

## Report of Four Children with Gaucher Disease and Review of Literature

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### **Abstract**

Gaucher Disease (GD) is the most common type of Lysosomal Storage Disorder and it is divided into three distinct subtypes. The authors here report four different cases of Gaucher Disease, with varying clinical manifestations, and the diagnosis of each established by the low level of Beta-Glucosidase enzyme as well as genetic DNA testing.

The study also highlights the importance of early diagnosis of the disease in order to initiate the appropriate therapeutic management to help prevent further progression of the disease.

**Key Words:** Children, Case report, Gaucher disease, Lysosomal storage diseases.

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## 1- INTRODUCTION

Gaucher disease is a genetic disorder that affects different organs and tissues of the body. It is characterized by a spectrum of phenotypes that can present with varying degrees of severity. The presentation depends on the type of the disease. Patient may present with hepatosplenomegaly, easy bruise during childhood period and in some infants with swallowing difficulties, feeding disorder, respiratory disease, seizure and death.

Gaucher disease is divided into three subtypes according to the presence or absence-non-neuronopathic (GD Type 1); or presence - acute neuronopathic (GD Type 2) and chronic neuronopathic (GD Type 3) of neurological symptoms.

We are presenting 4 cases from 2 families with GD with review of literature.

## 2- CASE REPORTS

### 2-1. Case 1: HL

A 3-year-old female was found to have splenomegaly on her well child visit, but was otherwise asymptomatic. Physical examination significant, for splenomegaly about 4-5 cm below the costal margin and palpable liver edge. Her CBC showed thrombocytopenia 117, LFT with AST of 40, ALT 13, PTT 36 and negative for EBV. Platelet aggregation study was normal. She had an abdominal ultrasound that confirmed splenomegaly. Doppler study did not show extra hepatic portal obstruction. Endoscopy revealed small esophageal varices, but normal biopsies. Follow up visits indicated normal growth and was fully asymptomatic.

Her family history was positive for her brother with splenomegaly and thrombocytopenia. Genetic consulted for possible Gaucher disease. Her Beta-glucosidase activity was 0 (ref range > 8.7), ACE was 226 (ref range 13-100), Chitotriosidase was 5,652 (ref range 4-

120) and TRAP was 52 (ref range 3-10). Her results were consistent with Gaucher disease. An MRI of the extremities showed abnormal marrow signal with mild widening of the femoral metaphyses (Erlenmeyer flask sign). DNA revealed one copy of the N370S mutation done by LabCorp (8 mutations screened).

Patient was started on Cerezyme (Imiglucerase) 60 IU/kg, IV every 2 weeks. She was followed in genetic and development clinic every 6 months. One year after treatment, her present physical examinations with no palpable spleen or liver. Her platelets 153,000/uL

### 2-2. Case 2: NL

An 8-year-old male who is brother of case one was seen in GI clinic, because of splenomegaly. He has been seen and followed in Hematology clinic for his thrombocytopenia. He was an active boy in karate sport, having occasional bruise, and his physical examination with protruded abdomen and spleen 10 cm below left costal margin. His laboratory tests CBC, Hb 11.1, platelets 65,000 u/L. Had normal platelet function test. LFT, AST 44, ALT 29, and normal PT and PTT. Abdominal ultrasound revealed hepatosplenomegaly. Doppler study no extra hepatic portal obstruction or hypertension. His upper endoscopy was normal with no esophageal varices. Since his sister had similar issues, a Genetics referral was made. Laboratory genetic tests showed his Beta-Glucosidase activity, 0. ACE was 423, Chitotriosidase was 18,358 and TRAP was 111.6. His results were consistent with Gaucher disease.

