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A REVIEW ON GAUCHER DISEASE

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ABSTRACT

Gaucher disease is a rare, autosomal recessive genetic disorder. It is caused by a deficiency of the lysosomal enzyme, glucocerebrosidase, which leads to an accumulation of its substrate, glucosylceramide, in macrophages. In the general population, its incidence is approximately 1/40,000 to 1/60,000 births, rising to 1/800 in Ashkenazi Jews. The main cause of the cytopenia, splenomegaly, hepatomegaly, and bone lesions associated with the disease is considered to be the infiltration of the bone marrow, spleen, and liver by Gaucher cells. Type-1 Gaucher disease, which affects the majority of patients (90% in Europe and USA, but less in other regions), is characterized by effects on the viscera, whereas types 2 and 3 are also associated with neurological impairment, either severe in type 2 or variable in type 3. A diagnosis of GD can be confirmed by demonstrating the deficiency of acid glucocerebrosidase activity in leukocytes. Mutations in the GBA1 gene should be identified as they may be of prognostic value in some cases. Patients with type-1 GD— but also carriers of GBA1 mutation—have been found to be predisposed to developing Parkinson's disease, and the risk of neoplasia associated with the disease is still subject to discussion. Disease specific treatment consists of intravenous enzyme replacement therapy (ERT) using one of the currently available molecules (imiglucerase, velaglucerase, or taliglucerase). Orally administered inhibitors of glucosylceramide biosynthesis can also be used (miglustat or eliglustat).

KEYWORDS: Gaucher disease, Lysosomal storage disease, Glucocerebrosidase, GBA 1 gene, enzyme replacement therapy, substrate reduction therapy and biomarkers.

INTRODUCTION

Gaucher disease is the result to build up fatty substances. in certain organs, particularly in spleen and liver. this cause these organs to enlarge and can affect their function. GD is a rare genetic disorder passed down from parents to childrens when you have gaucher disease, you are missing an enzyme that breaks down fatty substances called as lipids. lipids start up to build up in certaining organs such as your spleen and liver. both males and females are effected by the GD. gaucher cells are normally scavenger cells called macrophages. people with GD may be at higher risk for certain medical issues and nutrious diet can keep them on a healthy path. GD affects one in 20,000 births GD is an enzyme deficiency thar prevents the breakdown of fatty acid. 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 required for 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. Gaucher disease (GD, OMIM #230800, ORPHA355) is the most common sphingolipidosis. It was first described by Philippe Gaucher in 1882 in a patient with massive splenomegaly without leukemia. GD is a rare, autosomal, recessive genetic disease caused by mutations in the GBA1 gene, located on chromosome 1 (1q21). This leads to a markedly decreased activity of the lysosomal enzyme, glucocerebrosidase (GCase, also called glucosylceramidase or acid βglucosidase, EC: 4.2.1.25), which hydrolyzes glucosylceramide (GlcCer) into ceramide and glucose. More than 300 GBA mutations have been described in the GBA1 gene. Very rarely, GD can also be caused by a deficiency in the GCase activator, saposin C. The phenotype is variable, but three clinical forms have been identified: type 1 is the most common and typically causes no neurological damage, whereas types 2 and 3 are characterized by neurological impairment. However, these distinctions are.

Historical Background

Gaucher disease is a rare inherted disease.it was described by dr. philippe gaucher in 1882. it is caused by genetic mutations. (a permanent change in dna of gene) received from both parents. GD diagnosed can be delayed due to non specific symptoms. lack of awareness leading to unnecessary procedure and irreversible complications. parts of the country, it seems likely that the frequency of Gaucher disease may be higher in India. Of more than 300 mutations catalogued in Gaucher disease, L444P appears to be the most prevalent in India.[5] This mutation occurs normally in the pseudogene sequence; vulnerability of GBA locus to gene conversion events underlies relatively high prevalence of this mutation worldwide. We have found that homozygosity for L444P mutation is most common genotype in most parts of the country while in the northern region, in addition to L444P, there is a relatively higher rate of rare private mutations.[5,6] Homozygosity for L444P mutation typically results in neuronopathic. Traditionally, Gaucher disease patients are classified into three broad phenotypes based on the presence or absence of neurological manifestations and their severity (Table I). However there is a continuum of phenotypes, ranging from mildly affected adults to the severe, lifethreatening manifestations of type 2 patients presenting with non-immune hydrops fetalis and neurodegenerative disease.[8] Patients with type 1 Gaucher disease in India present from as early as infancy to late childhood with a median age of 3.6 years. This highly aggressive phenotype with spleno-hepatomegaly, cytopenia, irritability, bone involvement and failure to thrive is associated with early mortality without treatment. The common differential diagnosis of the most prevalent presenting phenotype of splenohepatomegaly in Gaucher disease include hemolytic anemias typically hemoglobinopathies, non-cirrhotic portal hypertension, tropical splenomegaly, lymphoreticular malignancies.

