Gaucher Disease in Six Filipino Children: a Case Series

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ABSTRACT

Six Filipino children with Gaucher disease are presented. All patients manifested marked hepatosplenomegaly, hematologic and skeletal abnormalities. The diagnosis was confirmed through bone marrow aspiration by demonstration of the characteristic 'Gaucher cells' and by leukocyte enzyme assay indicating deficient acid beta-glucosidase. Mutation analysis of the GBA gene was done in one patient. Two patients are receiving enzyme replacement therapy.

Key Words: Gaucher Disease, acid beta-glucosidase, glucocerebroside, hepatosplenomegaly, erlenmeyer flask deformity, enzyme replacement therapy

Introduction

Gaucher disease was originally described in 1882 by a French dermatologist, Philippe Charles Ernest Gaucher, who reported the case of a patient who had massive hepatosplenomegaly and findings suggestive of leukemia but did not become ill or die. Gaucher believed the disease to be a "benign" leukemic disorder. In 1924, Epstein described the presence of a lipid, cerebroside, in the cells of patients with this condition and declared it to be a lipid storage disorder. In addition, the bone lesions (necrotic segments and osteopenia), which in many patients are quite striking, were first defined at almost the same time. Groen, in 1948, was apparently the first to describe the genetic transmission of the disorder, that being autosomal recessive. In a landmark discovery in 1965, Brady and co-workers defined the enzyme deficiency as a failure in the synthesis of glucosylceramide hydrolase (acid beta-glucosidase, also known as glucocerebrosidase), which results in the accumulation of glucosylceramide (or glucocerebroside), a normal intermediate in the catabolism of globoside and gangliosides, in lysosomal bodies of monocyte derived macrophages in tissues of the reticuloendothelial system.[1]

Gaucher disease is a pan-ethnic genetic disorder with an estimated general prevalence between 1:7,750 and 1:10,000, although much more common in Ashkenazi Jewish populations.[2] It is characterized by a remarkable degree of variability in its clinical signs and symptoms, ranging from severely affected infants to asymptomatic adults. Many patients suffer from anemia, bone damage, hepatomegaly and splenomegaly, while a few develop severe central nervous system damage.

Although Gaucher disease is now understood to form a continuum of phenotypes, the classical classification of Gaucher disease into three major clinical subtypes is useful in determining prognosis and management. Type 1 is non-neuronopathic, while Type 2 is acute neuronopathic (infantile) which has an infantile onset of severe central nervous system involvement with predominant brainstem involvement, strabismus and swallowing impairment, and death in early childhood. Type 3 is subacute neuronopathic which has a more indolent neurologic course, from isolated childhood onset non-progressive oculomotor apraxia with aggressive systemic disease, to progressive central nervous system involvement with myoclonus and dementia in childhood, adolescence or early adulthood.

We present six Filipino children with Gaucher disease. One had Type 2 acute neuronopathic infantile type while the rest had the Type 1 non-neuronopathic type.

Clinical Cases

Patient 1 was a female born at term by spontaneous vaginal delivery after an uncomplicated pregnancy to non-consanguineous Filipino parents. Her birth weight was 3.5 kg and her neonatal course was unremarkable. The mother had two previous pregnancies which bore normal children. The second child died at 1 year old due to leukemia.

Patient 1was apparently well until 1 year of age when she had gradual abdominal enlargement and pallor. A diagnosis of leukemia was considered. However, bone marrow aspiration (BMA), alpha fetoprotein and liver function tests were normal. Liver biopsy revealed diffuse hepatocyte ballooning, focal mild fibrosis and paucity of portal triads. She was lost to follow up and returned for a re-evaluation at 3 years of age for respiratory distress with wheezing and rales over both lung fields. The abdomen was globular with the liver edge palpable 8 cm below the right costal margin and the splenic edge palpable 15 cm below the left costal margin. Digital clubbing was noted. She had bilateral clonus and hyperactive deep tendon reflexes on the lower extremities. Ophthalmologic examination was normal. Repeat BMA revealed numerous histiocytes with characteristic "crumpled silk" morphology, consistent with Gaucher disease. Acid beta-glucosidase activity was 310

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pmol/min/mg protein (n.v. 600-3200, National Referral Laboratory, Women's and Children's Hospital, Adelaide, Australia), in the range observed in patients with Gaucher disease. Her clinical course was characterized by frequent hospital admissions for respiratory infections and anemia. Management included antibiotics, blood transfusions and analgesics. She died at the age of 4.5 years due to respiratory failure secondary to severe pneumonia.

