Review Article

Gaucher's disease

Vijay Bohra, Velu Nair

Department of Internal Medicine, Armed Forces Medical College, Pune, Maharashtra, India

ABSTRACT

Gaucher's disease (GD) is the most common amongst the various disorders classified under the lysosomal storage disorders. GD is a model for applications of molecular medicine to clinical delineation, diagnosis, and treatment. The multiorgan and varied presentation of the disease makes it a challenge to diagnose GD early. The advent of enzyme replacement therapy in the early 1990s changed the management, and survival, of patients with GD. In addition to this, development of substrate reduction, pharmacological chaperone, and gene therapies has broadened the horizon for this rare disease. However, in resource-poor countries like ours, optimal management is still a distant dream.

Key words: Enzyme replacement therapy, Gaucher's disease, glucocerebroside, β-glucosidase, histiocytes, imiglucerase

Introduction

Lysosomal storage disorders are a group of diseases which occur due to accumulation of glucosylceramide/glucocerebroside and some related compounds within the lysosomes. Gaucher's disease (GD) is the most common amongst the various disorders under this group. GD is a model for applications of molecular medicine to clinical delineation, diagnosis, and treatment. The prevalence of GD is approximately 1/57,000 to 1/75,000 births worldwide,[1,2] but the disease is more prevalent in individuals of Ashkenazi Jewish descent in whom the incidence is 1/800 births.[3,4] There is a paucity of reported cases in the literature with reference to the Indian subcontinent, possibly due to the rarity of this disease in this part of the world. A series of seven cases from Malabar region in Kerala showing increased incidence in the tribal population of Mappila Muslims has been published.[5]

Access this article online	
Quick Response Code:	Website: www.ijem.in
	DOI: 10.4103/2230-8210.83402

Historical Aspects

GD was first described by Phillippe Gaucher in 1882, two decades prior to the dictum of "Inborn errors of metabolism" given by Sir Archibald Garrod. Gaucher observed large cells in a splenic aspirate during the evaluation of a large spleen and he thought that it was evidence of a primary neoplasm of the spleen.[6] In 1924, Epstein first recognized the storage of glucocerebroside,[7] while Brandy *et al.* delineated that the metabolic defect was due to the deficiency of the enzyme β-glucosidase (GBA).[8]

Genetics

GD is inherited as an autosomal recessive disorder. The protein saposin C presents glucocerebroside to GBA and directly activates the enzyme. Deficiency of saposin C, which is even rarer, results in a severe disorder similar to GD.[9] The *GBA* gene is located on chromosome 1q21.[10] More than 300 distinct mutations of the *GBA* gene have been described in which 80% are single nucleotide substitutions while rare or unknown alleles account for the remaining 20%.

Classification and Clinical Features

GD has three phenotypic variants depending on the age and presence of the neurological deficit [Table 1]. However, the

Corresponding Author: Dr. Vijay Bohra, Department of Internal Medicine, Armed Forces Medical College, Pune - 40, Maharashtra, India.
E-mail: aadivijay@gmail.com

Table 1: Classification of Gaucher's disease

	Type 1	Type 2	Type 3
Onset of disease	Childhood/ adulthood	Infant	Childhood or adolescence
Age at death	Childhood/ adulthood	Median 9 months	Childhood or early adulthood
Hepatosplenomegaly	Present	Present	Present
Bone involvement	Present	Absent	Present
Neurodegeneration	Absent	Present	Present
Other systems	Hepatic fibrosis, pulmonary hypertension, lymphoma	Congenital ichthyosis	Cardiac and vascular calcifications
Ethnicity	Panethnic and Ashkenazi Jews	Panethnic	Panethnic and Norrbottnian type from Sweden
Mutation association	N370S	Diverse	L444P

