

## Gaucher's Disease and Treatment-An Overview

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### ABSTRACT

Gaucher's disease is a Phenotypically heterogenous autosomal recessively inherited lysosomal storage disease, resulting from deficient activity of the enzyme glucocerebrosidase (GCCase, acid  $\beta$ -glucosidase) due to mutations in GBA1. It is the most common amongst the various disorders classified under the lysosomal storage diseases. It is estimated that approximately 1 in 40,000- 60,000 persons in the general population has gaucher disease, or about 10,000 people worldwide. There are three types of gaucher disease Type 1 - non neuronopathic form, type 2 - acute neuronopathiic form and type 3 - chronic neuronopathic form respectively. All forms of the disease are autosomal recessively inherited. Mutations in the GBA1, located on chromosome 21, result in reduced/defective catalytic activity and/or stability of glucocerebrosidase. The glycolipid storage gives rise to characteristic Gaucher cells, macrophages engorged with lipid with a crumpled-tissue-paper appearance and displaced nuclei. Gaucher disease should be considered in the differential diagnosis in individuals with clinical features suggestive of the disease, including hepatomegaly, splenomegaly, anemia, thrombocytopenia, and skeletal disease. Analyses of several thousand affected individuals have broadened the range of the pan-ethnic disease variants provided initial genotype and phenotype correlations, and established the effectiveness of enzyme therapy. This review article provides a comprehensive review, critical examination of the prevalence, pathophysiology, and management of Gaucher disease.

**Keywords:**  $\beta$ -glucosidase, gaucher disease, glucocerebrocedase, lysosomal storage disease

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### INTRODUCTION

Gaucher's disease (GD) is a chronic, progressive, inherited disorder named for the french physician who first discovered it. It is a rare, autosomal recessively inherited lysosomal storage disease, resulting from defective and insufficient activity of the enzyme glucocerebrosidase (GCCase, acid  $\beta$  - glucosidae) due to mutations in GBA1. This leads to accumulation of its major glycolipid substrate, glucosylceramide (GC; glucocerebroside, ceramide  $\beta$  - glucoside). It is also observed that to a lesser extent there is an accumulation of highly toxic substrate, glycosylsphingosine (GS), in the lysosomal cells [1].

Gaucher disease is traditionally been divided into the following 3 clinical subtypes, delineated by the absence or

presence of neurological involvement and its progression [1].

Type 1 - non neuronopathic form

Type 2 - acute neuronopathiic form

Type 3 - chronic neuronopathic form

All forms of the disease are autosomal recessively inherited. These three types represent different degrees of severity along a spectrum. Amongst these, Type 1 is non-neuronopathic while types 2 and 3 are acute (rapidly progressive) and sub-acute (slowly progressive) neuronopathic forms respectively.

### EPIDEMIOLOGY

It is estimated that approximately 1 in 40,000- 60,000 persons in the general population has gaucher disease, or about 10,000 people worldwide. It is the most

common disorder in group of more than 40 diseases classified as lysosomal storage disorders (LSDs). Grouped together LSDs affect 1 in every 7700 babies born. It is most common among Ashkenazi Jews (individuals of particular Jewish descent from Eastern or Central Europe) [2].

In particular, the high frequency of type 1 in the Ashkenazi Jews (about one in 8000 livebirths) has led to characterization of disease phenotypes mainly on the basis of that population. However, the growing recognition of substantial population with type 1 disease in Asia, South America, the Indian subcontinent and other demographic areas is broadening our appreciation of the range of phenotypes in this variant. Type 1 accounts for 99% of cases and is the most common lipid storage disorder known. It is the only type with a racial predilection, occurring in about 1 of 450-865 people of eastern European (Ashkenazi) Jewish descent. The incidence of type 2 and 3 occurs in less than 1 in 100000 people.

The characterization of population in Asia, particularly the Indian subcontinent, and Africa will continue to broaden this range, as it has in type 1 disease. In Indian population the overall cases reported seems to be less, i.e., one in 100000 people [3].

A series of seven cases from Malabar region in Kerala showed increased incidence in the tribal population of Mappila Muslims has been published [4].

#### **ETIOLOGY**

All the 3 forms of Gaucher disease are caused by glucocerebrosidase activity deficiency due to mutations in GBA1, structural gene that encodes the enzyme. Widespread accumulation of glucosylceramide-laden macrophages results from the enzyme deficiency. More than 200 different mutant GBA alleles have been identified in patients with Gaucher disease [1].