Patient 2, was a female born at term, first of twins, to non-consanguineous Filipino parents. Her mother died due to complications during delivery and she was adopted by a maternal aunt. At 2.6 years of age, she presented with abdominal enlargement, pallor, nose bleeding and bone pains. Acute leukemia and beta thalassemia were considered during various consultations with multiple doctors. Bone marrow aspirate and biopsy showed hypercellular marrow with numerous histiocytes strongly suggestive of Gaucher disease.

When seen at our institution at 3.5 years old, her height was 93 cm (10^{th}-25^{th} percentile) and weight was 13.5 kg (10^{th}-25^{th} percentile). She was pale and had hematoma in the lower extremities and petechiae over the eyelids. The liver was palpable 10 cm below the right costal margin and the spleen was 14.5 cm below the left costal margin. Neurologic examination was normal. Acid beta-glucosidase activity was low at 390 pmol/min/mg protein (n.v. 600 – 3200, National Referral Laboratory, Women's and Children's Hospital, Adelaide, Australia). Molecular analysis of the *GBA* gene showed the patient to be a compound heterozygote, with the p.L444P mutation in one allele and the p.P319A mutation in the other. Patient 2 was started on enzyme replacement therapy (ERT) with imiglucerase (Cerezyme, Genzyme Therapeutics, Mass., USA) at 3 years 8 months and after a year, the liver and splenic sizes decreased to 6 and 8 cm respectively below the costal margins. Anemia and thrombocytopenia resolved. She had significant gains in weight and height and there was remarkable improvement in her quality of life.

Patient 3, the twin sister of Patient 2 was brought to medical attention at 3 years of age. Although asymptomatic, her physical examination revealed that her liver was palpable 4.5 cm below the right costal margin and the spleen was palpable 5 cm below the left costal margin. A hematoma in the lower extremity was noted. Neurologic examination was normal. A presumptive diagnosis of Gaucher disease was made and a plan of management was discussed with her biological father. However, it was only at the age of 4 years that the diagnostic evaluation was completed. By this time, patient 3 was anemic and thrombocytopenic, with liver and spleen markedly enlarged to 9 cm and 14 cm below the right and left costal margins, respectively.

Bone marrow aspiration showed the characteristic "Gaucher cells". She had low leukocyte acid beta-glucosidase activity of 0.88 nmol/mg/prot/hr (normal range 4.7->5.10, National Taiwan University Hospital, Department of Medical Genetics, Taiwan) compatible with Gaucher disease. Prior to the commencement of ERT, supportive medical treatment for hematologic abnormalities and bone pains were given. One year after the start of ERT, the anemia and thrombocytopenia resolved.

Patient 4, was a male born at term to non-consanguineous Filipino parents. Abdominal enlargement and pallor were noted at 1 year of age. Initial BMA was interpreted as myelodysplastic syndrome, for which he underwent chemotherapy for a month. However, no significant improvement was noted prompting consultation with another physician who gave a diagnosis of thalassemia syndrome. Due to the progressive hepatosplenomegaly, a second BMA was done at 3 years of age: this showed the characteristic "Gaucher cells". Significant findings on physical examination were pallor, a hematoma in the left supraorbital area, petechiae on the extremities, liver edge palpable 12 cm below the right costal margin and spleen palpable 12 cm below the left costal margin. Low beta-glucosidase activity of 1.23 nmol/mg/prot/hr (4.7 ->5.1 National Taiwan University Hospital, Department of Medical Genetics, Taiwan) was compatible with Gaucher disease.

Patient 4 was started on ERT (imiglucerase) at the age of 4 years old. Unfortunately, he was admitted for pneumonia around the time when he was due for his 4^{th} infusion. He eventually succumbed to a severe nosocomial pneumonia.