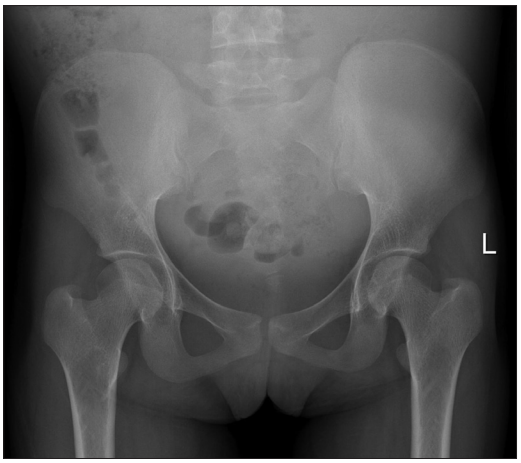

Figure 1: X pelvis showing osteolytic lesion of proximal end of the right femur

growing recognition of substantial populations with type 1 disease in Asia, South America, the Indian subcontinent, and other demographic areas has elucidated the range of phenotypes in this variant. Similarly, with the broader recognition of types 2 and 3, widespread variation and range of involvement from early onset has become increasingly evident.[11,12]

The main manifestation in the different visceral organs involved is the excess accumulation of the glucosylceramide in the macrophages.[4] Type 1 is the most common, and occurs predominantly in the Ashkenazi Jewish population. Types 2 and 3 are less common. Type 2 is panethnic, while type 3 is limited to the Norrbottnian population in Sweden.

Type 1 (GD1)

Adult onset (non-neuronopathic type) GD1 is characterized by variability in signs, symptoms, severity, and progression even among siblings with the same genotype. The most common visceral involvement is a splenomegaly which may vary from moderate to massive in volume. Liver enlargement is seen with two to three times the normal volume. Hepatic fibrosis occurs commonly, but liver failure, cirrhosis, or portal hypertension is uncommon.[13] The degree of anemia and thrombocytopenia in patients with GD is often related to whether or not they have had splenectomy. In a study done among patients with an intact spleen, mean hemoglobin concentration was 11.2 g/dL and the mean platelet count was 99,000/μL compared to patients who had undergone splenectomy, in whom the mean hemoglobin concentration was 11.9 g/dL and the mean platelet count was 242,000/μL.[14] Skeletal disease is manifested as bone pains with painful crises in some, similar to the crises seen in sickle cell anemia (especially if the diagnosis is before 10 years of age). Osteolytic lesions [Figure 1], pathologic fractures, vertebral compression, and osteonecrosis (avascular necrosis) of the proximal and distal femur, proximal tibia, and proximal humerus also occur. The radiograph of the lower end of femur in some cases may show the Ehrlenmeyer flask deformity.

Many affected children grow poorly and have delayed puberty. In a series, puberty was delayed in 60% of the 57 patients in whom a primary endocrine abnormality was excluded.[15] Enzyme replacement therapy (ERT) started before puberty improved growth and appeared to normalize the onset of puberty. Associations have also been shown with Parkinsonism, particularly of the akinetic rigid type.[16] The clinical course and life expectancy of GD1 is variable. Phenotypic expression cannot be reliably predicted by genotype since severity may vary among siblings, even identical twins.[17]

Type 2 (GD2)

Infantile cerebral GD (acute neuronopathic GD) is the rarest form, with an estimated incidence at 1 in 150,000.[18] It is characterized by early onset, typically in infancy, and by a rapidly progressive neurologic deterioration. Visceral involvement is also extensive and severe. Oculomotor dysfunction, strabismus, saccade initiation abnormalities and bulbar palsy or paresis are common. Death occurs before the child reaches 2 years of age, with a median age of 9 months. Histopathologic examination of brain at autopsy of patients with GD2 shows neuronal loss, gliosis, periadventitial Gaucher cells, neuronophagia and free Gaucher cells. Variable involvement of the frontal cortex, thalamus, caudate, globus pallidus, pons, and cerebellum has been described.

Type 3 (GD3)

Subacute or chronic neuronopathic form consists of three different subtypes. Type 3A or Norrbottnian Gaucher was first described in the Norrbottnian region of Northern Sweden. It is characterized by progressive

dementia, ataxia, and myoclonus. Patients with type 3B have a panethnic distribution and have extensive visceral and bone involvement with central nervous system involvement limited to supranuclear gaze palsy. Type 3C is rare and characterized by supranuclear gaze palsy, corneal opacity, and cardiovascular calcification, with little visceral disease. Neurologic involvement may begin late, with a variable progression.

