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GAUCHER DISEASE TYPE-I: PHENOTYPIC CHARACTERIZATION, PATHOLOGICAL MECHANISM AND CLINICAL MANAGEMENT

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ABSTRACT

Gaucher disease is a rare and recessive form of genetic disease in autosomal cells which occurs due to the deficiency of β-glucocerebrosidase enzyme. Philippe Gaucher for the very first described the gaucher disease in his doctoral thesis which was presented in 1882. Gaucher cells are 20-100µm in diameter with irregular nucleus and distinctive wrinkles in cytoplasm. Gaucher's disease appears during infancy but very less in adolescence. Type 1 gaucher disease is the most common and non-neuronopathic. It prevails in the Ashkenazi Jewish population. Beta-glucocerebrosidase enzyme is coded by glucocerebrosidase gene (GBA) which is located on chromosome 1q21. More than 200 mutations in GBA have been reported to be associated with GD. glucocerebroside is broken down into a sugar (glucose) and a simpler fat molecule (ceramide) by the action of glucocerebrosidase. Glucocerebroside and related substances accumulate within cells to toxic level in the absence of the activity of glucocerebrosidase enzyme. The characteristic features of GD include low white blood cell count, anemia, pain in abdomen, enlargement of spleen, deformity in distal femur resembling to Erlenmeyer flask. Mostly, macrophages are the first one to be targeted in Gaucher's disease. Frequently, enzyme assay of glucocerebrosidase is used to diagnose GD. Gaucher disease can be treated by proper management and treatment methods.

KEYWORDS: Gaucher disease; Glucocerebrosidase; Glucosylceramide; Enzyme Replacement Therapy.

INTRODUCTION

Gaucher disease is a rare form of genetic disorder that is associated with the accumulation of gaucher cells in body organs such as spleen, liver and bone marrow. It is a lysosomal storage disease which occur due to lack of glucocerebrosidase activity to degrade glucocerebroside into glucose and fat ceramide. Glucocerebroside accumulates in the lysosomes. Macrophages engulf and digest worn out cells into simpler molecules. Phagocytic vacuole fuses with lysosome. Lysosome contains glucocerebrosidase enzymes. In patients with Gaucher disease glucocerebroside accumulates in lysosome and prevent macrophages to carry out their function properly. Gaucher cells are enlarged macrophages with undigested glucocerebroside. Gaucher cells are 20-100µm in diameter with irregular nucleus and distinctive wrinkles in cytoplasm as shown in figure 1. The morphology of GC cells in patients may vary from classical explanation (Grabowski, 2008).

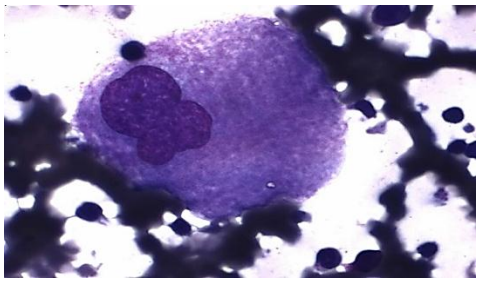

Figure 1: Gaucher cell in bone marrow cytology

Gaucher disease is apparent in infancy but very less appear in adolescence. It is a genetic disease which is recessive and occurs in autosomal cells. The immature form of gaucher's disease directly affects the central nervous system. This disease has clinical symptoms quite comparable to Niemann-Pick disease such as motor mental retardation, spasm of muscles, swelling of liver and spleen beyond their normal size. Death usually occurs in patients within one year in a decerebrate state. Microscopic study of infected tissues reveals they contain large, multiple number of nuclei in cells with dull and waxy appearance. Glucocerebrosides cause the buildup of lipids. When the underlying effect of glucocerebroside was analyzed it was found that there was the absence of lysosomal beta-D-glucosidase which

is required for the breakdown of glucocerebrosides (Grabowski, 2008).

Gaucher disease is caused by the deficiency of Glucosylceramide-β-glucosidase. Glucosylceramide-β-glucosidase, also called glucocerebrosidase, consists of 497 amino acids and has a molecular weight of about 65 kDa in its glycosylated form. It is a lysosomal enzyme that can associate to membranes. The X-ray structure of this enzyme has been reported, also when it was bound to the irreversibly acting inhibitor conduritol β-epoxide (Sidransky, 2004). Variant forms of the enzymes with 42 selected single amino acid substitutions have been generated, expressed in insect cells, purified, characterized for kinetic, stability and activator response properties, and mapped onto the crystal structure. The enzyme can be allosterically activated by Sap-C and by negatively charged phospholipids, of which the lysosomal bis (monoacylglycerol) phosphate seems to be of physiological relevance (Kolter, 2006).

Signs and Symptoms

The signs and symptoms may vary among affected people. Researchers have developed methods to classify GD types based on the characteristic features. The symptoms in the table 1 highlight gaucher disease three major types.