Once the diagnosis was established, MRI of the extremities was done and that revealed mild diaphyseal bone marrow signal abnormality within bilateral femurs. DNA revealed one copy of the N370S mutation. He was started on Cerezyme (Imiglucerase) 60 U/Kg, IV every 2 weeks. He was followed in the genetic and

metabolic clinic every 6 months. One year after treatment, his physical examinations with reduced abdominal size and his spleen to 8 Cm. His platelets increased to 82,000u/L

### **2-3. Case 3: MS**

An 8-year-old, previously healthy, female was noted to have an enlarged spleen on a routine well child check. Her physical exam was significant for a spleen extending in to the pelvis; her liver edge was just palpable. She had multiple marks of bruising on her extremities. Her primary physician checked her blood count as CBC, Hb 11.5, Platelets 66,000 u/L. The CMP, LFTs, EBV and CMV were normal. Her abdominal ultrasound showed splenomegaly, and normal liver size. She was referred to GI clinic at this time. A Doppler study showed patent portal vein with appropriate flow direction and was suggestive of the possibility of portal hypertension. She did not have extra hepatic portal obstruction. She was referred to genetic and metabolic clinic.

She was diagnosed with Gaucher disease once her Beta-Glucosidase activity level was 2, Chitotriosidase was 20,267 and the platelet count at that time was 85000. Her LFTs remained within normal limits. Her DNA testing revealed two mutations of Asn409Ser and Asn 409Lys.

She was also followed up with a MRI femur that showed bilateral hyper intense bone marrow signal, more on the left than the right. She was started on Cerezyme (Imiglucerase) 60 U/Kg, IV every 2 weeks. She has been followed in genetic and metabolic clinic every 6 months

1.5 years after treatment her Physical examination with spleen reduced to 2 cm below left costal margin and no hepaticomegaly. Her platelets increased to 153,000

### **2-4. Case 4: ES**

A 14- year- old female with no known past medical history was seen and evaluated at

the Genetics clinic because her sister was recently diagnosed with Gaucher disease. She had remained healthy with no complaints of fatigue, easy bruising or growing bone pains; and her physical exam was completely normal with no hepatosplenomegaly. She had just recently started menarche. Laboratory tests Hb 12.7, Platelets 146,000, ALT and AST were normal. Her Beta-Glucosidase testing revealed no activity, and a repeat enzyme testing confirmed it with 0 activity levels. Chitotriosidase was 5,539, TRAP was 32.7 and ACE was 282. Her DNA testing confirmed two mutations in exon 9, Asn409Ser and Asn409Lys.

An MRI of the abdomen showed an enlarged liver and spleen. MRI of femurs showed bilateral Erlenmeyer flask deformity. There was an additional increased T2 signal in the left femur consistent with an infarct. There were areas of hypointensity on T1 also. Bone burden was estimated at 3. She was started on Cerezyme 60 units/Kg every 2 weeks IV. 1.5 year after treatment, is doing well, asymptomatic and her platelets raised to 178,000.

## **4- DISCUSSION**

### **4-1. Epidemiology**

Gaucher disease is one of the most common Lysosomal Storage Disorder and it is present in approximately 1:20,000 live births. GD Type 1 is more prevalent in individuals of Ashkenazi-Jewish descent; however, most patients with GD Type 1 are not Jewish. In the Ashkenazi-Jewish population, approximately 1:450 have GD Type 1 and 1:12 are carriers. Of note, Types 2 and 3 are less common, but pan-ethnic in their distribution. GD Type 2 (or infantile cerebral or acute neuronopathic GD) has an estimated incidence of 1:150,000. The subtype is not prevalent due to the short life span of patients. GD Type 3 (or juvenile neuronopathic GD) has an estimated incidence of 1:200,000. The

prevalence is higher than GD Type 2, because of longer survival of the patients.

#### **4-2. Pathogenesis**

Glucocerebroside (also, called glucosylceramide) is the major substrate for glucocerebrosidase (also, called glucosylceramidase or acid-beta glucosidase, GBA) that ordinarily degrades it to glucose and lipid components to be stored within the lysosomes of cells. In GD, also known as glucocerebrosidase deficiency, there is an inborn error of metabolism that affects recycling and storage of these cellular glycolipids. The glucocerebroside then accumulates in the cells of the macrophage-monocyte system (primarily in the bone marrow, lungs, liver and spleen) and gives rise to the characteristic Gaucher cells. Depending on the organs involved, signs and symptoms vary accordingly.

