblings. *J Inherit Metab Dis*. 2004;27:659-669.
- Velayati A, DePaolo J, Gupta N, et al. A mutation in SCARB2 is a modifier in Gaucher disease. *Ref Hum Mutat*. 2011;32:1232-1238.
- Lo SM, Choi M, Liu J, et al. Phenotype diversity in type 1 Gaucher disease: discovering the genetic basis of Gaucher disease/hematologic malignancy phenotype by individual genome analysis. *Blood*. 2012;119:4731-4740.
- Zhang CK, Stein PB, Liu J, et al. Genome-wide association study of N370S homozygous Gaucher disease reveals the candidacy of CLN8 gene as a genetic modifier contributing to extreme phenotypic variation. *Am J Hematol*. 2012;87:377-383.
- Aerts JM, Kallemeijn WW, Wegdam W, et al. Biomarkers in the diagnosis of lysosomal storage disorders: proteins, lipids, and antibodies. *J Inherit Metab Dis*. 2011;34:605-619.
- Andersson H, Kaplan P, Kacena K, Yee J. Eight-year clinical outcomes of long-term enzyme replacement therapy for 884 children with Gaucher disease type 1. *Pediatrics*. 2008;122:1182-1190.
- Mistry PK, Cappellini MD, Lukina E, et al. A reappraisal of Gaucher disease—diagnosis and disease management algorithms. *Am J Hematol*. 2010;86:110-115.

# Prognosis of Patients with Gaucher Disease

Joel A. Weinthal, MD

**T**he outlook for patients with Gaucher disease has improved dramatically over the past few decades. With the availability of effective therapy, today's patients show improvements in virtually all of the long-term complications of Gaucher disease, including skeletal complications, lung problems, liver issues, and inflammatory conditions.

One resource that has improved clinicians' understanding of Gaucher disease is the Gaucher Registry, which has provided insight into patient outcomes. However, when evaluating registry data, clinicians should keep in mind that the patients enrolled in this registry are not perfectly representative of the overall Gaucher disease patient population. Patients enrolled in the registry are skewed to a group who is more symptomatic and present at a younger age than Gaucher disease patients who are not enrolled in the registry.

Registry data indicate that cytopenias improve fairly rapidly after initiation of treatment. Although the extent of existing splenomegaly affects the rapidity of improvement, hemoglobin levels and platelet counts typically improve within 3–6 months and normalize within 1 year. Bone problems and symptoms take much longer to improve and resolve; often, patients require years of treatment before showing documented radiographic improvement or resolution correlating with clinical symptoms. Concerns remain about later-onset effects of Gaucher disease, including neurologic complications, such as Parkinsonism and peripheral neuropathies, and the increased incidence of hematologic malignancies. The effect of treatment on the risk of malignancy is not known or well understood at this time.

Among children, treatment can have a particularly positive impact. Analyses of children show that anemia and thrombocytopenia nearly always normalize within 6–8 years.<sup>1</sup> Liver and spleen sizes also decrease dramatically with treatment, and bone marrow density normalizes, which has tremendous implications for long-term bone health. Finally, bone crises tend to disappear with treatment, although bone manifestations improve more slowly than other complications. Bone symptoms and radiograph normalization require 3–5 years of treatment. Although improvement in bone manifestations is slow, average height normalizes after 8 years of treatment compared with age-matched sibling controls.

## Importance of Early Diagnosis

Obtaining a timely diagnosis is essential for maximizing outcomes in patients with Gaucher disease. An early diagnosis of Gaucher disease allows patients to avoid inappropriate or unnecessary procedures and reduces the risks of irreversible organ damage and serious complications, chronic pain, and disabling symptoms. According to a group of Gaucher disease experts, patients with Gaucher disease are often misdiagnosed with leukemia, immune thrombocytopenia purpura, autoimmune disease, hepatic cirrhosis, idiopathic avascular necrosis, or viral disease with splenomegaly or anemia due to chronic disease.<sup>2</sup> As a result of these incorrect diagnoses, patients can develop serious symptoms, including avascular necrosis, osteopenia, liver disease, and coagulopathies. Misdiagnosed patients can also undergo inappropriate treatments and procedures, including splenectomy, liver biopsy, and corticosteroid and other medical therapies.