Table 1: Clinical classification of gaucher disease

Type of GD	Type 1: Non neuronopathic (Adult)	Type 2: Acute Neuronopathic(Infantile)	Type 3: Chronic/Subacute Neuronopathic (Juvenile)
Whom it strikes	Young adults/adults; most common in Ashkenazi Jewish population (1 in 450) 1 in 100000 general populations	Infants rarely, with no ethnicity 1 in 100000 live births	Children/young adults, with no ethnicity; 1 in 50000 live births Norrbottnian variant: Sweden; until early adulthood
Distinguishing symptom	Liver, spleen, and bone; no nervous system problems	Early nervous system problems, brainstem abnormalities	Later onset of nervous system problems: incoordination, mental deterioration, myoclonic seizures
Effects of disease	Varies from mild to severe	Death in infancy (age < 2 y)	Slowly progressive; becomes severe later in childhood
Glucocerebrosidase activity	Some activity, but much less than normal	Very little activity	Little activity

The most common and widely occurred type of disease is Type 1. It is also known as non-neuronopathy because it does not affect brain and spinal cord. It can appear at any time from childhood to adulthood and conditions may vary from mild to severe. Type 1 is associated with leukocytopenia, pain in abdomen, enlargement of spleen and liver due to hepatosplenomegaly, thrombocytopenia and anemia. Radiography of GD patients shows deformity in distal femur closely resembling to Erlenmeyer flask. Patients suffer from bone fracture if they accidently fall due to weakness in bones (Elstein et al., 2001). In type 2 and 3 neurologic symptoms are present such as fits, mental retardation, and severe loss of metal abilities and involuntary jerking of muscles. On the other hand, bones become fragile and brittle, tension in bones abnormally increase with reduction in muscular stretch, shortening of breath occur and yellowish brown pigments are deposited under the skin of patients (James, 1981). Renal, pulmonary and cardiac symptoms are usually not present. Phenotypic variation is present among different types of gaucher disease. The variation in phenotype is characterized among few populations of patients (Sibille et al., 1993). Detailed symptoms of GD are shown in figure 2. The seriousness and susceptibility of disease in an individual can be found by correlating genotype to phenotype (Grabowski, 2008).

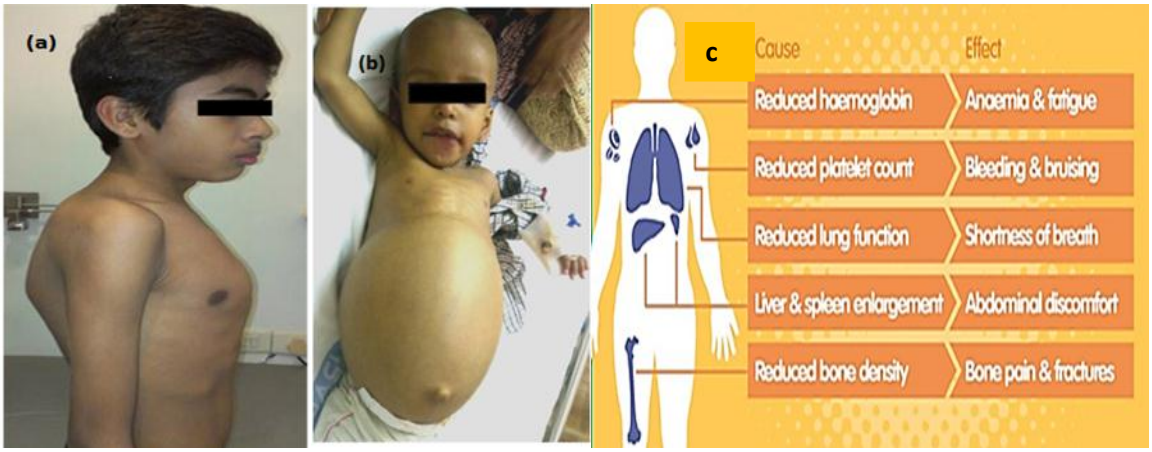

Figure *2*: (a) Severe kyphosis and chest deformity in a 10-year-old child. (b) Massive splenohepatomegaly in an 18-month-old child with type 1 gaucher disease. (c) Signs and symptoms of gaucher disease type 1.

BACKGROUND

In 1882, Philippe Gaucher described GD for the very first time in his doctoral thesis. In his thesis, it was hypothesized that enlarged cells penetrate into spleen showing ‘‘neoplasm.’’ Roscoe Brady’s group at National Institutes of Health in 1965 gave biochemical basis of this disease (Brady et al., 1965). The identification of mutation in glucocerebrosidase gene in late 1980’s led to the elucidation of molecular basis of the disease (Beutler et al., 1993). The inheritance of this disease is autosomal and recessive that is it only expresses itself when both parents are either carrier or infected. Ashkenazi Jewish population is commonly affected by this disease. Moreover 2000 Ashkenazi Jews were surveyed and gene frequency was found to be 0.034. 6.8% Jewish population is heterozygous for GD and frequency in population is 1 in 1000.The population of northern Sweden has prevalence of Norrbottnian type of GD (Futerman et al., 2003).