The gene coding for the enzyme responsible for GD is located on chromosome 21. In this single gene, about 200 mutations are defined up to date. Most commonly observed mutations are N370S, L444P, RecNcil, 84GG, R463C, recTL and 84 GG. Amongst this 84GG is a null mutation in which there is no capacity to synthesize enzyme. However, N370S mutation is

almost always related with type 1 disease. Very rarely, deficiency of sphingolipid activator protein (Gaucher factor, SAP-2, saponin C) may result in Gaucher disease. This rare condition is due to congenital absence of carrier protein involved in sphingolipid catabolism [5].

#### **PATHOPHYSIOLOGY**

##### **Enzyme abnormalities**

Mutations in the GBA1, located on chromosome 21, results in reduced/defective catalytic activity and/or stability of glucocerebrosidase and leads to diminished enzyme flux through cells [6]. Gaucher disease is caused by an insufficient activity of the lysosomal enzyme acid  $\beta$  glucosidase (glucocerebrosidase, Enzyme Commission number 4.2.1.25), and the resultant lysosomal accumulation of its main substrate, glucosylceramide. This insufficient activity results from detrimental effect of more than 300 mutations in the GBA gene on glucocerebrosidase catalytic function, intracellular stability or subcellular trafficking, or both [1].

##### **Lipid accumulation and Inflammation**

The primary initiator of the pathogenic process is the abnormal accumulation of lysosomal glucocerebrosidase and, probably its deacylated analog, glucosylsphingosine. Importantly, Glucocerebrosidase is the ultimate glycolipid precursor in the synthesis and degradation of >300 neutral glycosphingolipids and gangliosides [7].

Glucosylceramide, the accumulated glycolipid, is primarily derived from the phagocytosis and degradation of senescent leukocytes and, to a lesser extent, from erythrocyte membrane. The glycolipid storage gives rise to characteristic Gaucher cells, macrophages engorged with lipid with a crumpled-tissue-paper appearance and displaced nuclei.

Two major pathophysiological mechanisms that account for macrophage activation are under investigation. The most obvious candidate for a pathological initiator is the excess accumulation of glucosylceramide. Sphingolipids have been implicated in inflammatory and apoptotic processes, and glucosylceramide might have direct activating or enhancing effect on

macrophage function, possibly mediated through selective calcium-channel dysregulation [8-10]. Indeed, several indicators of macrophage activation including chitotriosidase, CCL18, angiotensin-converting enzyme, and cathepsin S - have been identified in excess in plasma of patients with Gaucher's disease [3]. Histological assessment showed that such proinflammatory molecules, including tumour necrosis factor  $\alpha$ , are variably increased in some splenic Gaucher cells. However, the absence of tissues from these patients has restricted such investigations. There is an evidence that majority of the patients with disease have increased levels of macrophage-derived inflammation related molecules such as interleukin-1 $\beta$ , interleukin-6, interleukin-10 and TNF- $\alpha$ . Although additional investigation is needed, the association of these pathways in the propagation of tissue damage in Gaucher's disease provides the theoretical basis for alternative or additional adjunctive treatments [3].

An alternative mechanism by which these proinflammatory and anti-inflammatory pathways could be activated is through abnormal folding of mutant proteins in the endoplasmic reticulum. Such abnormal folding initiates an unfolded protein response that can trigger apoptotic or inflammatory pathways in various tissues. Direct evidence of unfolded protein response involvement is not available for Gaucher disease. These pathways are of notable interest in many disorders, including Parkinsons Disease, Alzheimer's disease and other Neurodegenerative disorders [11].

### CLINICAL MANIFESTATIONS

The insufficient catabolism of glucosylceramide and the engorgement of macrophages by this substrate lead to visceral manifestations of gaucher disease. Symptoms of gaucher disease can vary from the very mild, or even none, to severe. Bone pain or fracture is often the first symptom [2]. Other symptoms may include –

- Skeletal abnormalities
- Hepatomegaly (enlarged liver)
- Splenomegaly (enlarged spleen)

- Anemia (reduced number of red blood cells)
- Excessive fatigue
- Bleeding and easy bruising due to thrombocytopenia (low platelet count)
- Mental retardation
- Dementia
- Pingueculae (yellow spots in the eyes)

At onset, patients with type 1 commonly present with painless splenomegaly, anemia, or thrombocytopenia. They may also have chronic fatigue, hepatomegaly (with or without abnormal liver function test findings), bone pain, or pathologic fractures and may bruise easily because of thrombocytopenia. Other symptoms like nose bleed, bruising, or both are observed. Patients have radiologic evidence of skeletal involvement, including an Erlenmeyer flask deformity of the distal femur, which is an early skeletal change. They occasionally develop Parkinsonism, or portal hypertension [2].