Once a patient has been diagnosed, clinicians should consider whether therapy should be initiated. The greatest therapeutic gains in Gaucher disease are achieved with pre-emptive therapy that is administered before any irreversible complications have developed.<sup>2</sup> Thus, the decision to initiate treatment is straightforward when patients have disease that is mild-to-moderate, severe, or rapidly progressive. However, the potential benefit of treatment for patients who have minimal or no disease manifestations (typically patients with the N370S/N370S genotype) is unknown. Many experts believe that earlier initiation of treatment could improve patients' long-term outcome, but the degree of benefit has not been documented in clinical trials. Several other factors need to be considered before starting treatment in asymptomatic patients, including financial implications and the psychologic impact of undertaking a life-long scheduled treatment regimen. If the decision is made to delay treatment, patients should be regularly monitored to detect any signs of disease progression.

## Importance of Engaging an Expert

Hematologists and oncologists play an essential role in identifying and diagnosing Gaucher disease, as these specialists commonly encounter patients who have an enlarged liver or spleen, or low blood counts. More than 40% of patients on the ICGG Gaucher Registry were added by hematology or oncology physicians.

Although hematologists and oncologists are the specialists most likely to encounter Gaucher disease patients, the overall rarity of this condition means that most community-based hematologists and oncologists will see such patients infrequently, if ever. Even in a large practice such as Texas Oncology Group, we have only 1 hematologist who manages more than 2 or 3 adult patients with Gaucher disease.

Given the relative rarity of this condition and the complexity of its management, patients who are diagnosed with Gaucher disease should initially be referred to a center with experience in treating such patients. Care coordinated by specialists ensures that an entire team—including radiologists and other subspecialists—are familiar with the disease. Specialists with experience in Gaucher disease are best equipped to manage the overall condition, predict and discuss the prognosis, and provide education and supportive care recommendations for the likely course of the disease and treatment.

However, hematologists and oncologists do have tremendous expertise regarding the therapeutic aspects of care. Therefore, I think most hematology/oncology centers can administer therapy and even transition patients to home infusions if such therapy is appropriate and reimbursable. If routine care is being provided in a hematology or oncology setting, patients should still follow up with a specialist routinely, with the frequency of these follow-up visits depending on the patient's clinical status. A patient who is doing very well could probably follow up with an expert annually, or even once every few years if he or she is doing very well. However, a patient who is symptomatic, who is planning to undergo an elective surgical procedure, or who is planning a pregnancy should seek care from an expert, as experience is paramount in the effective management of this disorder. Pediatric patients require substantially more individualized attention and need to have multiple subspecialists involved in their care.

## Conclusion

Given the importance of timely diagnosis and treatment for Gaucher disease, hematologists and oncologists need to maintain awareness of this condition and other lysosomal storage diseases, even though they will rarely

encounter such patients. Unfortunately, Gaucher disease specialists often meet individuals who have lived with symptomatic Gaucher disease for years—into middle age or beyond—at which point treatment is much less effective. Although these patients can gain some benefit from treatment, irreversible damage has often already occurred. Early consideration of Gaucher disease in the differential diagnosis could allow patients to avoid this outcome and gain maximal quality of life with effective therapy.

When evaluating patients with splenomegaly, most hematologists will consider a variety of possible causes. Including Gaucher disease in the differential of unexplained splenomegaly is paramount. A careful clinical evaluation can provide much important information, and a detailed family history should also be taken, particularly in patients of Jewish descent or those in specific ethnic groups. The family history should attempt to tease out prior cases of Gaucher disease, even those that may not be obvious—for example, a family member who had a hip replacement at a very young age or someone who had bone problems that were not well explained. Evaluating patients thoroughly and asking the right questions can help to reveal difficult and rare diagnoses such as Gaucher disease. Improved education of caregivers to consider the possibility of Gaucher disease is especially important if patients have sought medical attention for an unusual constellation of symptoms and clinical and laboratory findings over time and have seen multiple physicians without a definitive diagnosis.

## Acknowledgment

*Joel A. Weinthal, MD, has no real or apparent conflicts of interest to report. Dr. Weinthal would like to thank his colleagues and mentors and, most importantly, his Gaucher patients and their families for inspiring him throughout his career.*

## References

1. Andersson H, Kaplan P, Kacena, et al. Eight-year clinical outcomes of long-term enzyme replacement therapy for 884 children with Gaucher disease type 1. *Pediatrics*. 2008;122:1182-1190.
2. Mistry PK, Cappellini MD, Lukina E, et al. A reappraisal of Gaucher disease—diagnosis and disease management algorithms. *Am J Hematol*. 2010;86:110-115.

