GAUCHER'S DISEASE – A Review

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ABSTRACT

A uncommon genetic illness that is autosomal recessive is Gaucher disease (GD, ORPHA355). It is brought on by a lack of glucocerebrosidase, a lysosomal enzyme, which causes an accumulation of glucosylceramide, its substrate, in macrophages. Its incidence ranges from roughly 1/40,000 to 1/60,000 births in the general population, and it rises to 1/800 in Ashkenazi Jews. The infiltration of Gaucher cells into the bone marrow, spleen, and liver is thought to be the primary source of the cytopenia, splenomegaly, hepatomegaly, and bone lesions linked to the illness. The majority of cases of Gaucher disease, type-1, involve the viscera (around 90% in Europe and the USA, but less in other countries). Types 2 and 3 are also linked to brain disorders. Impairment, which in type 2 can be severe or varied. The inadequacy of leukocyte acid glucocerebrosidase activity can be used to confirm a GD diagnosis. GBA1 gene mutations should be found as, in certain circumstances, they may have predictive significance. Parkinson's disease is more likely to occur in patients with type-1 GD, but also in carriers of the GBA1 mutation. The risk of neoplasia related to the condition is still up for debate.Intravenous enzyme replacement therapy (ERT) utilising one of the currently available molecules (imiglucerase, velaglucerase, or taliglucerase) is the disease-specific treatment. It is also possible to employ oral glucosylceramide biosynthesis inhibitors.

INTRODUCTION

Lysosomal storage diseases (LSDs) are a group of heterogeneous inherited diseases caused by mutations affecting genes that encode either the function of the lysosomal enzymes requiredfor the degradation of a wide range of complex macromolecules, but sometimes the function of specific transporters needed to export degraded molecules from the lysosomes. The resulting lysosomal dysfunction leads to cellular dysfunction and clinical abnormalities. In one group of LSDs, the sphingolipidoses, there is a dysfunction in the enzyme-degrading abilities of the metabolites which are essential components of cell membranes and regulators of various signaling pathways[1]

The prevalence of GD is approximately 1/57,000 to 1/75,000 births worldwide,[2,3]but the disease is more prevalent in individuals of Ashkenazi Jewish descent in whom the incidence is 1/800 births.[4,5] 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.[6]

A very small minority of GD is caused by saposin C deficiency[7,8]Pathogenic mutations of the GBA gene (encodes glucocerebrosidase) located on chromosome 1q21.31or PSAP gene (encodes prosaposin) located on chromosome 10q22.1, underlie GD. The progressive accumulation of glucocerebroside causes clinical manifestations of the disease [7,8,9,10,11]

Inadequate enzymatic activity causes progressive accumulation of the sphingolipid glucosylceramide in lysosomes of macrophages (referred to as Gaucher cells), mainly in the liver, spleen, bone, and bone marrow.[12]

Accumulation of potentially pathogenic secondary substrates such as glucosylsphingosine also occurs in multiple cell types.[13]

GD was once regarded as the most frequent lysosomal disease; however, Fabry disease has ultimately proved more frequent. The birth incidence is calculated to be approximately 1/100,000, depending on the ethnic composition of the population. The inheritance pattern is autosomal recessive. More than 250 mutations responsible for the enzymatic

deficiency have been identified in the human glucocerebrosidase gene (chromosome 1q22), and approximate genotype–phenotype correlations can be applied.[14]

PATHOPHYSIOLOGY

Mutations in the GBA1 gene lead to a marked decrease in GCase activity. The consequences of this deficiency are generally attributed to the accumulation of the GCase substrate, GlcCer, in macrophages, inducing their transformation into Gaucher cells. Under light microscopy, Gaucher cells are typically enlarged, with eccentric nuclei and condensed chromatin and cytoplasm with a heterogeneous "crumpled tissue paper" appearance (Figure 1B). This feature is related to the presence of GlcCer aggregates in characteristic twisted, fibrillar arrangements that can be visualized using electron microscopy [15]. Gaucher cells mainly infiltrate bone marrow, the spleen, and liver, but they also infiltrate other organs and are considered the main protagonists factors in the disease's symptoms. The monocyte/macrophage lineage is preferentially altered because of their role in eliminating erythroid and leukocytes, which contain large amounts of glycosphingolipids, a source of GlcCer. GlcCer accumulation in Gaucher cells is considered the first step towards bone involvement, leading to the vascular compression which is the source of necrotic complications [16]. The pathophysiological mechanisms of neurological involvement remain poorly explained; GlcCer turnover in neurons is low and its accumulation is only significant when residual GCase activity is drastically decreased, i.e., only with some types of GBA1 mutations [17]. Consistent with this, recent work on a Drosophila model of neuronopathic GD demonstrated autophagy impairment in the GCase-deficient fly brains [18]. Very rarely, GD may be caused by a mutation in the PSAP gene, leading to a deficiency in saposin C without GCase deficiency [19] These patients generally present with neurological features similar to that of type-3 GD.