TYPES

They are 3 types

TYPE -1.

GD type 1 is the most common form of the disease in western countries. making up roughly 95% of patients there symptoms include: spleen and liver enlargement, bone problems, fatigue, brain development, is normal. it is most common form of this condition. type -1 is also called as non-neuronopathic GD because brain and spinal cord are usually nor effected. the feature of this condition range from mild to severe and may appear anytime from childhood to adulthood. GD caused by changes in the GBA gene. Type-1 GD (GD1), usually

distinguished by the absence of neurological impairment, is the most common form of the disease (prevalence: 90%–95% in Europe and North America). Its clinical presentation is variable, ranging from asymptomatic throughout life to early-onset forms presenting in childhood. The initial symptoms vary considerably and patients can be diagnosed at any age. Depending on the study, the median age of diagnosis is from 10 to 20 years old. Although the overall mean onset of patients in the Gaucher Registry (run by the International Collaborative Gaucher Group) is at 20.4 years old, the majority (56%) of patients experienced onset before 20. However, this Registry primarily includes symptomatic and treated patients, and thus the mean age is probably skewed. Two thirds (68%) of this group were diagnosed before 10 years old and almost half (48%) before the age of 6.

TYPE-2

A rare form of disorder. GD type 2 appear in babies younger than 6 months old. It causes an enlarged spleen, movement problems, and severe brain damage. there is no treatment of GD type 2. babies with this condition usually pass away within two to three years. GD type 2 TYPES Dept. of Pharmacology, Ratnam Institute of Pharmacy, Nellore. 5 is an inherited metabolic disorder in which harmful quantities of a fatty substance called glucocerebrosidase. accumulated in the spleen, liver, lungs, bonemarrow and brain. symptoms developed by 3 months of age include brain damage, seizures, abnormal eye moments, poor ability to suck and swallow and enlargement of liver and spleen.

TYPE-3

GD type 3 is the subacute neurological form of gaucher disease characterized by progressive encephalopathy and associated with the systemic manifestations (organomegaly, bone involvement, cytopenia) of GD type 1. another form of GD known as cardiovascular type. because it primarly affects the heart, causing the heart valves to harden (calcify). people with cardiovascular form of GD and mild enlargement of spleen. treatment of GD only address problems affecting the blood. organs and bone it dosenot improve brain function or reverse neurological damage. Also called juvenile or subacute neurological GD, the type-3 form (usually 5% of cases, but up to 33% in some cohorts) exhibits the visceral manifestations described in GD1, usually combined with oculomotor neurological involvement which appears before 20 years of age.

DIAGRAMATIC REPRESENTATION

MECHANISM OF ACTION

GD is caused by mutation in the Gba -1 gene encoding an acid Bglucocerebrosidase, the lysosomal hydrolase which breaks down glucosylceramide. in GD type 1 disease the accumulation of this simple glycolipid is mainly restricted to tissue phagocyte lysosomes resulting to tissue phagocyte resulting ultimately in hepatomegaly, splenomegaly, osteopenia. lower residual GBA 1 levels leads to neuronal storage, in type 2 and 3 neurological symptoms are charactrised by acute (death at age 2) or subacute onset, respectively. the link between cellular changes and clinical manifestations are largely unknown but are key to the development and monitoring of new therapies. the newcomes to gaucher disease is likely attracted to the apparent simplicity of an autosomal recessive disorder. which promises to unravel the critical GlcCer function in normal cells (GlcCer is widespread, it's even present in some bacteria—also, mouse and fly GlcCer knockouts die at embryo stage). However, closer acquaintance reveals not a classic Mendelian disorder—sometimes even monozygotic twins have different symptoms—and studies at the cellular level have so far failed to reveal clear GlcCer functions. Now a team led by Ellen Sidransky at the NIH has taken what appears to be a big step forward by producing two in vitro models of Gaucher cells. Research has been hampered by the inaccessibility of Gaucher macrophages and the lack of in vitro models. The simplest approach has been to induce a Gaucher phenotype by treating cells with the GBA1 inhibitor, conditurol-β-epoxide. Whilst this method has the virtues of being cheap and experimentally easy, off-target effects are not controlled for. For instance, conduritol-βepoxide also inhibits a related enzyme, GBA2. Inhibition of this non-lysosomal enzyme has been reported to rescue mutations in lysosomal GBA1. GlcCer is unusual amongst glycolipids with intracellular trafficking connecting both lysosomal and non-lysosomal pools on both sides of the bilayer membrane. GlcCer transporters have been identified but the

relationships between different pools of GlcCer are still unclear. A second approach has been to use fibroblasts from Gaucher patients. Although the macrophage-centric view of Gaucher disease has recently been questioned, Gaucher skin fibroblasts are not important in Gaucher disease.

