AMERICAN JOURNAL OF PHARMTECH RESEARCH
Journal home page: http://www.ajptr.com/

An Overview On Gauchers Disease and Its Management

Ch.Venkata.Hemanth[1]*,T.Chandana Madhuri [1], K.Sai Tejaswi[1], B.Ganesh
1.Department of pharmacy practice, Hindu college of pharmacy, Guntur, A.P, India

ABSTRACT

Gauchers disease affects both males and females. It is a rare hereditary disorder of lipid metabolism caused by an enzyme deficiency and characterized by enlargement of the spleen and liver, bone lesions and sometimes neurological impairment. About 1 in 100 people in the United States are carriers of common type of Gauchers disease. It is classified in to three types. Type 2 Gaucher disease is a very rare, rapidly progressive form of gaucher disease which affects the brain (central nervous system) as well as the spleen, liver, lungs and bones. Formerly called infantile gaucher disease, it is characterized by severe neurological (brain) involvement in the first year of life. The accurate diagnosis is mainly based upon enzyme and genetic testing. There are several treatment for Gauchers disease. The glucocerebrosidase genes are carried on autosomal chromosome number 1. If a person has at least one normal glucocerebrosidase gene, then the person will not develop Gaucher disease. The symptoms of Gauchers disease are classified based on organ systems like heart, liver, skin, eyes, haematological and lymphatic. Psychological counseling is important for patients and families with GD given the likelihood of incapacitating symptoms and chronic nature of the disease.

Keywords: Gauchers disease, Types, Symptoms, Treatment options.

*Corresponding Author Email: hemanthv132@gmail.com
Received 01 July 2017, Accepted 15 July 2017

Please cite this article as: Singh J *et al*., A Comparative Study of Timolol Maleate 0.5% v/s Latanoprost 0.005% In the Treatment of Primary Open Angle Glaucoma. American Journal of PharmTech Research 2017.

INTRODUCTION

Gaucher disease is the commonest lysosomal storage disease seen in India and worldwide. It should be considered in any child or adult with an unexplained splenohepatomegaly and cytopenia which are seen in the three types of Gaucher disease. Type 1 is the non-neuronopathic form and type 2 and 3 are the neuronopathic forms. Type 2 is a more severe neuronopathic form leading to mortality by 2 years of age. Gaucher disease (GD) is a genetic disorder in which glucocerebroside (a sphingolipid, also known as glucosylceramide) accumulates in cells and certain organs. The disorder is characterized by bruising, fatigue, anemia, low blood platelet count and enlargement of the liver and spleen, and is caused by a hereditary deficiency of the glucocerebroside. When the enzyme is defective, glucocerebroside accumulates, particularly in white blood cells and especially in macrophages (mononuclear leukocytes). Glucocerebroside can be collected in the spleen, liver, kidneys, lungs, brain, and bone marrow. The disease is caused by a recessive mutation in a gene located on chromosome 1 and affects both males and females. Gaucher's disease is the most common of the lysosomal storage diseases. It is a form of sphingolipidosis (a subgroup of lysosomal storage diseases), as it involves dysfunctional metabolism of sphingolipids. The disease is named after the French physician Philippe Gaucher, who originally described it in 1882.[1]

Symptoms

1) Easy bleeding and bruising.

2) Excessive fatigue.

3) Anemia.

4) Weak bones fracturing too easily.

5) Bone and joint pain.

6) Enlargement of the belly through increase in the volume of spleen and liver.

Epidemiology

As around the world, Gaucher disease is also the commonest lysosomal storage disease in India.3 The risk of developing GD increases with consanguinity in the family. Its frequency differs with different populations–being most prevalent—1:450 birth incidence in individuals of Ashkenazi Jewish descent.4 Ashkenazi Jews form about 75% of the world's Jewish population. However, the overall estimated prevalence of symptomatic disease is much lower—occurring in approximately 1 in 100,000 live births.

The majority of patients have type 1 Gaucher disease (GD1), which is the non-neuronopathic form of GD. It is the main type seen in the Ashkenazi Jewish population. Type 2 Gaucher disease

(GD2), is also called acute neuronopathic GD or infantile cerebral GD. It comprises about 1 percent of patients in the ICGC Registry.5 Type 3 GD (GD3) is the chronic neuronopathic form and is seen in 5% of patients overall. GD3 is mainly seen in Northern Europe, Egypt and East Asia.6 A high incidence of GD3 is found in the Swedish province of Norrbotten and is therefore also referred to as the Norrbottnian type of GD.7 In India, there are no prevalence studies but in our study of treated patients, about a third had GD3 and two thirds were GD1.8 The numbers of patients with GD1 are likely to be higher as the severe GD3 patients were not considered for treatment. Also, there are no estimates of GD2 from India. The prevalence of Gaucher's disease is low. Types II and III, which have a variable degree of involvement of the neurologic system, have a very rare incidence, and occur in less than1:100,000 of the population. Type I Gaucher's disease occurs mainly in adults and is the commonest lysosomal storage disorder. Experience in the UK suggests over 90 to 95% of patients have predominantly Type I disease, although it is still rare, occurring in about one in 30–40,000 of the population. However, epidemiological studies conducted in the USA and Israel have shown that the incidence of this disorder amongst Ashkenazi Jews is significantly higher than this, with a prevalence of about 1in 1000 in this population, and an estimated carrier frequency of 1:14.