Diagnosis

The advent of DNA testing has improved the diagnostic accuracy for affected individuals and also for the detection of the carriers. However, detection of insufficient enzyme activity is the gold standard for the diagnosis of all variants of GD. DNA sequencing can identify sequence variants in the *GBA* gene; but enzyme diagnosis is still needed to show the association of new nucleotide variants with enzymatic deficiency.

Enzyme analysis is the basis of confirmation of the diagnosis of GD. The finding of reduced glucocerebrosidase activity in peripheral leukocytes confirms the diagnosis.[19] The enzyme activity varies in each white cell type, decreasing from monocytes to lymphocytes to granulocytes in that order. The diagnosis also can be made by measuring glucocerebrosidase activity in cultured skin fibroblasts or other nucleated cells. The peripheral leukocyte assay requires an artificial substrate, 4-methylumbilliferyl-beta-glucoside, and a residual enzymatic activity (10–15% of the control enzyme activity) is considered to be deficient. Patients with types 2 and 3 GD generally have much lower activity but cannot be reliably distinguished from each other. Activity in heterozygote carriers and normal individuals show overlap, and hence enzyme analysis cannot be used alone to distinguish carriers from noncarriers.

Mutation analysis is an effective method for patient classification and carrier diagnosis as it detects the common mutations. Sporadic and uncommon alleles occur more often in the non-Ashkenazi than in Ashkenazi ethnic groups. DNA sequencing of the entire GBA coding region is clinically available as a second-tier test when targeted mutation analysis fails to identify both mutant alleles in a patient with deficient glucocerebrosidase activity.

Identification of causal mutations provides an opportunity to develop genotype and phenotype correlations for prognostication. It is useful in two situations: first is correlation with GD1 where the N370S allele in affected individuals, even in combination with a different GBA mutant allele, is predictive of the disease. The second situation is correlation with neuronopathic GD. Various alleles containing the L444P substitution are strongly, although not exclusively, associated with the development of neuronopathic disease. Many of these GBA alleles contain additional mutations and are termed complex alleles, with adverse clinical implications.[20,21] The combination of two complex alleles or a complex allele and the L444P allele are strongly associated with type 2 disease. By comparison, L444P homozygosity is strongly associated with type 3 variants.[22]

The presence of complex alleles and findings of additional nucleotide mutations on the N370S alleles make full gene sequencing of GBA a requisite for mutation analysis in GD.

Other tests like the demonstration of Gaucher cells in the involved organs such as the bone marrow [Figure 2], liver and spleen are no longer considered essential for the diagnosis of this disorder.[23] However in resource poor countries, while evaluating for visceromegaly, HPE of the specimen obtained from the involved organs may provide the first clue.

Prenatal diagnosis can be performed by enzyme analysis of fetal cells obtained by chorionic villus sampling or amniocentesis.[24] Knowledge of the DNA mutations in the proband or in the heterozygous parents would also allow DNA mutation analysis to be used together with enzyme analysis for prenatal diagnosis and is a recommended confirmatory assay.

Treatment

The advent of the ERT in the early 1990s changed the outlook of management of a patient with GD. In addition to this, development of substrate reduction, pharmacological chaperone, and gene therapies has broadened the horizon for this rare disease. ERT consists of infusions of mannose-terminated glucocerebrosidase which have helped in the regression of many visceral manifestations of the disease.

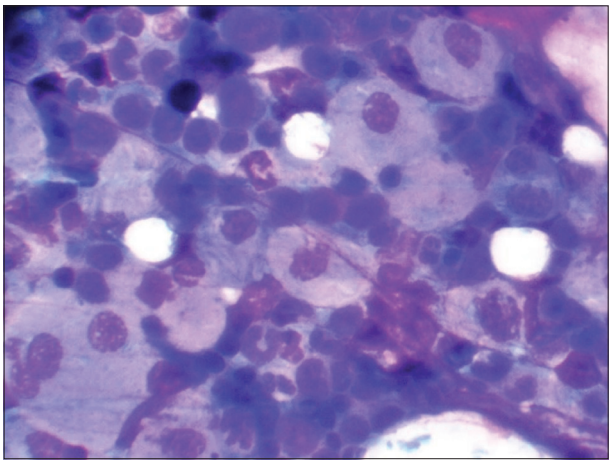

Figure 2: Photomicrograph of bone marrow showing PAS positive foamy histiocytes with crinkled paper appearance

Imiglucerase (Cerezyme) and velaglucerase alfa (VPRIV) are produced by recombinant DNA technology and are currently marketed for use in ERT for GD. The usual starting dose is 30–60 U/kg administered intravenously over 2 hours every 2 weeks.