Gaucher cells are identified in bone marrow aspirate during diagnosis. However, the standard of diagnosis is based on enzymatic assay to analyze the activity of beta-glucocerebrosidase in leukocytes and molecular evaluation. The study of genetics reveals that glucocerebrosidase gene (GBA) resides on 1q21 chromosome. More than 200 mutations in GBA are responsible for GD. N370S point mutation dominants in Ashkenazi Jewish population. In addition, Jewish patients have 75% of the mutant alleles and 30% of mutant alleles are present in non-Jewish patients. 84GG frame shift mutation is prevalent in Jewish population. Norrbottnian population commonly has L444P mutation. The homozygous state closely relates gaucher disease to neuronopathy. N370S and 84GG mutation originated from single ancestor from Ashkenazi Jewish population. The high frequency of these mutations is primarily due to founder effect followed by changes in genetics. Genetic data is in accordance with founder effect resulting from population size between 1100 AD and 1400 AD in Jewish Diaspora although there is an uncertainty in Ashkenazi Jew’s demographic history (Cormand et al., 1997).

Genetics

Glucocerebrosidase gene has 11 exons and present on 1q21 chromosome. This gene instruct cell to manufacture beta-glucocerebrosidase enzyme. Mutation in GBA gene decreases or completely obliterates the activity of beta-glucocerebrosidase enzyme. Mutations greater than 200 occur in GBA gene and most of them are single nucleotide substitutions. ICGC Registry (Charrow et al., 2000) described N370S substitution in the alleles as the commonest form of mutation. Moreover, this mutation is a missense mutation (Orvisky,2002). Substitution in L444P and 84GG occurring in alleles are second and third commonest form of mutation respectively. Type 1 is inherited in autosomal recessive pattern (Figure 3). Parents that are heterozygous to this condition do not show any signs and symptoms but result in offsprings with affected GD type 1 (Nagral, 2014).

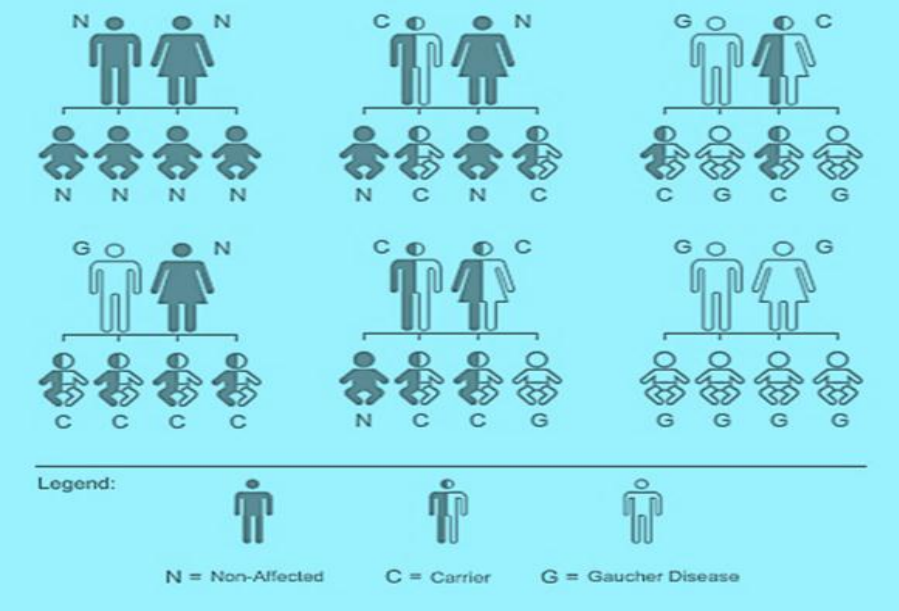

Figure 3: Pattern of inheritance of Gaucher's disease

Frequency of Gaucher's disease

In general population 1 in 50,000 to 100,000 people suffers from gaucher disease. The most common type of gaucher disease is Type 1. Most often Type 1 is common in Ashkenazi (eastern and central European) Jewish heritage compared with other backgrounds. 1 in 500 to 1,000 people of Ashkenazi Jews are affected by Type 1 GD. Other variants of GD are uncommon among the population of Ashkenazi Jews (Wang, 2008).

Pathological mechanism

In 1934 glucosylceramide (GlcCer) was identified as the lipid which accumulates in Gaucher disease (Aghion, 1934). The origin of GlcCer is different in our tissues because the fatty acid chains present in GlcCer are different. For instance, steraric acid in GlcCer is present in central nervous system and palmitic acid in peripheral system (Gornati et al., 2002). The patients of GD have increased level of GlcCer. The enlargement of organs such spleen simply does not account of high level of GlcCer. There are other biochemical pathways that must be initiated to contribute to development of disease. For example, only 2% GlcCer contributes in 25-fold increased spleen and rest of the enlargement occurs due to other factors. GD patients have 5-25% of normal GlcCerase activity. The mutation in the gene coding for GlcCerase accounts for the partial or entire reduction of catalytic activity of the enzyme. GlcCerase has three domains. Although the function of non-catalytic domains is not known yet mutation is present in all three domains which clearly indicate that they have a role in regulation. **Saposin C** is a sphingolipid activator protein required for the lysosomal breakdown of glucosylceramide into glucose and ceramide by Glucocerebrosidase (GCase) as indicated in figure 4 (Zimran et al., 2005).