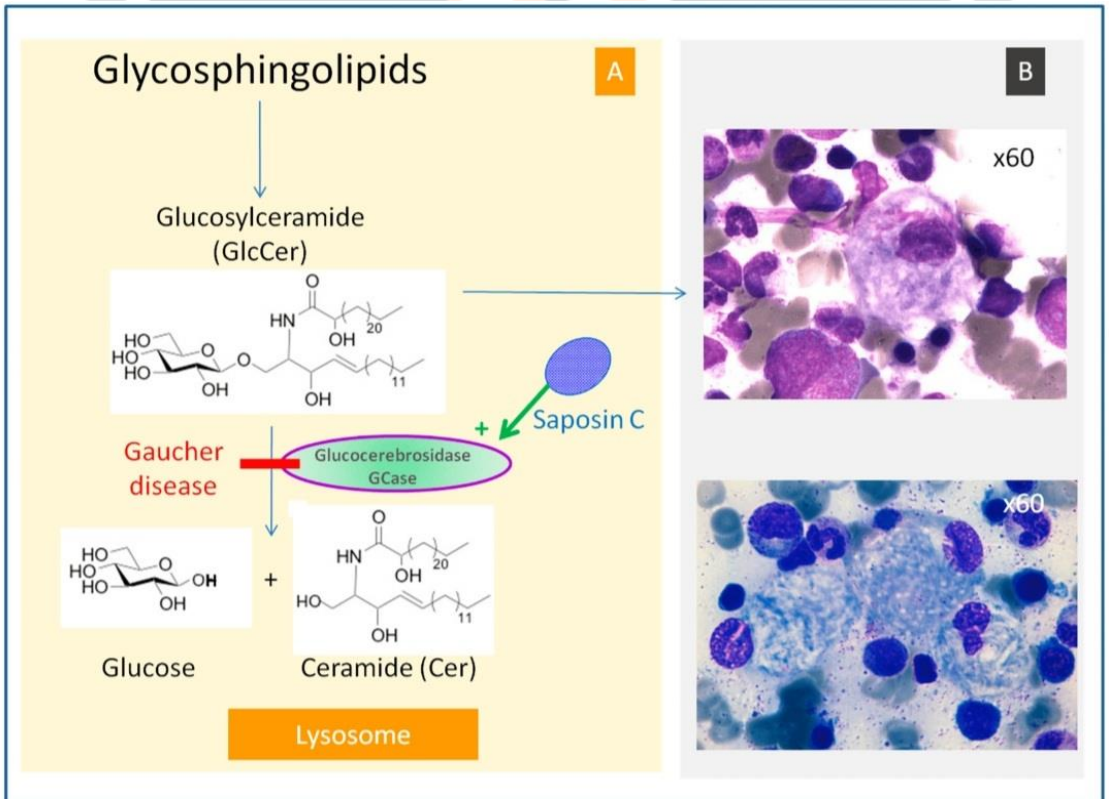

Fig no 1

Different mutations in the GBA (beta-glucosidase) gene determine the remaining activity of the enzyme. In type I, there is some residual activity of the enzyme, accounting for the lack of neuropathology in this type.[20] Although there is some correlation between genotype and phenotype, neither the amount of stored lipids, nor the residual enzyme activity correlates well with disease symptoms.[21]This circumstance has called for alternative explanations accounting for disease symptoms including

- Jamming of the endo/lysosomal system[22]
- ER stress[23]
- Altered lipid composition of membranes throughout the cell, including the plasma membrane,[24] and consequent changes in the dynamic and signaling properties of the cell membrane[25]
- Inflammation caused by cytokine secretion as a result of sphingolipid accumulation, and neurodegeneration caused by the accumulation of glucosylsphingosine, a neurotoxin[26]

SIGNS AND SYMPTOMS

Each person's symptoms may vary. For many people, symptoms start in childhood. Some people have very mild symptoms.