GENETICS

Gaucher disease is inherited in an autosomal recessive manner. At conception, each sib of an affected individual has a 25% chance of being affected, a 50% change of being an asympathomatic carrier, and a 25% chance of being unaffected and not a carrier. GD encompasses a continue of clinical findings from a perinatal lethal disorder to an asympathomatic type. The identification of 3 major clinical type (1,2,3) and two other sub types (perinatal -lethal & cardiovascular) is useful in determining prognosis and management. GD type -1 is characterized by the prescence of clinical or radiographic evidence of bone disease (osteopenia, focal lytic, & osteonecrosis), hepatosplenomegaly, anemia & thrombocytopenia, lung disease and the absence of primary CNS disease. GD type 2 & 3 are characterized by presence of primary neurologic disease; in the past, they were distinguished by age of onset and rate of disease progression, but these distinctions are not absolute. A preliminary gene transfer protocol was used on GD3 patients, with the aim of introducing the GBA1 gene into hematopoietic cells and then injecting the corrected cells into patients. Results were disappointing as the GCase levels proved too low for any clinical effect. Lentiviral vector gene transfer techniques have been used in mouse models of GD with promising results, but this approach is still at the basic research stage. the most severe type of GD is a very rare form of type 2 called called perinatal lethal form. this condition cause severe or lifethreatening complications starting before birth or infancy.

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PATHOPHYSIOLOGY

GLICOSYLCERAMIDE ACCUMULATION

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. This feature is related to the presence of GlcCer aggregates in characteristic twisted, fibrillar arrangements that can be visualized using electron microscopy. 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. 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. Consistent with this, recent work on a Drosophila model of neuronopathic GD demonstrated autophagy impairment in the GCase-deficient fly brains. Very rarely, GD may be caused by a mutation

in the PSAP gene, leading to a deficiency in saposin C without GCase deficiency. These patients generally present with neurological features similar to that of type-3 GD.

SUBPOPULATION OF GAUCHER CELL

Recent observations indicate that Gaucher cells do not only result from the transformation of macrophage cells, but correspond to a distinct M2 subpopulation from an alternative differentiation pathway. There are many functional states of macrophage polarization, and they can be fully polarized and acquire a specific phenotype like M1 (characteristic macrophage activation) or M2 (alternative macrophage activation). These specific phenotypes depend on the tissue and specific microenvironment where the macrophages are. The M2 subpopulation has been described as cells with anti-inflammatory, immunomodulatory and tissue repair properties, and includes macrophages that remove abnormal hematopoietic cells or phagocytose erythroblast nuclei. The in vivo situation appears more complex since the plasma cytokine profile and the characteristic monocytes circulating in the blood show concurrent activation of inflammatory M1 macrophages, presumably implicated in the "pseudoinflammatory" state that was described many years ago and in the heterogeneous manifestations of the disease. Thus numerous cytokines, chemokines and other molecules—including IL-1β, IL-6, IL-8, TNFα (Tumor Necrosis Factor), M-CSF (Macrophage-Colony Stimulating Factor), MIP-1β, IL-18, IL10, TGFβ, CCL-18, chitotriosidase, CD14s, and CD163s—are present in increased amounts in Gaucher patients' plasma and could be implicated in hematological and bone complications. Only some of these molecules are expressed by Gaucher cells themselves. This is the case for chitotriosidase and CCL18, which thus constitute quite specific disease biomarkers. Osteoporosis may be linked to IL-10, which inhibits osteoblast activity, but also to IL-1β, IL-6 and M-CSF, MIP-1α and MIP-1β, which stimulate bone resorption by increasing osteoclast activity.

SIGNS AND SYMPTOMS

- Enlarge spleen
- Enlarge liver
- Eye movement disorders.
- Yellow spot in the eye
- Not having enough healthy red blood cell
- Extreme tiredness

- Bruising
- Lung problems
- Bleeding problems
- Painful belly
- Enlarged organ

CAUSES

Gaucher disease is an inherited metabolic disorder. A genetic change (mutation) in the GBA gene causes the disease. The GBA gene is responsible for making an enzyme called glucocerebrosidase (GCase). People with Gaucher disease don't have enough of this enzyme. Enzymes like GCase are proteins that perform several tasks, including breaking down fats (sphingolipids) in your body. If your body doesn't have enough of these enzymes, fatty chemicals (called Gaucher cells) build up in your organs, bone marrow and brain. The excess fats cause a wide range of problems and symptoms. They affect how your organs work, and they destroy blood cells and weaken bones.