The pathology of gaucher disease starts in Lysosome. GlcCer enters lysosome through various processes such as phagocytosis, pinocytosis, endocytosis and autophagocytosis. Yet it is not known how GlcCerase is targeted from endoplasmic reticulum to lysosome. Subsequent to GlcCer accumulation in lysosomes, or its escape from lysosomes, GlcCer causes many cellular responses, particularly in gaucher cells, macrophages that actively phagocytose other cells, especially senescent blood cells, from the circulation. Mostly, macrophages are the first one to be targeted in Gaucher's disease. It is now evident that pathology occurs due to activation of macrophages along with excessive storage of glucosylceramide and glucosylsphingosine (Perez, 2000). The serum of Gaucher patients have increased levels of interleukin-1b (IL-1b), tumor necrosis factor-a (TNFa), The changes in serum of patient compared to normal person well explain some of the pathological features such as osteopenia, hyper metabolism and gammopathies (Brautbar et al., 2004). Activated macrophage produces chitinase which is elevated in plasma of gaucher patients. The level of chitinase is often used to examine severity of gaucher disease and to follow the effectiveness of treatment used. In gaucher patients, coagulation factor level is low along with reduction in platelet aggregation (Futerman et al., 2003; Pelled et al., 2004).

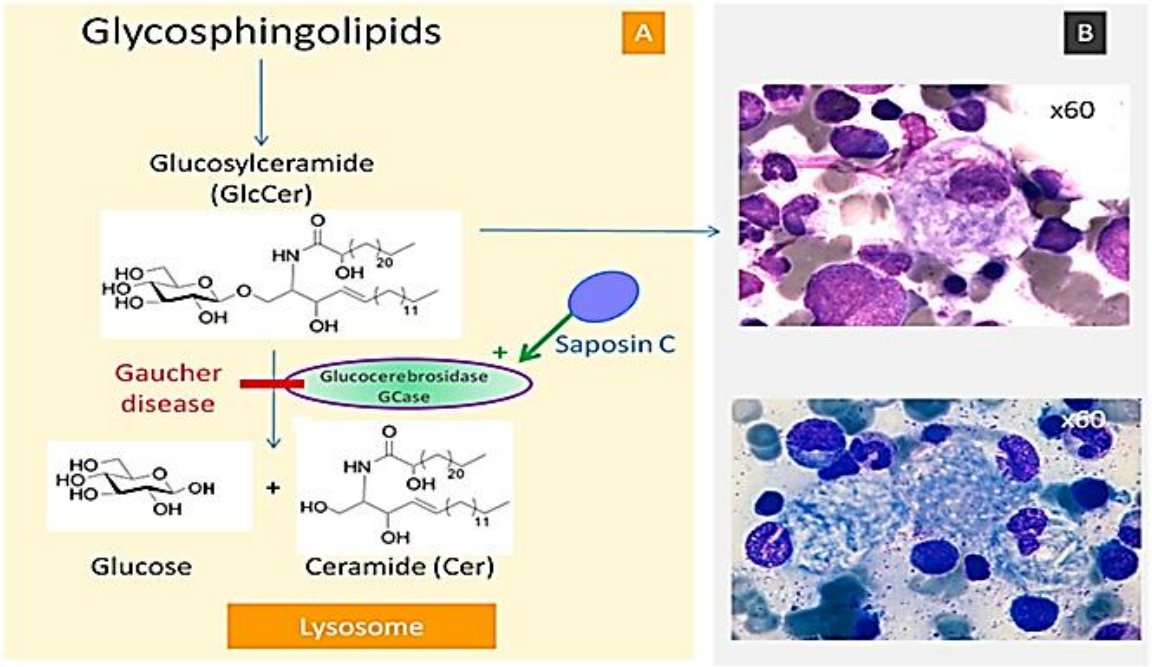

***Figure 4*: (A). Sapo*sin C activates GCase. (B) A* gaucher cells.**

Diagnosis

Simple method to diagnose gaucher disease is the enzyme assay that measures the activity of glucocerebrosidase in the blood sample of patients. Alternatively, skin sample can be used to find the activity of enzyme. Bone marrow sample is analyzed under microscope for gaucher cell. Figure 5 shows the diagnosis methods for GD. Other tests can also be carried out to check for the severity and progress of disease. These tests include:

1. Blood test to find low red blood cell count, any inflammation, low platelet count
2. X-ray to see any abnormality in bone.
3. MRI or CT scan to measure the liver and spleen
4. Examining day to day life of patient
5. Test to evaluate brain functioning.