Patient 5, was a female born at term to a non-consanguineous Filipino couple. She was well until 2 years of age when abdominal enlargement and pallor were first noted. She was brought to several medical facilities and was given a diagnosis of blood dyscrasia. Initial work-up showed that she was anemic and thrombocytopenic, with prolonged prothrombin and partial thromboplastin times. CT scan of the abdomen revealed hepatomegaly with focal areas interpreted as "fatty infiltration" and marked splenomegaly with areas of infarction. She was lost to follow up for three years but returned with similar symptoms at 5 years old. On physical examination, she was noted to be irritable and pale. A grade 3/6 pansystolic murmur was heard over the apex. The liver and spleen were massively enlarged, extending to the inguinal areas. There were no signs of bleeding into the skin or subcutaneous tissue. Neurological examination was normal. Electrocardiogram showed left ventricular hypertrophy with non specific T wave changes. 2D echocardiography showed good left ventricular systolic function and trivial pulmonary and tricuspid regurgitation. Bone marrow aspiration showed the characteristic "Gaucher cells". She underwent splenectomy and had a stormy clinical course after the procedure complicated by respiratory acidosis, nosocomial infection, and liver function derangement manifested by hypoalbuminemia, elevated liver enzymes, coagulopathy and jaundice. Fortunately, she recovered and was discharged improved after a month.

Patient 6, was a female born at term to a consanguineous Filipino couple (parents are third cousins). She was the youngest of five siblings and no other family member was known to have a similar condition. She was apparently well until 8 months of age when an abdominal mass was first noted with no associated signs and symptoms. No medical consultations were made until she was 6 years old and the

abdomen was noted to be enlarged. Physical examination findings showed a short and frail girl who had multiple cervical lymphadenopathy and hepatosplenomegaly. The liver was palpable 5 cm below the right costal margin with obliteration of the Traube's space. Neurologic examination was normal. Bone marrow aspiration revealed Gaucher cells. She was lost to follow up.

Discussion

The clinical manifestations of Gaucher disease result from engorged macrophages with accumulated glucocerebroside, causing enlargement and dysfunction of the liver and spleen, displacement of normal bone marrow by storage cells, and damage to bone leading to infarctions and fractures. Involvement of other organs such as the central nervous system and lungs can contribute to the overall clinical picture and prognosis.

All patients had severe hepatosplenomegaly, hematologic problems and skeletal abnormalities. Patient 1 had severe central nervous system involvement manifested by delayed psychomotor development, infantile onset seizures and pyramidal signs, therefore classifying her as having Type 2 Gaucher disease The rest had either definite (cases 2-5) or probable (case 6) Type 1 Gaucher disease.

Type 1 Gaucher disease has a broad spectrum of severity.[3] At one extreme, individuals are asymptomatic and may be diagnosed as late as the 8th or 9th decade of life. Some are ascertained only in the course of family or population surveys. At the opposite extreme of Type 1 Gaucher disease are children with massive hepatosplenomegaly associated with severe abnormalities of liver function, pancytopenia and extensive skeletal abnormalities. Some patients with severe visceral enlargement have no obvious skeletal symptoms while some with severe bone disease have minimal visceral disease. In other patients, both visceral and skeletal involvement are approximately equal in severity. Patients 2, 3, 4 and 5 had similar disease manifestations in terms of the severity of their visceral and skeletal abnormalities. Patient 6 however may have had a milder form of the disease because of the slower progression of the disease in spite of the earlier onset. Her hepatosplenomegaly and hematologic manifestations were not as severe as the other patients.

Hepatomegaly is always present in patients with Gaucher disease. Frank hepatic failure and /or cirrhosis with portal hypertension and ascites are uncommon but do occur in a small percentage of patients. Minor abnormalities of liver function tests, (as was seen in Patients 1, 2, 4 and 6) are commonly present, even in mildly affected patients.[2,4]

Splenomegaly is present by physical examination in all but the most mildly involved, and can be massive. Even in those who are otherwise asymptomatic, it is commonly the presenting sign. Splenic infarction is not uncommon, but smaller infarcts can be asymptomatic. Large infarcts can present with an acute abdomen, fever, metabolic acidosis and hyperuricemia.[2,4] Patient 5 is the only one in our series in whom splenic infarcts were documented, but she did not present with acute abdomen.