TREATMENT

Enzyme replacement therapy: People with Gaucher disease need ERT regularly (every two weeks) for treatment to be effective. Your healthcare provider will give you an enzyme infusion intravenously (through a vein in your arm). Which is effective for type 1 & 3 Medicines: which include eliglustant, miglustant, osteoporpsis drugs. Regular physical exams and bone density screening to check your disease. Bone marrow transplant which replaces unhealthy blood forming cells with healthy one. Surgery to remove all or part of your spleen. Joint replacement surgery. Blood transfusion to provide blood or blood components.

PREVENTION

There is no way to prevent GD if you have the genetic mutations. its wise to have testing if you are at risk. early treatment may prevent damage to bones and organs from GD type 1. There's no way to prevent Gaucher disease if you have the genetic mutation. It's wise to have testing if you're at risk. Early treatment may prevent damage to bones and organs from Gaucher disease type 1. If a DNA test shows that you're a Gaucher carrier, and you're planning on starting a family, talk to your healthcare provider. A genetic counselor can give you more information and help you make a plan to decrease the chance of passing on the gene.

DIAGNOSIS

To diagnose Gaucher disease, your healthcare provider will examine you and ask about your symptoms. Providers diagnose Gaucher disease using a blood test that checks for enzyme levels or a DNA test to see if the gene mutations causing Gaucher disease are present. To determine if you're a carrier for Gaucher disease, your provider will perform a DNA test using your saliva or blood. Gaucher disease carriers don't have any symptoms, but they can pass the disease to their children. If you're a carrier and considering having children, your provider will refer you to a genetic counselor so you can decide on a plan for your family.