Symptoms of Gaucher disease can include:

1. Enlarged spleen
2. Enlarged liver
3. Eye movement disorders
4. Yellow spots in the eyes
5. Not having enough healthy red blood cells (anemia)
6. Extreme tiredness (fatigue)
7. Bruising
8. Lung problems
9. Seizures[27]
10. Painless hepatomegaly and splenomegaly: the size of the spleen can be 1500–3000 g, as opposed to the normal size of 50–200 g. Splenomegaly may decrease the affected individual's capacity for eating by exerting pressure on the stomach. While painless, enlargement of spleen increases the risk of splenic rupture.
11. Hypersplenism and pancytopenia, the rapid and premature destruction of blood cells, leads to anemia, neutropenia, leukopenia, and thrombocytopenia (with an increased risk of infection and bleeding).
12. Cirrhosis of the liver is rare.
13. Severe pain associated with joints and bones occurs, frequently presenting in hips and knees.
14. Yellowish-brown skin pigmentation.[28]

CLASSIFICATION

	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

Table no 1

- **Type 1 (GD1)**

Variability in indications, symptoms, severity, and progression even amongst siblings with the same gene characterises adult onset (non-neuronopathic type) GD1. Splenomegaly is the most prevalent visceral involvement; its volume can range from modest to large. When the liver is two to three times larger than usual, it is called enlargement. Although liver failure, cirrhosis, or portal hypertension are rare, hepatic fibrosis is a prevalent condition.[29] The degree of thrombocytopenia and anaemia in GD patients is frequently associated with the presence or absence of a splenectomy. Patients who had undergone splenectomy had a mean haemoglobin concentration of 11.9 g/dL and a mean platelet count of 242,000/μL, while those who had an intact spleen had a mean haemoglobin concentration of 11.2 g/dL and a mean platelet count of 99,000/μL.[30]Variability exists in the clinical trajectory and life expectancy of GD1. Due to the possibility of variation in severity across siblings, even identical twins, genetics cannot be a reliable predictor of phenotypic expression.[31]Type I (N370S homozygote), the most common, also called the "non-neuropathic" type occurs mainly in Ashkenazi Jews, at 100 times the occurrence in the general populace. The median age at diagnosis is 28 years of age,[32] and life expectancy is mildly decreased.[33]

- **Type 2 (GD2)**

Acute neuronopathic GD in infants is the most uncommon kind, with an estimated frequency of 1 in 150,000 cases. It is distinguished by an early onset, usually in infancy, and a fast-moving decline in neurologic function. There is also significant and widespread visceral involvement. Common conditions include bulbar palsy or paresis, strabismus, aberrant saccade initiation, and oculomotor dysfunction. The child dies at a median age of nine months, before the youngster turns two. GD2 patients' autopsies reveal neuronal loss, gliosis, periadventitial Gaucher cells,

neuronophagia, and free Gaucher cells in the histopathologic study of the brain. There have been reports of variable involvement of the thalamus, caudate, globus pallidus, pons, and cerebellum in addition to the frontal cortex.[34]Type II (one or two alleles L444P) is characterized by neurological problems in small children. The enzyme is hardly released into the lysosomes. Prognosis is poor: most die before the age of three.[35]

- **Type 3 (GD3)**

There are three subtypes of the chronic neuronopathic form, also known as subacute form. The Norrbottnian region of Northern Sweden is where Type 3A, often known as the Norrbottnian Gaucher, was initially identified. Myoclonus, ataxia, and progressive dementia are its hallmarks. Patients with type 3B have a panethnic distribution, substantial involvement of the viscera and bones, and only supranuclear gaze palsy as a result of central nervous system involvement. Cardiovascular calcification, ocular opacity, supranuclear gaze palsy, and minimal visceral illness are the features of the uncommon type 3C. Neurologic involvement can develop gradually and start later. [36]Patients from the Norrbotten region of Sweden have type III (including one or two copies of L444P, potentially delayed by protective polymorphisms) in their blood. While the disease strikes this group a little later, the majority of them pass away before turning thirty.[37]

DIAGNOSIS

Since the development of DNA testing, both the diagnosis of carriers and the accuracy of the diagnosis for affected persons have increased. However, the gold standard for diagnosing all GD variations is the identification of insufficient enzyme activity. Sequence variants in the GBA gene can be found by DNA sequencing, however the correlation between novel nucleotide variants and enzymatic deficiency needs to be demonstrated by enzyme diagnostics.