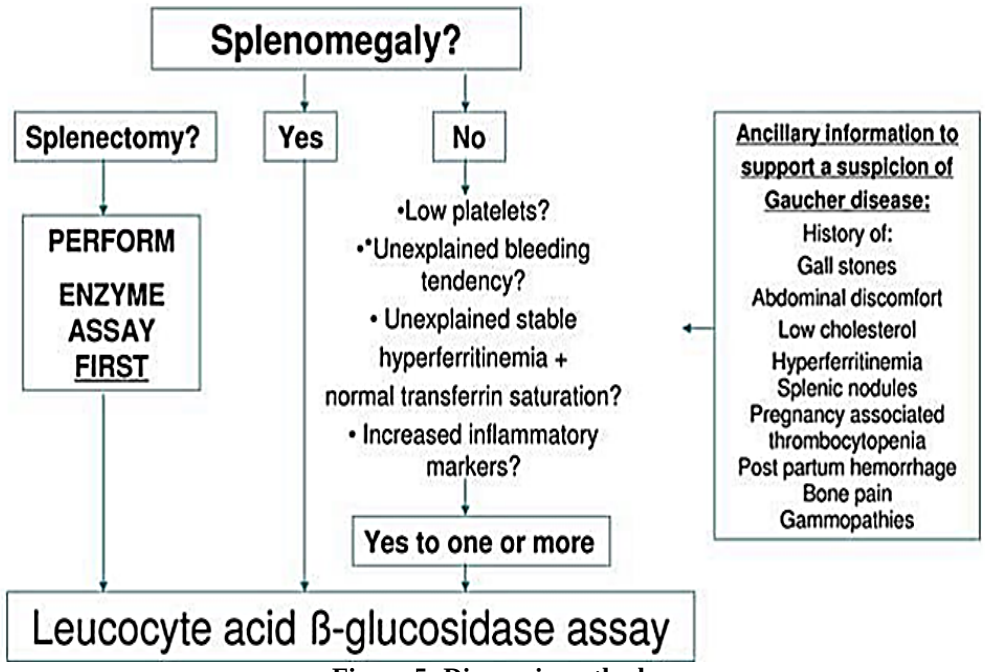

Figure 5: Diagnosis methods

DNA testing is beneficial not only to diagnose the patient with gaucher disease but the potential carriers as well (Sireesha, 1995).

Management

This disease causes the accumulation of toxic substances that are substrates for many enzymes e.g. glucocerebroside and many glycolipids like this. Management means to manage the effects of the disease i.e. to reduce the accumulation or increased levels of specific substances (Nagral, 2014).For complete management of this disease, there is a need to develop a comprehensive evaluated system that can ensure the optimal care of the patients of these diseases (Sireesha, 1995). Lysosomal diseases other than gaucher disease have relatively advantageous treatment options but the management plan for type 1 gaucher disease is more advantageous which include following methods:

1. Enzyme replacement therapy.
2. Substance reduction theory.

Following are the indications for selection of the treatment therapy for gaucher disease in table 2:

Table 2: Indications for choice of currently available GD treatments

Enzyme replacement therapy using Cerezyme®	Substrate reduction therapy using Zavesca®
First-line treatment for Gaucher disease	Second treatment option when ERT is unavailable or unsuitable
Severe disease	Mild disease
Paediatric disease	Non-paediatric disease
Need for prompt response	Slower response option
Patients planning to have children or unable/unwilling to use contraceptives	Patient must use contraceptives
Lack of improvement/side effects with SRT treatment	Supplemental to ERT in severe cases

There are many other management and treatment options for Gaucher's disease. But first of all, there is a need to assess the patient with great care otherwise the patient will not get a proper and complete treatment (Abe et al., 200; 1Futerman et al., 2003).

Patient Assessment

Patient Assessment is the first step in the treatment of disease. The symptoms of type 1 Gaucher's disease are different for different individuals so there is a need to develop a management system for all the patients individually. The type of symptom diagnosed will give the direction for treating the patient individually. The general symptoms of the disease which have been observed by different individuals are anemia, leading tendency because of thrombocytopenia, abnormal ties of liver function and function of lungs, organomegaly or disease of bones. Type 1 Gaucher's disease can be symptomatic or non-symptomatic. Sometimes symptomatic patients are relatively easy to be diagnosed and they are assessed generally initial clinical examination with all the symptoms explained above. On the other hand, the non-symptomatic patients are diagnosed by histological analysis. Another option for diagnosis of Gaucher's disease is genetic screening which is the most reliable method for diagnosis of a disease. The confirmation of the diagnoses is done by the enzyme assays and analysis of mutations in the genome of the affected person.

"A decision on the use of appropriate therapy is made on the base of the whole clinical picture of the patient."

As a result of patient's assessment of the disease, best treatment therapy is selected that can eliminate the symptoms of disease, improves the health of the patient and prevent the irreversible damage. The severity of the disease decides the re-evaluation of the treatment system (Futerman et al., 2003).

Enzyme replacement therapy (ERT)

Enzyme replacement therapy (ERT) is the most accept treatment tool for gaucher disease. It has revolutionized the treatment for GD. In earlier times, i.e. before the development of ERT, patients were not satisfied the treatment and most of them were not recovered completely and properly but due to ERT, they can hope to have a better life. So, the ERT has become a standard of care. It is only effective for the type I and III of GD because it can easily reduce the symptoms of these diseases. ERT gave a new direction for the treatment of many lysosomal and even metabolic diseases which are due to certain enzyme deficiency. Following are the indications for Enzyme Replacement therapy in figure 6 (Nagral, 2014).