Glucocerebroside accumulation contributes to fatigue, bleeding and easy bruising (due to pancytopenia from bone marrow and splenic sequestration), distended abdomen (due to hepatosplenomegaly), diffuse infiltrative pulmonary disease, and severe bone pain and pathologic fractures (due to bone marrow infiltration and macrophage-produced cytokines). Ichthyosis in GD Type 2 is due to the ceramide-to-glucoceramide ratio disruption in the epidermal layer of the skin. The neurologic involvement in GD Types 2 and 3 appears to be related to the accumulation of cytotoxic glucosylsphingosine in the brain and/or to Neuroinflammation.

#### **4-3. Clinical manifestation**

GD presents with variable signs, symptoms, severity and progression, depending on the type and organ system involvement. Generally, Type 1 is differentiated from Type 2 and 3 by lack of neurologic involvement, while Type 2 and 3 are differentiated by the length of time of

CNS involvement, that is acute versus chronic respectively.

##### **4-3-1. Type 1: Non-neuronopathic form**

Onset can be anytime from childhood to adulthood. Includes hematologic, skeletal, gastrointestinal and pulmonary manifestations, although splenomegaly is the most common presenting sign. Spleen can enlarge from 5 to 70 times its normal size, while the liver increases relatively less, by only 2 to 3 times. Affected children can grow poorly due to the increased energy expenditure by the enlarged spleen. Increased rates of malignancies have also been reported. Progression of disease is slow, and life span can be normal to shortened. Genetic mutation associated is the c.1226A>G (N370S allele).

##### **4-3-2. Type 2: Acute neuronopathic form**

Onset is generally in the first year of life. Includes minimal hematologic and skeletal involvement, but has more pronounced neurologic symptoms of generalized seizures, oculomotor dysfunction, swallowing impairment and hypertonia, dermatologic symptoms of ichthyosis (also, known as collodion baby) in addition to the hepatosplenomegaly. Progression of disease is rapid and death is usually before 2 years of age. There are many genetic mutations associated with Type 2.

##### **4-3-3. Type 3: Chronic neuronopathic form**

It has a later onset than Type 2. Progression is variable and life span is shortened (second to fourth decade). There are further three subtypes of GD Type 3 but the overlap is marked.

##### **4-3-3-1. Type 3a**

Is characterized by earlier development of neurological symptoms including myoclonus, ataxia, strabismus and

progressive dementia; the genetic mutation associated is the c. 1448T>C (L444P allele).

#### **4-3-3-2. Type 3b**

Is characterized by massive hepatosplenomegaly, severe anemia and skeletal findings, and CNS involvement primarily includes supranuclear gaze palsy.

#### **4-3-3-3. Type 3c**

Is characterized by cardiovascular calcification, corneal opacities and supranuclear gaze palsy, with minimal visceral and bone disease. It is rare and the patients homozygous for D409H mutation (c. 1342>C allele) usually exhibit its unique phenotype.

It is important to note that several studies have mentioned neurologic features in Type 1 as well but, they are very distinguished from Type 2 and 3. Hence, one must understand that GD and its subtypes come with many overlaps, and that GD is a spectrum of a disease manifestations rather than a disorder with three distinct subtypes.

### **4-4. Diagnostic findings**

#### **4-4-1. Lab findings**

It is common to see thrombocytopenia and anemia on initial blood count, minor elevations of liver enzyme levels, elevated serum angiotensin-converting enzyme, elevated acid phosphatase, hyperferritinemia and increased incidence of polyclonal and monoclonal gammopathy on serum protein electrophoresis. There is also, the presence of Gaucher cells, that include macrophages with glycolipids that have a characteristic histologic appearance of wrinkled tissue paper.

#### **4-4-2. Radiologic findings**

Although radiologic findings are not specific for GD, they do help narrow down the differential diagnosis. Findings include

Erlenmeyer flask deformity of the distal femur caused by relative constriction of the diaphysis and flaring of the metaphysis, presence of fractures and lytic lesions on plain films, MRI findings of marrow infiltration and bone infarction, and osteopenia on DEXA scans.

