Gaucher Disease

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Gaucher disease is the commonest lysosomal storage disease seen in India and worldwide. It should be considered in any child or adult with an unexplained splenohepatomegaly and cytopenia which are seen in the three types of Gaucher disease. Type 1 is the non-neuronopathic form and type 2 and 3 are the neuronopathic forms. Type 2 is a more severe neuronopathic form leading to mortality by 2 years of age. Definitive diagnosis is made by a blood test–the glucocerebrosidase assay. There is no role for histological examination of the bone marrow, liver or spleen for diagnosis of the disease. Molecular studies for mutations are useful for confirming diagnosis, screening family members and prognosticating the disease. A splenectomy should not be performed except for palliation or when there is no response to enzyme replacement treatment or no possibility of getting any definitive treatment. Splenectomy may worsen skeletal and lung manifestations in Gaucher disease. Enzyme replacement therapy (ERT) has completely revolutionized the prognosis and is now the standard of care for patients with this disease. Best results are seen in type 1 disease with good resolution of splenohepatomegaly, cytopenia and bone symptoms. Neurological symptoms in type 3 disease need supportive care. ERT is of no benefit in type 2 disease. Monitoring of patients on ERT involves evaluation of growth, blood counts, liver and spleen size and biomarkers such as chitotriosidase which reflect the disease burden. Therapy with ERT is very expensive and though patients in India have so far got the drug through a charitable access programme, there is a need for the government to facilitate access to treatment for this potentially curable disease. Bone marrow transplantation is an inferior option but may be considered when access to expensive ERT is not possible. (J Clin Exp Hepatol 2014;4:37–50)

Lysosomal storage disorders (LSDs) are inherited metabolic disorders and currently more than 45 LSDs are known. Gaucher disease (GD) is the most prevalent LSD world wide.[1] Gaucher (pronounced as GO-SHEY) is named after Philippe Gaucher who first described a 32-year-old woman with an enlarged spleen and described it as "primitive epithelioma of the spleen" in 1882, while he was still a medical student. GD is an autosomal recessive disorder where the metabolic defect is an inherited deficiency of glucocerebrosidase due to mutations in the GBA1 (acid-β-glucosidase) gene.[1] The result is an accumulation of an abnormal lipid glucocerebroside (glucosylceramide) in the lysosomes of macrophages[2] leading to a wide spectrum of phenotypic manifestations. With the availability of enzyme replacement therapy (ERT), it is also now the most treatable LSD.

EPIDEMIOLOGY

As around the world, Gaucher disease is also the commonest lysosomal storage disease in India.[3] The risk of developing GD increases with consanguinity in the family. Its frequency differs with different populations–being most prevalent—1:450 birth incidence in individuals of Ashkenazi Jewish descent.[4] Ashkenazi Jews form about 75% of the world's Jewish population. However, the overall estimated prevalence of symptomatic disease is much lower—occurring in approximately 1 in 100,000 live births.[1] The International Collaborative Gaucher Group (ICGC) (http://www.gauchercare.com/healthcare/registry.aspx) launched a registry in 1991 to document clinical, laboratory, demographic, genetic and therapeutic responses in patients with GD. Most of the published data and recommendations originate from this registry.

The majority of patients have type 1 Gaucher disease (GD1), which is the non-neuronopathic form of GD. It is

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Abbreviations: LSD: lysosomal storage disorders; GD: Gaucher disease; GD1: Gaucher disease type 1; GD2: Gaucher disease type 2; GD3: Gaucher disease type 3; GBA: acid beta-glucosidase/glucocerebrosidase; ICGC: International Collaborative Gaucher Group; TRAP: tartarate resistant acid phosphatase; ACE: angiotensin converting enzyme; USG: ultrasonography; MRI: magnetic resonance imaging; SF-36: short form 36; DEXA: dual energy X-ray absorptiometry; EEG: electroencephalography; IQ: intelligence quotient; ERT: enzyme replacement therapy; INCAP: India Charitable Access Programme
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the main type seen in the Ashkenazi Jewish population. Type 2 Gaucher disease (GD2), is also called acute neuronopathic GD or infantile cerebral GD. It comprises about 1 percent of patients in the ICGC Registry.[5] Type 3 GD (GD3) is the chronic neuronopathic form and is seen in 5% of patients overall. GD3 is mainly seen in Northern Europe, Egypt and East Asia.[6] A high incidence of GD3 is found in the Swedish province of Norrbotten and is therefore also referred to as the Norrbottnian type of GD.[7] In India, there are no prevalence studies but in our study of treated patients, about a third had GD3 and two thirds were GD1.[8] The numbers of patients with GD1 are likely to be higher as the severe GD3 patients were not considered for treatment. Also, there are no estimates of GD2 from India.