## Discussion: Awareness of Gaucher Disease

### H&O How can hematologists and oncologists more readily recognize Gaucher disease?

**Neal J. Weinreb, MD, FACP** Primary care physicians—and particularly hematologists—need to be frequently reminded that Gaucher disease is a possibility in patients of any ethnicity who present with splenomegaly, with or without hematologic cytopenias and bone pain, if splenomegaly is not obviously attributable to one of the other illnesses that Dr. Mistry discussed. They should particularly focus on Gaucher disease when the patient is of Ashkenazi Jewish ancestry. Physicians who are likely to encounter a patient with Gaucher disease also need to be frequently reminded that this condition is eminently treatable. I know of some physicians who have dismissed a diagnosis of Gaucher disease because they mistakenly believed that, even if the patient were diagnosed, nothing further could be done to help the patient. Even among hematologists, there is need for further education about Gaucher disease. A study conducted in 2005 indicated that only about 20% of hematologists worldwide identified Gaucher disease as a possible diagnosis when presented with a hypothetical case with classical manifestations.

**Pramod K. Mistry, MBBS, PhD, FRCP, MA** I agree. When physicians evaluate a patient with hepatosplenomegaly and cytopenia, they mostly think of malignancy, but they should consider Gaucher disease at the same time.

### H&O How can greater awareness of Gaucher disease among hematologists and oncologists improve patients' prognosis?

**Joel A. Weinthal, MD** Early diagnosis of Gaucher disease with appropriate referral and therapy can prevent or minimize many long-term complications of the disease. Treatment can prevent or reverse bone changes, which enhances quality of life for patients. Enzyme replacement therapy will result in decreased storage of glucocerebroside throughout the ER system, which also enhances a patient's quality of life by improving hemoglobin levels, minimizing pulmonary changes and disease, and avoiding hepatic injury and other long-term complications. Improving awareness about Gaucher disease among physicians, particularly hematologists and oncologists, will shorten the painfully long interval between the onset of symptoms and

diagnosis, which is a recurring theme among patients, many of whom describe lengthy diagnostic journeys to many specialists and clinics before the definitive diagnosis is made.

**NJW** In addition to the complications that can develop when diagnosis is delayed, patients may also undergo an unnecessary splenectomy, which has negative prognostic implications. Splenectomy often leads to long-term complications and adverse outcomes. One reason why Gaucher disease is not always considered is because some physicians, including hematologists, are unaware that this condition can be diagnosed by an easily obtained blood test; bone marrow biopsy is not necessary to make the diagnosis.

### H&O When is referral to a specialist indicated?

**PKM** I think all patients should be seen by a specialist at least once in order to develop a roadmap for treatment goals and monitoring.

**NJW** I agree. I feel that all newly diagnosed Gaucher disease patients should be evaluated at one of the major Gaucher disease centers. Comprehensive assessments, especially magnetic resonance (MR) evaluations of the skeleton, are best performed by radiologists who have expertise in Gaucher disease. I have encountered a large number of MR scans in which signs of Gaucher disease have been misinterpreted or overt findings consistent with Gaucher disease have been totally missed. Decisions regarding when to initiate treatment, what type of treatment to offer, and how to monitor and regulate treatment to achieve the desired therapeutic goals are frequently tricky questions even for experts; these decisions will be even more challenging for clinicians who do not have substantial experience in the management of Gaucher disease.

**JAW** I also believe referral is indicated for any patient who is newly diagnosed with Gaucher disease. An experienced physician or clinic can provide education and an overview of Gaucher disease, after which infusions can be done by an experienced infusion center. The actual intravenous administration of Gaucher disease enzyme replacement therapy is well within the expertise of hematologists and oncologists, but the overall management of Gaucher disease involves much more than infusing an intravenous medicine or prescribing a pill.

### **H&O** What are the major unmet needs for Gaucher disease? How might they be addressed?

**PKM** Earlier treatment is needed for patients with bone disease, and clinicians need to avoid splenectomy since asplenia is a major risk factor for pulmonary hypertension. Also, there is no treatment at present for the Parkinson-type symptoms of Gaucher disease, so further research in this area would be beneficial.

**NJW** For type 1 Gaucher disease, there is a need for a validated set of easily obtained biomarkers that will predict which presymptomatic patients will remain asymptomatic and which patients are destined to develop progressive manifestations and complications. This need can be met only by continued basic research, including use of animal models; continued support of the Gaucher Registry with enrollment of a large roster of patients of varying phenotypes; and a commitment to bio-banking. For neuronopathic disease, the biggest need is for a safe treatment that will reverse or prevent the inexorable progression of neurologic signs and symptoms if treatment is started sufficiently early in life.