Causes:

The three types of Gaucher disease are inherited in an autosomal recessive fashion, this means, both parents must be carriers. If both parents are carriers, the chance of the disease is one in four, or 25%, with each pregnancy for an affected child. Genetic counseling and genetic testing are recommended for families who may be carriers of mutations.

Each type has been linked to particular mutations. In all, about 80 known mutations are grouped into three main types:

Type I (N370S homozygote), the most common, also called the "non-neuropathic" type occurs mainly in Ashkenazi Jews. The median age at diagnosis is 28 years of age, and life expectancy is mildly decreased. There are no neurological symptoms.

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.

Type III (also one or two copies of L444P, possibly delayed by protective polymorphisms) occurs in Swedish patients from the Norrbotten region. This group develops the disease somewhat later, but most die before their 30th birthday.

Table 1: Differences in the Three Types of Gaucher Disease.

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

Table 2: Organ-wise Involvement in Gaucher Disease.

Organ system	
General	Reduced quality of life, delayed milestones, growth retardation, pubertal status
Skeletal	Chronic bone pain (33%), acute bone crises (7%) Kyphosis including gibbus, scoliosis and chest deformities Bone fractures (7%) Skeletal growth retardation (36%) Bone remodeling failure (Erlenmeyer flask deformity) Osteopenia (55%) Osteonecrosis, avascular necrosis head femur Osteolysis, osteosclerosis
Visceral organs	Abdominal pain, early satiety, feeling of fullness, diarrhea Splenomegaly (85%), splenic infarcts Hepatomegaly (63%) (may progress to cirrhosis, portal hypertension) Cholelithiasis
Hematological	Anemia (34%)—Fatigue, exertional dyspnea, need for blood transfusions Thrombocytopenia (68%) spontaneous bleeding—epistaxis, bruising, menorrhagia or hemostatic problems after trauma, surgery or post-partum bleeding Leukopenia: increased risk of infection Gammopathy
Lungs	Dyspnea (exertional), cough, recurrent respiratory infections Pulmonary hypertension with dyspnea on exertion or at rest, syncope Hepatopulmonary syndrome—clubbing, cyanosis, orthopnea
CNS (Type 2/3)	Strabismus, saccade initiation failure, supranuclear gaze palsy, slow object tracking, hypertonia, rigidity, opisthotonus, bulbar palsy, seizures, ataxia, myoclonus, dementia, mental retardation
Skin	Yellow/brownish discoloration Bruises, petechiae
Heart	Valvular calcification, congestive heart failure, arrhythmias
Eyes	Pingueculae Corneal opacities Strabismus, saccade initiation failure (ocular motor apraxia) in type 3 disease
Lymphatic	Enlarged lymph nodes
Malignancies	Increased risk of multiple myeloma, hematological malignancy, hepatocellular carcinoma, renal cell carcinoma.[1,2]

Diagnosis:

Gaucher disease is suggested based on the overall clinical picture. Initial laboratory testing may include enzyme testing. As a result, lower than 15% of mean normal activity is considered to be diagnostic. Decreased enzyme levels will often be confirmed by genetic testing. Numerous different mutations occur; sequencing of the beta-glucosidase gene is sometimes necessary to confirm the diagnosis. Prenatal diagnosis is available, and is useful when a known genetic risk factor is present.

A diagnosis can also be implied by biochemical abnormalities such as high alkaline phosphatase, angiotensin-converting enzyme, and immunoglobulin levels, or by cell analysis showing "crinkled paper" cytoplasm and glycolipid-laden macrophages.

Some lysosomal enzymes are elevated, including tartrate-resistant acid phosphatase, hexosaminidase, and a human chitinase, chitotriosidase. This latter enzyme has proved to be very useful for monitoring Gaucher's disease activity in response to treatment, and may reflect the severity of the disease.

Enzyme test for gauchers disease:

A BGL test for enzyme activity will almost certainly show if you have Gaucher disease. All patients with Gaucher disease have low glucocerebrosidase (GCase) enzyme activity, which is why their bodies cannot break down glucocerebroside (a fatty chemical). Rarely, BGL test results can be inconclusive, in which case genetic testing can usually help clarify whether you have Gaucher disease.

Physicians measure enzyme activity with a blood test. They do so by taking a blood sample for adults, or a less invasive heel stick (a smaller prick) for babies.