The confirmation of the diagnosis of GD is based on enzyme analysis. The finding of decreased glucocerebrosidase activity in peripheral leukocytes confirms the diagnosis.[38]

Each type of white blood cell has different levels of enzyme activity; monocytes have the highest levels, followed by lymphocytes and granulocytes. Measurements of glucocerebrosidase activity in cultivated skin fibroblasts or other nucleated cells can also be used to make the diagnosis. The 4-methylumbilliferyl-beta-glucoside artificial substrate is needed for the peripheral leukocyte assay, and residual enzymatic activity (10–15% of the control enzyme activity) is regarded as sufficient. Although the activity of patients with types 2 and 3 GD is typically substantially lower, it is not possible to accurately distinguish between them. Since heterozygote carriers' and normal people's activities overlap, enzyme analysis cannot be utilised alone to identify carriers from noncarriers.Since mutation analysis finds common mutations, it is a useful tool for carrier diagnosis and patient classification. The non-Ashkenazi ethnic groups are more likely than the Ashkenazi ethnic groupings to carry sporadic and unusual genes. Clinically available as a second-tier test when focused mutation analysis is unable to identify both mutant alleles in a patient with deficient glucocerebrosidase function, is DNA sequencing of the complete GBA coding area.[39,40]

In one study, the age at GD1 diagnosis was broken down by genotype: patients with genotypes N370S/?, N370S/N370S, N370S/L444P, and N370S/rare allele had a mean age at diagnosis of more than ten years; patients with genotypes N370S/84GG, L444P/L444P, L444P/?, and N370S/IVS2+1, all of which are frequently linked to severe GD symptomatology, reported an age at diagnosis of less than ten years. [41]

Three other investigations found that the mean age at diagnosis ranged from 6 years in 11 patients in the Moroccan study to 50 years in 93 South Florida patients included in the ICGG Gaucher Registry.[42,43]

The age at diagnosis of seven GD3 cases ranged from 10 months to 2 years and 7 months in a study of Taiwanese patients; the Moroccan investigation also found two cases of GD2, diagnosed at 3 months and 18 months, respectively.[44] The mean age at diagnosis was 32.6 years in a multinational observational study (24 months of study duration) that included all non-Ashkenazi patients (who had been examined for a haematological assessment).[45]

Your healthcare professional will consider both your current and previous medical histories when diagnosing you. They will examine you physically.

Moreover, your provider will consider:

Your symptom description

Your medical history as a family

Blood test findings

Accurate diagnosis of Gaucher illness might be difficult to come by because of the wide range of symptoms it presents with.[15]

TREATMENT

Gaucher disease does not have a treatment. However, therapy might assist you in managing your symptoms.

on the type of Gaucher disease you have, your treatment plan will change. Treatment options could be:

- Treatment with enzyme replacement, which works for types 1 and 3,
- Medications
- Frequent physical examinations and bone density measurements to monitor your condition
- Transplant of bone marrow
- Surgery to remove your spleen entirely or in part
- Replacement of the joints
- Transfusions of blood[15]