Brain stem abnormalities presenting in infancy suggest type 2 disease. Type 3 disease usually presents later in childhood and is accompanied by slowly progressive neurologic symptoms such as incoordination, mental deterioration, or myoclonic seizures. Patients with type 3 disease have been further subclassified. Type 3a patients have less severe systemic disease but die from slowly progressive neurologic deterioration. Type 3b patients have aggressive and severe systemic disease, with horizontal supranuclear gaze palsy as the only neurologic sign. Death in these patients is caused by hepatic or pulmonary complications [2].

### DIAGNOSIS

Gaucher disease should be considered in the differential diagnosis in individuals with clinical features suggestive of the disease, including hepatomegaly, splenomegaly, anemia, thrombocytopenia, and skeletal disease. The diagnosis is frequently suspected due to detection of characteristic pathological findings (lipid laden cells of monocyte/macrophage origin, termed Gaucher cells) [1].

DNA testing has improved diagnostic accuracy in gaucher disease not only for affected individuals but also for the

detection of carriers. Detection of insufficient enzyme activity is the gold standard for the diagnosis of patients with all variants of gaucher disease [3]. DNA testing can be done in peripheral blood leukocytes or cultured skin fibroblasts. One can recognize the existence of a phenotype consistent with disease, but diagnosis is not confirmed until proven by laboratory testing. Other phenotypical manifestations, including liver and splenic volumes and degree of bony involvement, show similar correlations with the genotypes. The implication is that early onset disease, and probably needs early intervention to prevent later disease manifestations [3].

#### **LABORATORY STUDIES:**

**Enzyme activity studies:** Measurement of glucocerebrosidase activity in peripheral blood leukocytes confirms the disease. The “gold-standard” for diagnosis is finding deficient activity of acid  $\beta$ -glucosidase activity in nucleated cells, i.e., peripheral leukocytes, cultured fibroblasts, or aminocytes; the enzyme is not normally present in serum/plasma. The enzyme activity is assessed using a fluorometric artificial substrate, i.e., 4-methylumbelliferyl- $\beta$ -glucoside. Prenatal diagnosis by enzymatic assay is possible from cultured amniotic cells or chorionic villi [12].

**Genotype testing:** Molecular genetic analysis is the standard for confirmation of the diagnosis of GD, and offers certain advantages over enzyme assays. Molecular diagnosis in some patients is beneficial, in whom 6 GBA mutations (i.e., N370S, c.84insG, L444P, IVS2+1g>a, V394L, and R496H) account for most disease alleles.

**Liver function tests:** Minor elevations of liver enzyme levels are common. The presence of Jaundice or impaired hepatocellular synthetic function merits a full hepatic evaluation. Coagulation studies should be monitored [12].

**Associated marker testing:** Angiotensin-converting enzyme levels are typically elevated, as are total acid phosphatase and ferritin levels. Chitotriosidase, another enzyme is useful in monitoring the disease.

**Imaging Studies:** Ultrasonography of the abdomen reveal the extent of organomegaly. MRI is more accurate than

ultrasonography. Hpi MRI reveals early avascular necrosis.

It also determines the degree of marrow infiltration and evaluating spinal involvement. Skeletal radiography can be used to detect and evaluate skeletal manifestations of GD.

Chest radiography evaluates pulmonary manifestations. Dual-energy x-ray absorptiometry (DEXA) is useful in evaluating osteopenia [12].

**Other tests:** CBC count and ECG are helpful in evaluating the possibility of pulmonary hypertension. An electron immunoblotting technique using polyclonal and monoclonal antibodies carried out with subtype differentiation [5].

Liver biopsy is occasionally performed to assess unexplained hepatomegaly.

#### **TREATMENT**

Comprehensive evaluation and development of a personalized management plan is essential for the optimal care of affected patients with all variants of gaucher disease. Potential specific therapies for disease include Enzyme replacement therapy (ERT), Substrate reduction therapy (SRT), Symptom management, Psychological care.