**JAW** There are many unmet needs in Gaucher disease. We are still accumulating registry data to understand the history of Gaucher disease among patients treated with various therapies. We also need a better understanding of different genotypes and the resulting phenotype, and we need to understand why individuals with Gaucher disease have an increased risk of cancer—particularly hematologic malignancies. Finally, the Parkinson-type symptoms and neuropathic symptoms need to be better understood so that we can develop preventative strategies for these patients.

#### **Acknowledgment**

*Neal J. Weinreb, MD, FACP has received honoraria and expense reimbursement for serving on the Board of Advisors of the ICGG Gaucher Registry, as well as travel reimbursements and/or honoraria and/or research support from Genzyme (a Sanofi Corporation), Shire HGT, Amicus Therapeutics, and Actelion Corporation. Pramod K. Mistry, MBBS, PhD, FRCP, MA, has received research grants from Genzyme Corporation and Shire Human Genetic Therapies. Joel A. Weinthal, MD, has no real or apparent conflicts of interest to report.*



# Slide Library

## Gaucher Disease Is a Lysosomal Storage Disorder

- There are over 40 known genetic lysosomal disorders
  - All are caused by inborn errors of metabolism
  - In most of these disorders, a genetic defect results in deficiency of a particular enzyme or enzymes
  - These disorders are estimated to affect 1 in every 7,700 people
- Gaucher disease (GD) is the most common lysosomal storage disorder
- Prevalence is 1 in 40,000–60,000
  - In Ashkenazi Jews: 1 in 500–800
  - Worldwide, the majority of patients with GD are not Ashkenazi Jews
- Most known patients have Type 1 GD, but some countries have a disproportionate number of patients with neuropathic subtypes of GD (Types 2 and 3)

## Gaucher Disease Subtypes

- Non-neuropathic Gaucher disease (Type 1)
  - Anemia, thrombocytopenia
  - Hepatosplenomegaly with or without lung involvement
  - Skeletal pathology and growth retardation
  - Late-onset neurologic manifestations
    - Parkinsonism
    - Peripheral neuropathies
- Primary Central Nervous System Pathology
  - Type 2 Gaucher disease (acute neuropathic)
    - Early presentation, early death
    - Bulbar involvement, ataxia, dysphagia, spasticity (head retroflexion, opisthotonus, neck rigidity, negative inspiratory)
  - Type 3 Gaucher disease (subacute or chronic neuropathic)
    - Clinically heterogeneous within genotypes and families
    - Occulomotor apraxia, hydrocephalus syndrome, myoclonic or generalized seizures, cerebral ataxia, intellectual regression

## Highly Variable Clinical Manifestations of Gaucher Disease

- Variable extent of severity among affected organ systems
- Varying rate of progression or response to treatment among disease compartments
- Duration from presentation to diagnosis is highly variable
  - Early diagnosis without symptoms
    - Can occur due to screening of siblings
  - Significant signs and symptoms but late diagnosis
- Gaucher disease is not solely a hematologic disorder

Wenrich NJ. Expert Opin Pharmacother. 2008;9(10):1205-1210.


## Bone Pathology: A Process Progressing Potentially to Irreversibility

Necrosis, sclerosis →  
arthropathy, collapse,  
shortening, joint  
replacement

Bone mineral loss and lysis →  
fractures

**Radiograph of Femur**

- Deficient mineralization
- Erlenmeyer flask deformity
- Cortical bone erosion and lytic fracture



Wenrich NJ. Expert Opin Pharmacother. 2008;9(10):1205-1210.

↓

Limited mobility, need for mobility aids,  
joint replacement, loss of quality of life

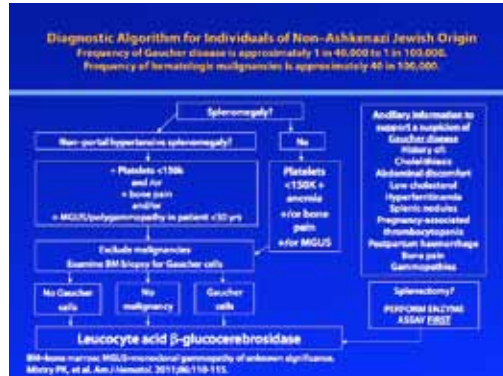
## Genetic Mutations in Gaucher Disease

- Approximately 300 mutations in the gene for glucocerebrosidase<sup>1,2</sup>
  - The vast majority of mutations are missense mutations<sup>3</sup>
  - Most mutations are restricted to single families<sup>1,4</sup>
- Enzyme deficiency results from effects of mutations on the enzyme<sup>5</sup>
  - Catalytic function
  - Intracellular stability
  - Subcellular trafficking
- The most common mutations are N370S, L444P, R403G, and Y721H<sup>6</sup>
- In Ashkenazi Jewish populations of Eastern European origin:
  - 1 in 12–18 individuals are carriers<sup>1,7</sup>
  - 4–8 of the most common mutations account for 90–95% of mutations in affected patients