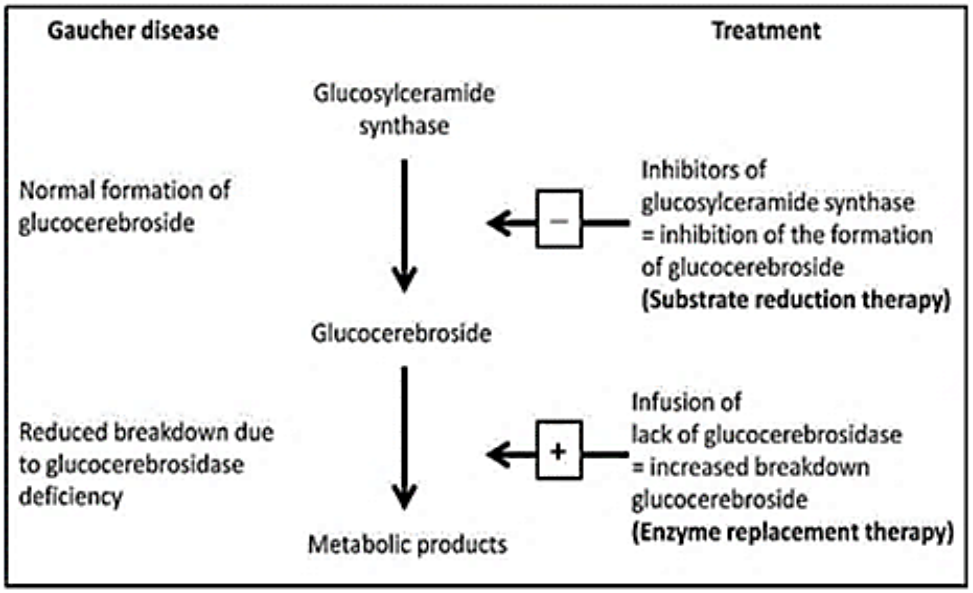

Figure 6: Indications for Initiating Enzymes Replacement Therapy

It is worth doing to store a serum sample of patient at 70^0C before initiating the treatment for many future tests or in case the patient develops antibodies to ERT (Nagral, 2014). The goal of ERT is to provide the enzyme of which patient is deficient. For this purpose, Food and Drug Administration (FDA) approved a treatment system with enzyme. Algucerase was extracted from human placenta for the first time in 1991. This enzyme resulted in huge improvements in the affected individuals. After some time, another enzyme took the place of this enzyme due to certain limitations like risk of blood borne diseases, low tendency of reproducibility of this enzyme and very short half-life of this enzyme. The enzyme which was then developed with increased efficiency was a recombinant enzyme named "Imiglucerase." This enzyme is an altered form of glucocerebrosidase enzyme which is involved in the cleavage of bonds of accumulated Glycosylceramide in the gaucher's disease. This was given as IV infusion. Algucerase comes in liquid form but imiglucerase comes in lyophilized powder form, hence can be stored for a long time without changes in this composition. Vipriv is a product of human glycerebrosidase approved by FDA in 2010 for ERT in the treatment of Gaucher's disease. This product was produced by company's proprietary gene activation technology. It is mostly suggested for pedriatic and patients of adult age. This product too has many limitations like rashes, infections in upper respiratory tract, pyrexia and prolonged activated partial thromboplastin time.

There is a human Glucocerebrolidase produced in carrot cells and it can also be used in ERT. It increases the risk of developing immunogenicity as compared to that glucocerobrolidase that is produced in mammalian cells (Sireesha, 2014). Initial dose of administration of the ERT for the first time is an intravenous infusion over 2 hours every 15 days. This includes the replacement of deficient enzyme with its modified form. The standard dose for a patient of Gaucher's disease is 60 units of enzyme/kg of accumulated substrate and it can be variable for different individuals having different symptoms and different levels of severity of disease. The variability of dose has a range of 20-120 units/kg. 60 units/kg dose is recommended with patients having an age of 10 years and with severe bone disease. Patients with symptoms like organomegaly and cytopenia need lower levels of dose i.e. 15-20 units/kg.

There are many side effects reported for ERT but all of them are mild and can be easily controlled. These side effects include "nausea, vomiting, abdominal pain, diarrhea, rash, fatigue, headache, fever, dizziness, chills, backache, and rapid heart rate." There are many other effects that can occur on the site of injection including "discomfort, itching, burning, and swelling." The most adverse effects of ERT are that the immune system of the patient becomes hyper sensitive. The patients which have produced antibodies against the injected enzyme are approximately 13%. All these side effects can be minimized by increasing the time of infusion pretreatment with anti-histaminics and corticosteroids. This treatment improves the growth pattern of patients and also the quality of life is improved. As a result of this therapy, size of spleen and liver is reduced, blood count is improved, and bone symptoms are ameliorated. Table 3 highlights other outcomes of this treatment.