Indications for ERT developed by consensus of international experts, using data from the Gaucher registry, are: 1) symptomatic children (including those with malnutrition, growth retardation, impaired psychomotor development, and/or fatigue) and 2) patients with severe disease (i.e. platelet count <60,000/μL, liver >2.5 times normal size, spleen >15 times normal size, radiologic evidence of skeletal disease).

In a double-center study done in Amsterdam (The Netherlands) and Dusseldorf (Germany), low-dose enzyme therapy was compared to high-dose therapy. The high-dose group had a better response of the bone marrow burden scores and reductions in bone marrow and the biomarker chitotriosidase than did the low-dose group.[25] Other studies have focused on different doses (15, 30, and 60 U/kg/fortnight) and found incremental differences in responses to enzyme therapy. An initial response was more rapid in the higher-dose group (60 U/kg) than in the other groups; other markers of response, such as the hemoglobin concentration, platelet count, and decrease in hepatic and splenic volumes, were greater in the group given 60 U/kg during follow-up at 60 months.

Effect of enzyme therapy on the lung (pulmonary hypertension or interstitial or alveolar disease) has not been demonstrated. The CNS and lymph nodes also are inaccessible to intravenously administered enzyme that is mannose terminated. The commonest adverse effect of the ERT is immune mediated hypersensitivity. The shortcoming of the ERT is its high cost (US$ 100,000–US$ 200,000 per year). The rarity of the disease has inhibited large-scale randomized trial for the optimum dose, and therefore controversies have developed about the appropriate dose and dosing schedules. Large numbers of randomized control trials (RCTs) have begun to evaluate these issues. Treatment goals for GD type 1 after initiation of ERT have been given in Table 2.

Substrate reduction therapy (SRT) may be offered to patients who are either unwilling or unable to afford the cost of ERT. It reduces glycolipid accumulation by decreasing the synthesis of glucocerebroside, the substrate of the deficient enzyme. Miglustat, an FDA approved therapy, is an oral agent (*N*-butyldeoxynojirimycin) which has shown decreases in hepatic and splenic volumes, and increases in platelet counts during 1–3 years in affected adults.[26-28] Another oral formulation, eliglustat tartrate, is under phase III trials. Ceramide analogues were developed as alternatives to the deoxynojirimycin derivatives by Shukla *et al*.[29] Short-chain ceramide analogues are being tested preclinically in mouse models of GD.[30]

Table 2: Treatment goals for Gaucher's disease type 1 for patient started on enzyme replacement therapy

Disability and goal	Time frame to achieve goal
Anemia; to maintain hemoglobin at normal values for age and sex	By 12–24 months
Thrombocytopenia; to maintain platelet count to avoid bleeding difficulties	
1. In splenectomized patients	By 12 months
2. In patients with intact spleen	By 12–24 months
Hepatomegaly	
1. Decrease in liver volume* by 20–30%	12–25 months
2. Decrease in liver volume by 30–40%	About 36 months
Splenomegaly	
1. Decrease in spleen volume* by 30–50%	12 months
2. Decrease in spleen volume by 50–60%	About 24–36 months
Bone involvement	
1. Lessen or eliminate bone pain	By 12–24 months
2. Prevent bone crises	By 12–24 months
3. Attain ideal peak bone mass in children	By puberty
Pediatric growth	
1. Achieve normal growth rate	By 36 months
2. Achieve normal puberty	Family adjusted
Quality of life	
1. Restore daily activities	Patient adjusted
2. Improve quality-of-life scores tests	24–36 months

*Assessed by quantitative imaging, preferably MRI, at initiation of ERT and during follow-up at the target time frame

An alternative approach called the pharmacological chaperone has been devised to modify *in situ* the endogenous mutant enzyme with the use of specific agents that interact with these dysfunctional enzymes. This counterintuitive approach used competitive inhibitors of the enzyme to improve lysosomal activity.[31] The range of mutations that might be responsive to one chaperone needs further investigation. In the era when ERT was not available, splenectomy was considered a treatment option in the face of life-threatening anemia and thrombocytopenia. Bone marrow transplantation (BMT) has the potential and has been demonstrated to provide a definitive cure for GD.[32,33] However, this procedure is associated with substantial morbidity and mortality and thus has been effectively replaced by ERT in clinical practice. Progress in gene therapy has slowed because of issues of gene delivery and expression, especially in stem cells derived from bone marrow. Concerns about toxic effects are related to insertional mutagenesis and malignant cell transformation.