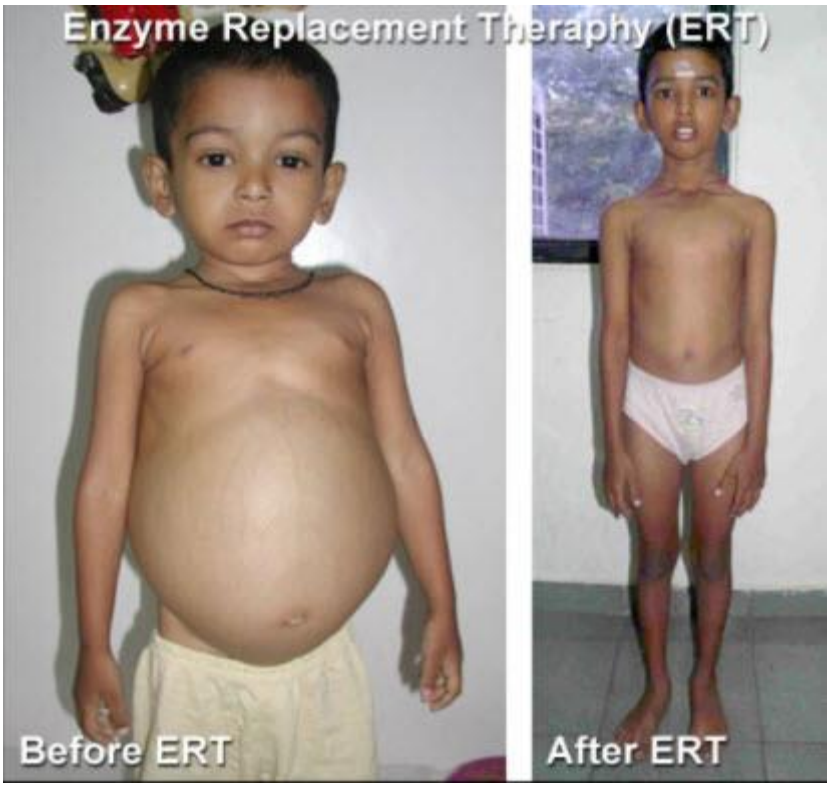
PROGNOSIS

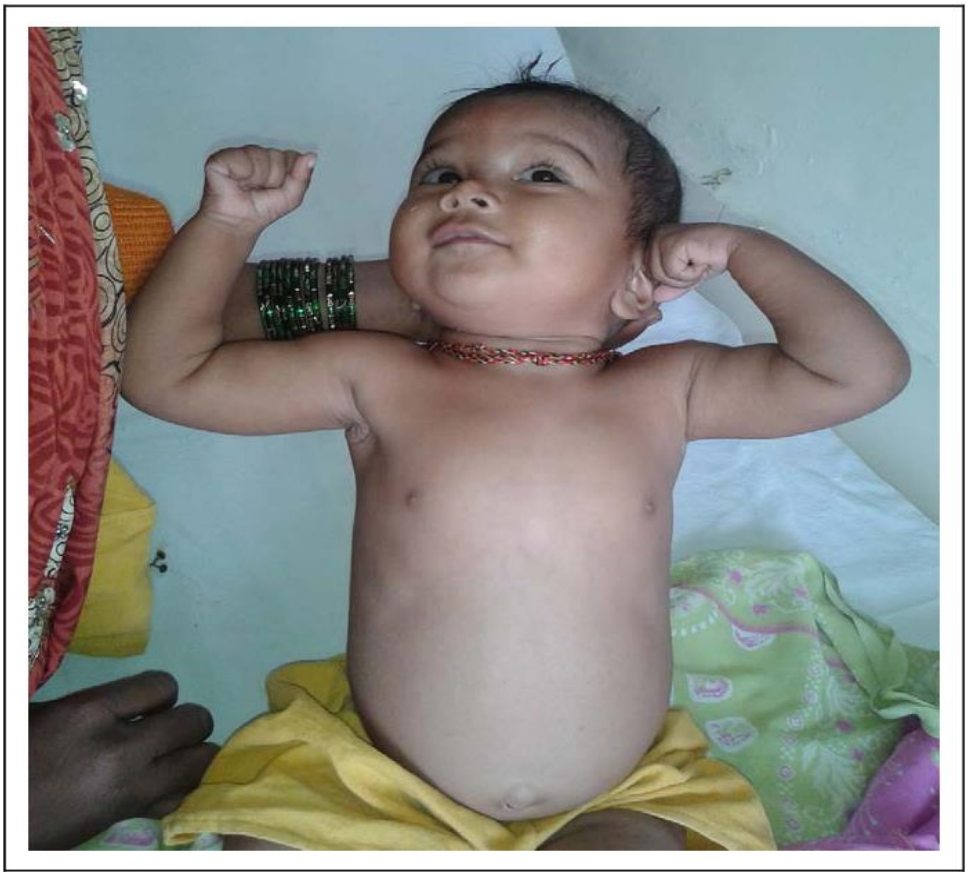
Gaucher disease type 1 can manage the disorder and lead full lives. It's essential to work with a specialist and continue long-term treatments. Without treatment, Gaucher disease can cause permanent damage. Treatments can help people with Gaucher disease type 3 live to their 20s or 30s. But the treatment for Gaucher disease type 3 only addresses problems affecting the blood, organs and SIGNS & SYMPTOMS Dept. of Pharmacology, Ratnam Institute of Pharmacy, Nellore. 14 bones. It doesn't improve brain function or reverse neurological damage. Due to severe brain damage, babies with Gaucher disease type 2 pass away within the first 3 years.

BIOLOGICAL TEST

Liver function tests (e.g., free and conjugated bilirubin, transaminases, alkaline phosphatase, gamma GT) are not usually abnormal but may be carried out, sometimes revealing cholestasis (increase in alkaline phosphatase, bilirubin, and gamma-GT), but rarely cytolysis (increase in transaminases).C Reactive Protein (CRP) levels may be high in bone crises (bone infarction) or infectious complications (cholecystitis more common in GD). Measurement of serum calcium (potentially serum phosphorus) and vitamin D is recommended. Vitamin D deficiency seems to be more common in GD than in the general population and supplementation is highly recommended when the 25(OH) D level is less than 75 nmol/L. Auto-antibodies (antinuclear, anti-phospholipid antibodies) have been found in GD patients, usually without clinical signs, but are not routinely tested for. Antibodies directed against the therapeutic enzyme (imiglucerase) are detected in 2%–14% of cases, but are of no consequence in practice. They are only assayed in the case of an allergic reaction or a loss of treatment functioning.

DIAGRAMATIC REPRESENTATION





CONCLUSION

Firstly, the GD originates when there is reduced autonomic damage of the gene usually produce an enzyme called glucocerebrosidase. that emulsifies fatty compounds from the human biological system. the disease can be treated using both modern and classical medical options available like x- ray scans & so on. The cause of all forms of GD is mutations in the GBA 1 gene resulting in a lysosomal deficiency of glucocerebrosidase activity. all forms of GD lead to the toxic accumulation of glucocerebrosidase lipids, primarily in the liver, spleen and bone marrow.

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