Table 3: Therapeutic Goals of ERT for Children

Anemia	• Increase Hb levels within 1–2 years to >11.0 g/dl and maintain Hb • Eliminate blood transfusion dependency • Reduce fatigue and dyspnea
Thrombocytopenia	• Increase platelet counts during the 1st year of treatment >60 × 10^3 cells/mm^3 • Moderate thrombocytopenia: Count should increase by 1.5- to 2.0-fold by 1 year and low-normal level by 2 years • Severe thrombocytopenia: Counts should increase by 1.5- fold by 1 year and double by 2 years but normalization is not expected • Avoid splenectomy
Hepatomegaly	• Reduce and maintain the liver volume to <1.5 fold. • Reduce the liver volume by 20–30% within 1–2 years and by 30–40% by 5 years
Splenomegaly	• Reduce and maintain spleen volume to <2–8-fold normal • Reduce the spleen volume by 30% within 1 year and 60% by 2–5 years • Alleviate symptoms due to splenomegaly
Bones	• Lessen or eliminate bone pain within 2 years of treatment • Prevent bone crises • Prevent osteonecrosis and joint collapse • Improve bone mineral density by 2 years of treatment • Attain normal or ideal peak skeletal mass
Growth	• Achieve normal height within 3 years of treatment • Achieve normal onset of puberty

Data collected in a long-term analysis by ICGC registry of Gaucher's disease type 1 is as follows:

1. 90% of patients have normal hemoglobin levels.
2. Spleen volume is reduced after 10 years of treatment in 97% patients.
3. Most of the patients have normal levels of platelets after 10 years of treatment.
4. All the patients have reduced volume of liver excluding those having significant fibrosis or cirrhosis at the onset of therapy (Nagral, 2014).

Substrate Reduction Theory

The goal of the substrate reduction theory is to minimize the production of the substrates like Glucocerebroside which are accumulated in Gaucher's disease. This is done by certain chemicals which inhibit the formation of Glucocerbroside. Miglustat and Eliglustat tartarate are such chemicals which are used for milder diseases. This therapy is used after the Enzyme Replacement Therapy in order to maintain the therapeutic goals achieved by ERT. Glucoceramide production stopped by inhibiting the glucosyceramide synthase enzyme. This is an oral therapy. It was hypothesized in 1900s that by inhibiting the biosynthesis of glycosphingolipids their concentrations can be reduced in lysosome. This hypothesis was presented by Norman Radin (Abe et al., 2001).1-phenyl-2-decanoylamino-3-morpholino-1-propanol (PDMP) was synthesized by Radin and his colleagues to inhibit GlcCer synthase. This enzyme plays a pivotal role in GlcCer biosynthesis (Hollak et al., 1995). PDMP has variety of homologues which retards growth of cell and cause unwanted cell death. The effects of variety of PDMP were closely observed and only that is selected which does not have above mentioned effects (Sa Miranda et al., 1990; Barbour et al., 1992).

N-butyl-deoxy NoJirimycin (NB-DNJ) is an N-alkylated imino sugar which inhibit GlcCer synthase. NB-DNJ is used to modify the glycosylation envelope. Infectivity in certain viral diseases like HIV is decreased by glycoproteins. However, there was no success rate when clinical trials where carried on HIV patients. This is so because NB-DNJ effective concentration dose cannot be acquired without any undesired side effects in human (Tierney et al., 1995). Even though the clinical trials did have any success but for STR studies regarding GD valuable data was collected (Ficicioglu, 2008).

NB-DNJ was the first agent which was approved by US-FDA. This was extracted from plants and microorganisms. This chemical acts as competitive inhibitor of glucoceramide synthase. As a result of this treatment, glucoceramide is reduced to harmless levels. Glycosidase is the enzyme which is involved in the improvement of functions of lysosomal enzymes (Pastores, 2005). This activity of Glycosidase is assisted by Miglustat which targets the protein folding and trafficking pathways of glycosidase. The side effects of this treatment with Miglustat are diarrhea, sudden weight loss, and intolerance of milk. It is used only in adults but not in children. The figure 7 shows the inhibition of glucosylceramide synthesis with miglustat (Nagral, 2014; Sireesha, 2014).

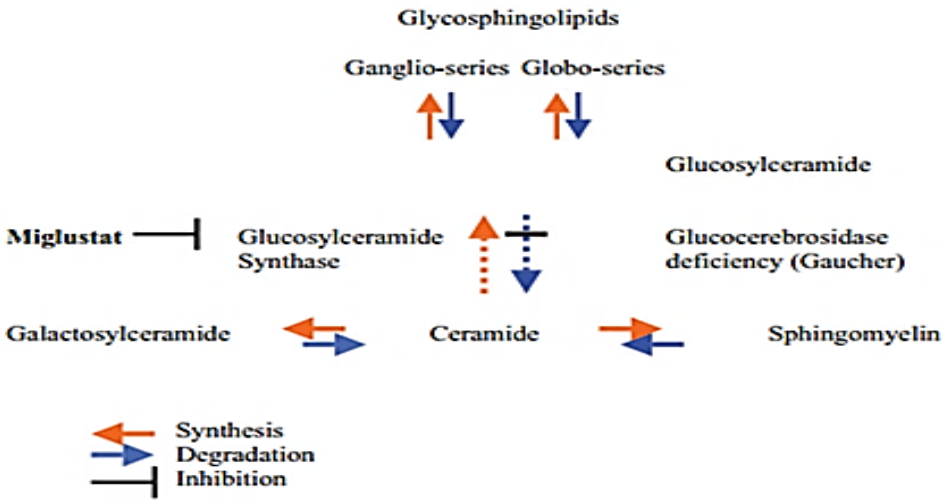

Figure 7: Inhibition of glucosylceramide synthesis with miglustat.