Conclusion

Advances in the management of this disorder continue

to be hindered by an individual's financial burden and staggering emotional support required for its successful cure. Development of optimal doses, treatment goals, and improved staging systems, and expert guidance in the use of these agents are essential in the care of patients affected with GD.

References

1. Meikle PJ, Hopwood JJ, Clague AE, Carey WF. Prevalence of lysosomal storage disorders. JAMA 1999;281:249-54.
2. Biegstraaten M, van Schaik IN, Aerts JM, Hollak CE. Non-neuronopathic' Gaucher disease reconsidered. Prevalence of neurological manifestations in a Dutch cohort of type I Gaucher disease patients and a systematic review of the literature. J Inherit Metab Dis 2008;31:337-49.
3. Beutler E, Nguyen NJ, Henneberger MW, Smolec JM, McPherson RA, West C, *et al*. Gaucher disease: Gene frequencies in the Ashkenazi Jewish population. Am J Hum Genet 1993;52:85-8.
4. Beutler E, Grabowski GA. Glucosylceramide lipidosis–Gaucher disease. In: Scriver CR, Beaudet AL, Sly WS, Valle D, editors. The metabolic and molecular bases of inherited diseases. 8th ed. New York: McGraw-Hill; 2001. p. 3635-68.
5. Feroze M, Arvindan KP, Jose L. Gaucher's disease among Mappila muslims of Malabar. Indian J Pathol Microbiol 1994;37:307-11.
6. Gaucher PC. De l'epithelioma primitif de la rate, hypertrophie idiopathique de la rate sans leucemie. Paris: MD Thesis; 1882.
7. Epstein E. Beitrag zurchemie der Gaucherschen krankeit. Biochem Z 1924;145:398-402.
8. Brady RO, Kanfer JN, Shapiro D. Metabolism of glucocerebrosides. II: Evidence of an enzymatic deficiency in Gaucher's disease. Biochem Biophys Res Commun 1965;18:221-5.
9. Schnabel D, Schroder M, Sandhoff K. Mutation in the sphingolipid activator protein 2 in a patient with a variant of Gaucher disease. FEBS Lett 1991;284:57-9.
10. Cormand B, Montfort M, Chabas A, Vilageliu L, Grinberg D. Genetic fine localization of the beta-glucocerebrosidase (GBA) and prosaposin (PSAP) genes: Implications for Gaucher disease. Hum Genet 1997;100:75-9.
11. Mignot C, Gelot A, Bessières B, Daffos F, Voyer M, Menez F, *et al*. Perinatal-lethal Gaucher disease. Am J Med Genet A 2003;120A:338-44.
12. Sidransky E. Gaucher disease: Complexity in a simple disorder. Mol Genet Metab 2004;83:6-15.
13. Lachmann RH, Wight DG, Lomas DJ, Fisher NC, Schofield JP, Elias E, *et al*. Massive hepatic fibrosis in Gaucher's disease: Clinico-pathological and radiological features. QJM 2000;93:237-44.
14. Charrow J, Andersson HC, Kaplan P, Kolodny EH, Mistry P, Pastores G, *et al*. The Gaucher registry: Demographics and disease characteristics of 1698 patients with Gaucher disease. Arch Intern Med 2000;160:2835-43.
15. Kauli R, Zaizov R, Lazar L, Pertzelan A, Laron Z, Galatzer A, *et al*. Delayed growth and puberty in patients with Gaucher disease type 1: Natural history and effect of splenectomy and/or enzyme replacement therapy. Isr Med Assoc J 2000;2:158-63.
16. Goker-Alpan O, Lopez G, Vithayathil J, Davis J, Hallett M, Sidransky E. The spectrum of parkinsonian manifestations associated with glucocerebrosidase mutations. Arch Neurol 2008;65:1353-7.
17. Lachmann RH, Grant IR, Halsall D, Cox TM. Twin pairs showing discordance of phenotype in adult Gaucher's disease. QJM 2004;97:199-204.
18. Sidransky E. New perspectives in type 2 Gaucher disease. Adv Pediatr 1997;44:73.