Bleeding is a common presenting symptom in patients with Gaucher disease. Thrombocytopenia is the most common peripheral blood abnormality. It may result from hypersplenism, splenic pooling of platelets, marrow infiltration or infarction. Anemia is usually mild-moderate but occasionally is quite severe with hemoglobin levels as low as 5 g/dL. Leukopenia may occur in some patients. These

Table 1. Summary of clinical features of the patients

Disease Characteristics	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Disease type	Type 2	Type 1	Type 1	Type 1	Type 1	Type 1
Age at onset of symptoms	1 y/o	1 y/o	3 y/o (when initially seen)	1 y/o	2 y/o	8 months old
Hematologic manifestations:						
Anemia	+	+	+	+	+	+
Thrombocytopenia	+	+	+	+	+	-
Hepatomegaly	+	+	+	+	+	+
Abnormal LFTs	+	+	-	+	Not initially taken	-
Splenomegaly	+	+	+	+	+	+
Skeletal abnormalities:						
Erlenmeyer flask	+	+	+	+	+	-
Osteopenia	+	-	-	-	-	+
Fractures	-	-	-	-	-	-
Lytic lesions	-	-	-	-	+	-
Pulmonary involvement	+	-	-	-	-	-
CNS involvement	+	-	-	-	-	-
Alive	No; died 4.5 yr	Yes	Yes	No; died 4 yr	Yes	Not known

changes are probably due to a combination of increased splenic sequestration and decreased production due to bone marrow failure because of the replacement of the marrow by Gaucher cells.[2,4]

Hematologic abnormalities, consisting primarily of anemia and thrombocytopenia, were seen in all the patients reviewed in this series, although Patient 6 had less severe hepatosplenomegaly and hematologic manifestations

The skeletal manifestations of Gaucher disease can be totally debilitating. The most prevalent abnormality, noted in approximately 80% of patients, is failure of the distal part of the femur and the proximal part of the tibia to remodel, resulting in the classic Erlenmeyer flask appearance. All patients except patient 6 had this classic x-ray finding. Episodic excruciating painful "bone crisis" occurs in 20-40% of patients and can mimic osteomyelitis.[1-2,4] Other findings include osteopenia, lytic lesions and fractures, osteomyelitis, osteonecrosis and progressive joint destruction due to avascular necrosis. Patients 1 and 6 had x-ray findings of osteopenia. Patient 5 had lytic lesions.

Pulmonary failure is one of the most serious consequences of Gaucher disease. Clinically significant pulmonary involvement in Gaucher disease is probably low (<5%) but interstitial lung disease, alveolar-lobar consolidation and pulmonary hypertension have been reported. Right to left intrapulmonary shunting secondary to liver disease (hepatopulmonary syndrome) has been reported, usually accompanied by clubbing.[2,4] Patient 1 had no evidence of pulmonary hypertension on 2D echocardiography and her recurrent dyspnea and clubbing could have been due to hepatopulmonary shunting.

Central nervous system involvement for Types 2 & 3 Gaucher disease manifests with oculomotor abnormalities, bulbar signs including stridor, strabismus and swallowing difficulty, and pyramidal signs including opisthotonus, head retroflexion, spasticity and tremors. Generalized tonic-clonic seizures and progressive myoclonic epilepsy have been observed in some patients. Dementia and ataxia have been observed in the latter stages of chronic neurologic disease. The underlying neuropathology is cell death rather than lysosomal storage of glucocerebrosides.[2,4]

In this series, Patient 1 can be categorized as having the neuronopathic type of Gaucher disease based on the clinical findings. She presented with seizures and developmental delays in all domains particularly in motor and language skills, and had long tract signs consisting of bilateral clonus and hyperreflexia; clinically her classification fits with Type 2-3 rather than classical Type 2.