Eliglustat tartarate is very specific and is a competitive inhibitor of glucosyceramide synthase enzyme which is involved in the synthesis of glucosyceramide. This drug has passed the clinical trials phase I and II successfully and phase III is still underway. It is effective in improving organomegaly and cytopenia. It is approved for the use in adults but is being investigated for the use of children. It has no visible side effects (Nagral, 2014; Sireesha, 2014).

Chemical Chaperones (Enzyme Enhancement Therapy)

Gaucher's disease can be caused by some mutations which results in improperly folded Glucocerebrosidase. This non-functional enzymatic protein is slowed down in Endoplasmic reticulum and is degenerated there. A chemical Chaperone is a molecule which is competitive inhibitor having analogy to substrate of specific enzyme. This chemical binds to the misfolded enzymatic protein required for certain pathway and causes the activity of that enzyme to be increased in lysosomes. A drug named Ambroxol is normally used Chemical Chaperone involved in enhancing the activity of glucocerebrosidase enzyme. It has been found to be beneficial for Type I gsaucher disease with oculomotor dysfunction and myoclonus which are neurological disorders in one or the other way. The procedure for chemical chaperon treatment is shown figure 8 (Sawker, 2002).

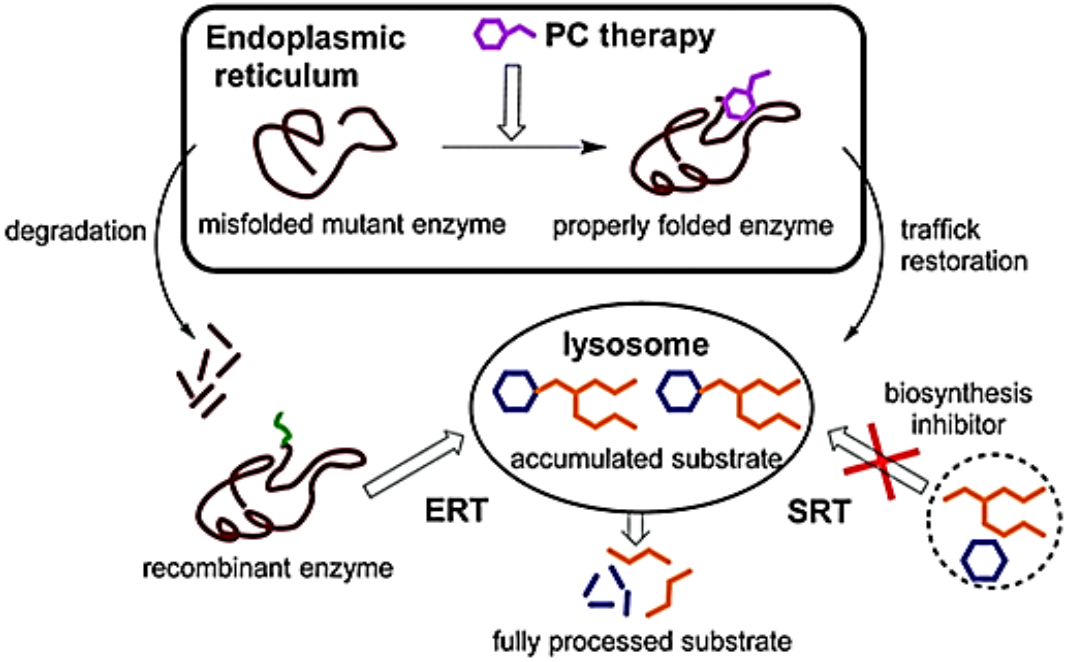

Figure 8: Action of chemical chaperones in treatment of GD

Gene Therapy

Replacing the improper and defected genome with healthy genome is also a type of treatment which can be done to the patients of gaucher's disease. This therapy can eliminate the limitations of both ERT and SRT i.e. dealing with neurological and pulmonary disturbances.

This therapy works by inoculating the gene coding for the production of specific enzyme in high levels e.g. the gene coding for production of high levels of human glucocerebrosides enzyme is ligated into recombinant adeno-associated viral vectors which is driven by human elongation factor 1-α promotor. This factor along with desired gene is inoculated in the body and it can increase the level of glcCerase both in normal individuals of Gaucher's fibroblasts. Although this is an attractive option of treatment but this is not as much accepted as it should be because of problems in delivery of gene and its expression especially in stem cells derived from bone marrow (Futerman et al., 2003; Nagral, 2014; Sireesha, 2014).

Conclusion and Future Prospects

Gaucher's disease is a heterozygous disease and it has variety of symptoms, even sometimes it is non-symptomatic which make it more difficult to be treated. It is a rare genetic disorder characterized by the deposition of glucocerebroside in cells of the macrophage-monocyte system. The disorder results from the deficiency of the enzyme glucocerebrosidase. There are a lot of treatment therapies are present for this disease which can be used according to the distinguished symptoms of each patient. In the near future, it is expected to use gene therapy as a common tool for the treatment of this disease. Gene therapy is relatively a better method.

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