19. Wenger DA, Clark C, Sattler M, Wharton C. Synthetic substrate beta-glucosidase activity in leukocytes: A reproducible method for the identification of patients and carriers of Gaucher's disease. Clin Genet 1978;13:145-53.
20. Grabowski GA, Kolodny EH, Weinreb NJ, Rosenbloom BE, Prakash-Cheng A Gaucher disease: Phenotypic and genetic variation. In: Scriver CR, Beaudet A, Sly WS, Valle D, editors. The metabolic and molecular bases of inherited diseases. 9th ed. New York: McGraw-Hill; 2006. p. 3635-58.
21. Beutler E, Gelbart T, Scott CR. Hematologically important mutations: Gaucher disease. Blood Cells Mol Dis 2005;35:355-64.
22. Hruska KS, Lamarca ME, Sidransky E. Gaucher disease: Molecular biology and genotype-phenotype correlations. In: Futerman AH, Zimran A, editors. Gaucher disease. Boca Raton, FL: Taylor & Francis; 2006. p. 13-48.
23. Beutler E, Saven A. Misuse of marrow examination in the diagnosis of Gaucher disease. Blood 1990;76:646.
24. Svennerholm L, Hakansson G, Lindsten J, Wahlstrom J, Dreborg S. Prenatal diagnosis of Gaucher disease. Assay of the beta-glucosidase activity in amniotic fluid cells cultivated in two laboratories with different cultivation conditions. Clin Genet 1981;19:16-22.
25. de Fost M, Hollak CE, Groener JE, Aerts JM, Maas M, Poll LW, *et al*. Superior effects of high-dose enzyme replacement therapy in type 1 Gaucher disease on bone marrow involvement and chitotriosidase levels: A 2-center retrospective analysis. Blood 2006;108:830-5.
26. Cox TM, Aerts JM, Andria G, Beck M, Belmatoug N, Bembi B, *et al*; Advisory Council to the European Working Group on Gaucher Disease. The role of the iminosugar N-butyldeoxynojirimycin (miglustat) in the management of type I (non-neuronopathic) Gaucher disease: A position statement. J Inherit Metab Dis 2003;26:513-26.
27. Giraldo P, Latre P, Alfonso P, Acedo A, Alonso D, Barez A, *et al*. Short-term effect of miglustat in every day clinical use in treatment-naive or previously treated patients with type 1 Gaucher's disease. Haematologica 2006;91:703-6.
28. Pastores GM, Barnett NL, Kolodny EH. An open-label, noncomparative study of miglustat in type I Gaucher disease: Efficacy and tolerability over 24 months of treatment. Clin Ther 2005;27:1215-27.
29. Shukla GS, Shukla A, Radin NS. Gangliosides inhibit glucosylceramide synthase: A possible role in ganglioside therapy. J Neurochem 1991;56:2125-32.
30. McEachern KA, Fung J, Komarnitsky S, Siegel CS, Chuang WL, Hutto E, *et al*. A specific and potent inhibitor of glucosylceramide synthase for substrate inhibition of therapy of Gaucher disease. Mol Genet Metab 2007;91:259-67.
31. Fan JQ. A contradictory treatment for lysosomal storage disorders: Inhibitors enhance mutant enzyme activity. Trends Pharmacol Sci 2003;24:355-60.
32. Ringden O, Groth CG, Erikson A, Granqvist S, Mansson JE, Sparrelid E. Ten years' experience of bone marrow transplantation for Gaucher disease. Transplantation 1995;59:864-70.
33. Erikson A, Groth CG, Mansson JE, Percy A, Ringden O, Svennerholm L. Clinical and biochemical outcome of marrow transplantation for Gaucher disease of the Norrbottnian type. Acta Paediatr Scand 1990;79:680-5.

Cite this article as: Bohra V, Nair V. Gaucher's disease. Indian J Endocr Metab 2011;15:182-6.

Source of Support: Nil, **Conflict of Interest:** None declared.