**Enzyme Replacement therapy:** The goal of ERT is to provide an appropriate amount of needed enzyme. This FDA approved by FDA in 1991 which was found to result in huge improvement in the patients with gaucher disease. Alglucerase (extracted from human placenta) is the first enzyme treatment modality for GD to provide specific treatment. Because of major limitations like low degree of reproducibility, risk of blood borne infections, very short half-life which lead to new research and development of a recombinant enzyme; Imiglucerase [13,14].

Imiglucerase is a modified form of glucocerebrosidase, created using recombinant DNA technology, and acts like naturally occurring enzyme glucocerebrosidase to break down the glucosylceramide that has accumulated in Gaucher cells. This will be given as IV infusion. Both alglucerase and imiglucerase are administered by diluting the dose in 100 ml of NaCl 0.9% and infusing it over 1-2 hrs, but not exceeding 1 unit/kg/min for

imiglucerase. Alglucerase comes as a 10 unit/ml (50-unit vial) or 80-unit/ml (400-unit vial) solution, and imiglucerase comes as a lyophilized powder (200-unit vial) [2].

Vpriv (velaglucerase alfa) was FDA approved in 2010 for ERT in Gaucher disease patients. It is a human glucocerebrosidase product developed using the company's proprietary gene activation technology. It acts by replacing  $\beta$ -glucocerebrosidase, the enzyme that catalyses the hydrolysis of glucocerebroside, reducing the amount of accumulated glucocerebroside. It is indicated for pediatric and adult patients. The recommended dose is 60 Units/kg administered every other week as a 60-minute IV infusion. Adverse effects include rash, upper respiratory tract infection, pyrexia and prolonged activated partial thromboplastin time [15].

Taliglucerase alfa is a human glucocerebrosidase produced in carrot cells and contains same arginine to histidine substitution at amino acid residue 495. As this is produced from plant cell, harbors a unique glycosylation pattern, produces increased risk of immunogenicity compared to preparations produced from mammalian cells [16].

**Substrate reduction therapy:** The goal is to minimize the amount of production and accumulation of waste material within the cells. Oral therapies have been explored using small molecules [9]. This therapy inhibits the formation of sphingolipids that accumulate during Gaucher disease. N-butyl-deoxynojirimycin (NB-DNJ) or miglustat was the first agent approved by US-FDA, extracted from plants and microorganisms that functions as a competitive glucosylceramide synthase inhibition. It acts by reducing the formation of glucosylceramide by inhibiting the glucosylceramide synthase enzyme. It also targets the protein folding and trafficking pathways of glycosidase to assist correction of lysosomal enzyme activity. It is given as 100 mg PO tid, but caution in renal impairment patients. Despite the convenience in therapy there are few drawbacks like GIT disturbances, weight loss, bloating and belching. The safety and efficacy in children has not been formally

evaluated, therefore, the long-term therapy is unclear [17].

Eligustat tartrate is a specific, competitive glucosylceramide synthase inhibitor that has a similarity to the ceramide component of glucosylceramide. This drug had undergone Phase I and II clinical trials and Phase III are currently underway [1].

**Symptomatic Treatment:** This treatment includes pain reduction therapies, blood transfusions, orthopedic surgery, and possible splenectomy.

**Psychological care:** Professional counseling can help patients better manage the difficulties of their disease and the lifestyle changes that might be required.

### GAUCHER DISEASE THERAPY IN "FUTURE"

**Gene therapy:** Incorporating a healthy genome by replacing a deficient genome appears to be the cure for GD. In early animal models of gene therapy the vectors responsible for "infecting" a healthy genome were viruses like adeno-associated virus, lentivirus and retrovirus [18-20]. Neither ERT nor SRT achieved excellent results in terms of neurological and pulmonary involvement due to problems such as inability to pass through the blood brain barrier. Gene therapy has been long-term promise for curative approaches for Gaucher disease on the basis of early success in bone marrow or stem-cell transplantation [21].

**Chaperone treatment:** The ability of imino sugars to increase the strength of the target enzyme (glucocerebrosidase) is shown previously in a study by Sawkar et al [22]. These chemicals increase the half life of the enzyme by inhibiting its degradation and providing stabilization. This did not give satisfaction in monotherapy so chaperones might be an option for combination treatment strategies.

### CONCLUSION

Gaucher disease is a heterozygous disease. It is a disorder that affects very few individuals in the population and its treatment is very costly. The availability of alternative therapies provide certain advantages. In the future, it might be possible to cure this genetic disease by gene vaccines. Therefore, we require making

more investment on this area of gene therapy.

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