1. Gahl WA, et al. J Inher Metab Dis. 1990;13(1):1-10.  
2. Brady R, et al. J Inher Metab Dis. 1990;13(1):1-10.  
3. Brady R, et al. J Inher Metab Dis. 1990;13(1):1-10.  
4. Brady R, et al. J Inher Metab Dis. 1990;13(1):1-10.  
5. Brady R, et al. J Inher Metab Dis. 1990;13(1):1-10.  
6. Brady R, et al. J Inher Metab Dis. 1990;13(1):1-10.  
7. Brady R, et al. J Inher Metab Dis. 1990;13(1):1-10.

## Indications for Genetic Testing

- Useful for family screening and carrier detection
- Can identify patients at high risk of neuropathic Gaucher disease
  - L444P homozygous mutation
  - D409H homozygous mutation
- Prenatal diagnosis is useful in families with history of neuropathic disease, especially type 2 disease
- Presence of 1 N370S allele absolutely precludes neuropathic Gaucher disease
- Imperfect genotype/phenotype correlation in type 1 Gaucher disease



### International Collaborative Gaucher Group (ICGG)

- Over 6,000 patients
- More than 50 countries
  - 33% United States
  - 13% Israel
  - Growth
    - Brazil
    - Egypt
- Recent growth of registry physicians
  - Over 700 investigators
  - 44% Hematologists/oncologists
  - 23% Pediatricians
- Active recruitment of patients and data continues

www.icgg.org/Gaucher. 2011.

### Lessons From the Real World

- Primary care physicians will see Gaucher disease (failure to thrive, growth retardation, swollen abdomen, bone pain)
- Hematologists, gastroenterologists, and geneticists will see Gaucher disease
- Message for hematologists/oncologists:
  - Need to have Gaucher disease in the differential
  - May see Gaucher disease presenting as cancer (leukemia or neuroblastoma: hepatosplenomegaly, cytopenia, etc.)
  - Hematology/oncology offices can utilize roadmaps, flow sheets, protocols, and registries
  - Hematology/oncology offices have the expertise to infuse, track, and report data and have consultants readily available

### The Clinical and Demographic Characteristics of Non-neuronopathic Gaucher Disease in 887 Children at Diagnosis

- Perception**
  - "Type 1 Gaucher disease is often thought to be an adult disorder primarily affecting Ashkenazi Jews"
- Results and Conclusion**
  - Over 50% of patients diagnosed at age 20 years or younger
  - Only 23% of children with Gaucher disease are Ashkenazi Jewish

Kaplan P, et al. Arch Pediatr Adolesc Med. 2006;160:603-608.

### Lifetime Probability of Cancer

By Attained Age in 434 (83705 Gaucher disease patients): 55 cancers reported in 40 of 434 patients (11.1%)

Type	Observed	Expected	Relative Risk (95% confidence interval)	P-value
All	55	35.37	1.55 (1.43-2.00)	<.0001
Multiple Myeloma	9	0.34	27.0 (7.19-71.38)	<.0001
Hematologic	8	2.33	3.08 (1.77-2.36)	<.0001
Breast	9	4.90	1.84 (0.84-3.08)	.03
Colorectal	6	2.04	1.71 (0.67-4.38)	.09
Lung	3	3.03	0.98 (0.35-2.89)	.94
Melanoma	5	1.77	2.83 (0.917-8.59)	<.01
Prostate	2	3.61	0.52 (0.047-1.78)	.73
Other	14	7.16	1.96 (1.07-3.58)	<.01

Chay PFM, Campbell TH, et al. J Clin Oncol. 2011;29:1133-1138.  
de Foa M, et al. Blood Cells Mol Dis. 2010;40:22-32.  
Hershenov D, et al. Blood. 2008;111:4514-4520.  
Hoffman B. In: Hematology in Lymphoid Neoplasia. St Louis, Austin, 2007.

For a free electronic download of these slides, please direct your browser to the following web address:  
[http://www.clinicaladvances.com/index.php/our\\_publications/hem\\_onc-issue/ho\\_june\\_2012/](http://www.clinicaladvances.com/index.php/our_publications/hem_onc-issue/ho_june_2012/)