PATHOGENESIS

Gaucher results from deficiency of a lysosomal enzyme glucocerebrosidase (also known as acid beta-glucosidase, GBA).[2] The enzyme acts on the substrate glucocerebroside which is a component of the cell membrane. In the normal lysosome, protein saposin C presents glucocerebroside to GBA which activates the enzyme.[9] This enzyme is responsible for hydrolytic breakdown of glucosylceramide to glucose and ceramide. Deficiency of the enzyme leads to accumulation of glucosylceramide and other glycolipids in the lysosomes of macrophages, primarily in the spleen, liver, bone marrow, brain, osteoclasts and less often the lungs, skin, kidneys, conjunctivae and heart. The deacylated form of glucosylceramide, glucosylsphingosine, is elevated in neuronopathic disease and correlates more with phenotype severity compared to glucosylceramide.[10]

GENETICS

GD is an autosomal recessive disorder secondary to mutations in the glucocerebrosidase gene which is 11 exons in length and located on chromosome 1q21.[11] More than 200 distinct GBA gene mutations are described (Human Gene Mutation Database www.hgmd.cf.ac.uk). Majority of these mutations are single nucleotide substitutions. The three mutations accounting for more than 90% of all mutations in Ashkenazi Jews[12] are 1. The commonest mutation in the ICGC Registry[5] is due to the N370S substitution in the alleles. It is a missense mutation that results in residual enzyme activity. The second and third common mutations are due to the L444P substitution and 84 GG substitution in the alleles respectively which result in affected patients who are compound heterozygotes. The mutations resulting from N370S and L444P substitutions account for approximately 70 percent of mutations in non-Ashkenazi European patients.[13] In the Korean Asian population studied, N370S substitution was not found.[14] To my knowledge, here are no mutation studies of GD patients from India.

Genotype–Phenotype Correlations

Mutation in alleles containing the N370S substitution is associated with the non-neurologic type 1 GD. It is commonly found in Ashkenazi Jews and non-Jewish Europeans.[15] Mutations in alleles containing the L444P substitution when present in homozygous form are strongly associated with the development of neuronopathic disease.[16] Therefore, the type of mutation may to some extent determine the type of Gaucher disease. However, there seem to be factors other than genotype affecting the phenotypic expression as severity may vary among siblings, even identical twins.[17]

CLASSIFICATION

Three types of GD have been described based on the clinical features, ethnicity and the natural history of the disease (Table 1 gives differences between the 3 types of GD). GD1 patients do not have neurological involvement, GD2 is the acute neuronopathic and GD3 is the chronic neuronopathic type. GD3 is further subdivided in to 3

Table 1 Differences in the Three Types of Gaucher Disease.

	Type 1	Type 2	Type 3
Disease onset	Childhood/adulthood	Infancy	Childhood/adolescence
Splenohepatomegaly	Present	Present	Present
High prevalence	Ashkenazi Jews	?	Swedish province of Norrbotten
Bone involvement	Present	Absent	Present
Ocular signs	Absent	Present	Present
Neurological involvement	Absent	Present, severe	Present, mild
Other organ involvement	Liver cirrhosis Pulmonary hypertension	Hydrops Congenital ichthyosis	Cardiac and vascular calcifications
Lifespan with or without therapy	Early childhood to late adulthood	Less than 2 years	Variable—up to early adulthood
Response to ERT	Good	Poor, not indicated	Variable

ERT: Enzyme replacement therapy.