Enzyme Replacement Therapy

The idea of ERT is to replenish the GCase that cells, especially Gaucher cells, are deficient.GenzymeSA created imiglucerase, a recombinant GCase (Cerezyme®, Sanofi-Genzyme), in the early 1990s by employing an enzyme called alglucerase that was isolated from human placentas. To enable their absorption by macrophage receptors and transport to lysosomes, enzymes are deglycosylated, exposing their mannose residues. Imiglucerase was approved for sale in 1996 and is made from Chinese hamster ovary cells, a type of mammalian cell. Other recombinant enzymes have since been created, including taliglucerase (Elelyso®, Pfizer), which was produced using carrot cells and was available during the 2009–2011 imiglucerase shortage, but did not receive a marketing authorization in all countries, and velaglucerase (Vpriv®, Shire, authorised in 2010). There aren't many distinctions between velaglucerase and imiglucerase. Particular glycosylation is applied to taliglucerase in relation to its synthesis in plant cells. The intravenous administration of these products is used. The dosage and frequency of administration differ by nation.[46]Often with dose modifications on an individual basis. A beginning dose of 60 U/kg every other week (EOW) has been suggested for children and "at riskadults."[47]This may be decreased to at least 30 U/kg EOW once treatment goals have been met in order to prevent deteriorating skeletal involvement during long-term maintenance therapy. Good results have been observed in certain studies using low-dose high-frequency regimens, which include dosages of three times a week (15–30 U/kg/month). [47,48,49,50]Patients with stable GD1 may benefit from smaller total doses, which can also cut therapeutic costs; however, in certain patients, lower dosages (15 U/kg EOW) may limit skeletal response.[51,52,53]The ideal ERT dosage was hotly contested for many years, although dose-response correlations for platelet and haemoglobin levels, as well as hepatic and splenic volumes, were established[54].It is vital to assess every facet of the disease, including bone pain and crises, marrow fat, bone mineral density, organ volumes, blood counts, and quality of life, in order to completely understand how GD affects a person and how that person is responding to treatment. Evaluation of a child's development with respect to their mid-parental height and their age- and sex-matched cohort is also crucial[55].The clinical course and biomarkers can be used to modify the dose of infusions and, less commonly, the time between them. Thrombocytopenia typically gets better after ERT, but in people who still have splenomegaly or have splenic nodules, it could stay the same[56]. After receiving ERT for 24–48 months, people with type-1 GD report an improvement in their health-related quality of life[57,58,59]. With ERT, osteopenia and bone marrow infiltration gradually reverse;[60] bone pain also becomes better and there are fewer bone crises[61].

And while ERT does not totally avoid skeletal events[63], their frequency does decrease[62]. ERT administered early in treatment lowers the likelihood of AVN[64]. Low dose disease control is still poorly understood, yet it may be associated with particular intracellular pharmacokinetics[65]. As of right now, there are no established standards for the preferential

application of either velaglucerase or imiglucerase as enzyme replacement therapy (ERT) for the treatment of GD1. Immaglicerase is the only ERT with a marketing licence for GD3. Since treatment has no effect on the severe neurological symptoms of GD2's rapid development, none of the ERTs are recommended[66]. There is no proof that ERT has stopped, stopped the advancement of neurological involvement, or stabilised it[67].All GD3 patients should be evaluated for specific treatment with ERT; however, this should only be done for GD1 individuals who have symptomatic clinical or biochemical problems [47].In general, safety is excellent. Depending on the product, antibodies against the enzyme can develop in 2% to 14% of patients; these antibodies are typically asymptomatic. Less than 1.5% of people experience allergic responses, which might cause urticaria, diarrhoea, hypotension, or soreness in the larynx. Taliglucerase seems to carry a somewhat higher allergy risk. Imiglucerase replacement therapy is not contraindicated during pregnancy because pregnant patients who have continued treatment have not reported any foetal abnormalities. Additionally, velaglucerase seems to be well tolerated [68]. In fact, ERT might be necessary to prevent thrombocytopenia, which could be dangerous during pregnancy or childbirth, as well as to control the disease as GD can worsen during pregnancy.

Other Particular Therapies

In an ideal world, bone marrow transplantation would be able to cure GD patients [69], but because to its low benefit/risk ratio and the availability of modern, well-tolerated treatments, this treatment is no longer available.

Gene Treatment

On GD3 patients, an initial gene transfer strategy was applied [70], with the goal of introducing the GBA1 gene into hematopoietic cells and subsequently injecting the patients with the corrected cells. The GCase levels found to be too low for any clinical effect, which led to dismal results. Although lentiviral vector gene transfer methods have shown promise in mice models of GD, basic research on this strategy is currently being done[71].

CONCLUSION

Improvements in the treatment of this condition are still impeded by the financial strain that an individual faces and the enormous emotional support needed to recover from it. For patients suffering from GD, it is crucial to develop the best possible doses, treatment objectives, and staging methods in addition to receiving professional advice on how to take these medications.

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