Genetic testing for gauchers disease:

Genetic testing shows whether a person has the specific mutations associated with Gaucher disease. Physicians perform this test using a blood or saliva sample. Genetic testing can also detect who is a carrier of Gaucher disease. Carriers do not have the disease, but they may pass the gene to their children.[3]

Examples of case studies of gauchers disease:

CASE 1:

The male infant was the second child of consanguineous (first cousin) Lebanese parents with no other relevant family history.9 An ultrasound study at 18 weeks of gestation was reportedly normal. An ultrasound performed at 26 weeks of gestation because of maternal abdominal pain was suggestive of fetal hydrops. Additional imaging studies over the following months showed

hepatomegaly, decreased fetal movement, and hyperextension of the neck. Amniocentesis and karyotyping were performed, revealing a 46,XY male fetus. He was born at 34 weeks of gestation and died shortly after birth. Postmortem examination revealed a thick, collodion like skin, ectropia of the eyes, and multiple dysmorphic features, including malformed and low set ears, a flattened nasal bridge, and a highly arched palate. He had pronounced hepatosplenomegaly, contractures of the knees and interphalangeal joints, and tight shiny fingers (fig 1A). Histological examinationof multiple organs revealed Gaucher cells. The diagnosis of Gaucher disease was confirmed enzymatically, with a leucocyte glucocerebrosidase activity of 9.5 pmol/min/mg (normal,600–3200).

CASE 2:

This child was the sister of case 5. Amniocentesis established that the fetus was glucocerebrosidase deficient. The parents elected to continue the pregnancy, and she was born at 37weeks' gestation, weighing 2560 g, with collodion skin and hepatosplenomegaly. The skin condition resolved during the 1stmonth of life, but she developed neurological abnormalities and died at age 9 months.[4]

Pathogenesis:

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

Treatment:

Enzyme replacement therapy is considered first line treatment for patients with type 1 Gaucher diseasein the 2014 draft joint proposal on treatment of Gaucher disease by European Medicine Agency(EMA) and the FDA.10 Enzyme replacement therapy can also be used for treatment of visceral symptoms in other types of Gaucher disease.1,2 Several studies have shown enzyme replacement therapy to be beneficial in relieving symptoms of type 1 disease including reversing visceral and hematologic manifestations.2,4.Enzyme replacement therapy may reduce systematic symptoms of type 2 and 3 Gaucher disease but is not effective for reducing or reversing neurologicsymptoms.8 While enzyme replacement therapy may reverse inflammation and the

hematologic effects of Gaucher disease, it has no impact on complications ,such as cell death, necrotic tissue injury, skeletal collapse, and tissue fibrosis. Delay and prevention of these complications can be managed by starting enzyme replacement therapy as soon as possible. Enzyme replacement therapy works by supplementing the deficient or defective acid β-glucosidase to break down GLC into glucose and ceramide, which accumulates in macrophages in the absence of acid β-glucosidase.

Long-term effects of imiglucerase were examined in a retrospective study using data collected in the International Collaborative Gaucher Group Registry including 757 type 1 Gaucher disease patients who received either imiglucerase or alglucerase for 10 years. Miglustat is given in the dose of 100 g three times a day orally and has little role in neurological or bone disease, it also takes much longer than ERT to control the organomegaly or cytopenia. It is approved for use in adults only and not in children. Adverse effects include transient weight loss and GI side effects especially flatulence and diarrhea and intolerance to milk with exacerbation of pre-existing tremors Eliglustat tartarate is an oral drug inhibiting production of glucosylceramide. It has been shown to be of benefit in improving organomegaly and cytopenias in patients of GD1 in phase 2 studies in adults and is being investigated for use in children. Bone marrow transplantation has the potential for cure of GD. Bone marrow transplant was the only treatments available prior to introduction of ERT. Since the availability of effective ERT bone marrow transplant is no longer the treatment of choice.[5,6,7]

CONCLUSION

Gaucher disease is a progressive lysosomal storage disease resulting from an autosomal recessive mutation in the 1q21 chromosome. Psychological counseling is important for patients and families with GD given the likelihood of incapacitating symptoms and chronic nature of the disease. When the parents are heterozygous carriers of one of the common alleles, parental genotype can provide some guidance for prenatal counseling, each child will have a 25% chance of having the disease. The severity of the disease in the child will depend on the parental genotype and counseling can be done accordingly. Consanguineous marriages need to be discouraged.

REFERENCES

1. http://www.checkorphan.org/diseases/gaucher-disease.
2. www.ncbi.nlm.nih.gov/pmc/articles/PMC4017182.
3. http://www.gaucherdisease.org/gaucher-diagnosis-treatment.

4. D L Stone,W F Carey, J Christodoulou, D Sillence, P Nelson,M Callahan, N Tayebi, E Sidransky, Arch Dis Child Fetal Neonatal Ed 2000;82:F163–F166, http://fn.bmj.com/ on July 4, 2017 - Published by group.bmj.com.
5. Alison Van Rossum, Megan Holsopple, PharmD, Hosp Pharm 2016;51(7):553–5632016
6. Thomas Land Publishers, Inc.www.hospital-pharmacy.comdoi: 10.1310/hpj5107–553.
7. O Goker-Alpan, R Schiffmann, M E LaMarca, R L Nussbaum, A McInerney-Leo, E Sidransky, J Med Genet 2004;41:937–940. doi: 10.1136/jmg.2004.024455.
8. Andrew J Walley, M Luiza Barth, Ian Ellis, Anthony H Fensom, Ann Harris, Med Genet 1993; 30: 280-283, http://jmg.bmj.com.