### **4-5. Diagnosis**

The gold standard for GD diagnosis is the measurement of Glucocerebrosidase enzyme activity in peripheral leukocytes. In Type 1 patients, it is reduced by 10%-15% of normal activity; whereas in GD Type 2 and 3, it reduced even further. However enzyme activity in heterozygote carriers and normal individuals shows considerable overlap.

Molecular genetic testing also, aids in not only confirming the diagnosis, but also providing prognostic information and helps in identifying carriers among family members. Bone marrow aspiration findings of aggregates of Gaucher cells is helpful but, not always necessary in making the diagnosis.

### **4-6. Treatment**

The goals of treatment are elimination of symptoms, prevention of irreversible complications, and improvement of health and quality of life. Enzyme replacement therapy (ERT) is the basis of all therapeutic plans and is recommended for all symptomatic children. IV recombinant Glucocerebrosidase is the enzyme used and the therapy is individualized.

FDA approved Imiglucerase alfa in 1994, Velaglucerase in 2010 and Taliglucerase most recently in 2012 for long term ERT. It is given every two weeks or every other week at high doses, and it has shown to be quite effective in Types 1 and 3. It has shown to be effective in ameliorating hematologic, visceral and skeletal manifestations, although it has not been successful in reversing the neurological and lung manifestations.

Another modality of management includes substrate reduction therapy (SRT) with Miglustat for patients who cannot take ERT due to anaphylactic reactions. This was FDA approved in 2003 for mild to moderate cases of GD Type 3 because of its ability to cross the blood-brain barrier. The recommended dose is 100 mg orally three times per day. Another SRT, Eliglustat, has recently begun phase 3 clinical trials and will likely get FDA approval soon. Eliglustat, however, does not penetrate the blood-brain barrier.

Bone marrow transplant (BMT) and splenectomy may also, be considered, although the availability and efficacy of ERT has limited their indications. BMT has some effect on limiting the neurological deterioration of GD Type 3, but in general it poses high risk for significant morbidity and mortality. Splenectomy may be indicated on rare occasions where other methods have failed to control life-threatening thrombocytopenia and bleeding. In recent years, more studies have been done in animals, evaluating gene therapy and chaperone therapy, as options for combination treatment strategies.

## 5. CONCLUSION

Gaucher disease, and all Lysosomal Storage Disorders for that matter, presents a diagnostic challenge to all healthcare providers. It requires a high index of suspicion do diagnose a patient with Gaucher disease, considering its vast spectrum of presentations as well as rarity in occurrence.

Basic knowledge of the Storage Disorders and a general understanding of the continuum of clinical manifestations and a methodical diagnostic approach would help correctly diagnose not only Gaucher ,but any Lysosomal Storage Disease. It is important to diagnose Gaucher disease correctly and early so that treatment plans and genetic counseling can be initiated,

and a better prognosis and outcome can be anticipated.

## 6- CONFLICT OF INTEREST

The authors had not any financial or personal relationships with other people or organizations during the study. So there was no conflict of interests in this article.

## 7- ABBREVIATION

**CBC:** Complete blood count,  
**LFT:** Liver function test,  
**ALT:** Alanine transaminase,  
**PTT:** Partial thromboplastin time,  
**EBV:** Epstein–Barr virus,  
**ACE:** Acute Care for Elders,  
**TRAP:** Twin reversed arterial perfusion,  
**MRI:** Magnetic resonance imaging,  
**IV:** Intravenous,  
**GI:** Gastrointestinal,  
**Hb:** Hemoglobin,  
**LFTs:** Liver function tests,  
**AST:** Aspartate aminotransferase,  
**PT:** Partial thromboplastin,  
**CMP:** Comprehensive Metabolic Panel,  
**CMV:** Cytomegalovirus,  
**GD:** Gaucher disease,  
**CNS:** Central nervous system,  
**FDA:** Food and Drug Administration.

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