CNS symptoms can be occasionally observed as a secondary manifestation of true type 1 disease. Neurologic complications such as spinal cord or nerve root compression may occur secondary to bone disease (i.e. severe osteopenia with vertebral compression, or emboli following long bone fracture) or coagulopathy (i.e. hematomyelia).[4]

The most efficient and reliable method of establishing the diagnosis of Gaucher disease is the assay of leukocyte acid beta-glucosidase activity. The typical individual with Type 1 Gaucher disease will have enzyme activity that is 10% to 30% of normal values. Children with Type 2 Gaucher disease will typically have values less than 10%. Patients 1,2,3 and 4 all had low acid beta-glucosidase activities, in the range compatible with Gaucher disease. Because of the wide range of the normal value quoted for patients 1 and 2, it is difficult to say whether Patient 1, who seemed to have a neuronopathic type of Gaucher disease, had enzyme activity <10%. Patient 2 had a similar level to Patient 1, and she did not seem to have a neuronopathic type of Gaucher although it could still be early to conclude this as her mutation analysis showed one mutation (p.L444P) which is associated with a neuronopathic phenotype. Consequently, it has been suggested that the activity of acid beta-glucosidase as measured by an artificial substrate in leukocytes or cultured skin fibroblasts is not a reliable predictor of clinical severity.[5]

Patients may first be suspected of having Gaucher disease following a bone marrow aspiration for the evaluation of chronic anemia, thrombocytopenia or splenomegaly. Bone marrow examination reveals the presence of lipid engorged macrophages ("Gaucher cells") characterized by a fibrillary, "crumpled silk" appearance to the cytoplasm and an eccentrically placed nucleus. Although these lipid laden macrophages in marrow are considered typical for Gaucher disease, they can be similar in appearance to other lysosomal storage diseases or the "pseudo-Gaucher" cells observed in several hematologic malignancies like leukemia. The definitive confirmation of the disorder must be based on the activity of acid beta-glucosidase in leukocytes or fibroblasts.[5]

The gene encoding for acid beta-glucosidase (*GBA*) has been cloned and mapped to chromosome 1q2.1 and more than 300 different mutations in *GBA* have been described.[6] Most of the disease alleles in Gaucher disease are missense mutations that lead to the synthesis of beta-glucosidase with decreased catalytic function or stability. Four mutations (p.N370S, p.L444P, c.84insG, IVS2+1G>A) account for the majority of disease causing alleles. In the Ashkenazi Jewish population, these four alleles account for 90% of the disease causing alleles. In non- Jewish populations, these four alleles account for about 50-60% of disease-causing alleles. Non-Jewish individuals with Gaucher disease tend to be compound heterozygotes with one common and one rare or unique mutant allele.[2,4,5] Presence on one allele of the most common mutation p.N370S is protective of neurologic involvement. Some mutations such as c.84insG and IVS2+1G>A are associated with more severe disease manifestations when appearing as compound heterozygotes with N370S, but when occurring in the homozygous state are not compatible with life. Other mutations such as p.L444P are associated with severe non-neurologic disease when occurring as compound heterozygote with p.N370S, but when occurring in the homozygous state are usually predictive of neurologic disease.[6]

Patient 2 had mutation analysis revealing a compound heterozygote for p.L444P and a unique mutant allele p.P319A, which has not been previously reported in other populations.

Enzyme replacement therapy (ERT) has revolutionized the treatment of Gaucher disease. It is based on the provision of sufficient exogenous enzyme to overcome the block in the catabolic pathway and effect the clearance of the stored substrate, glucosylceramide. Imiglucerase (Cerezyme) is a recombinant glucosylceramidase enzyme preparation based on the human *GBA* gene sequence, with subsequent modification of the protein product to expose the alpha-mannosyl residues, which enhances uptake by the macrophage mannose-6-phosphate receptors. Regular intravenous infusions of imiglucerase (usually fortnightly) have been demonstrated to be safe and effective in reversing the features resulting from hematologic and visceral (liver/spleen) involvement, including hepatosplenomegaly, skeletal manifestations including bone pain, marrow infiltration, osteopenia, impaired bony structure and growth stunting; thrombocytopenia, anemia and fatigue.[4] Most patients are significantly improved clinically after six months of treatment, and ERT has been documented to achieve significant quality of life benefits after 24 to 48 months.[7] ERT is not effective on neurologic symptoms, because it does not cross the blood-brain barrier, so it is not indicated for treatment of Type 2 Gaucher disease, and may have limited benefit in some with severe Type 3 disease, although it will improve systemic disease.

ERT is a very costly therapy ($4.00USD per unit/P 220.00). Although controversy exists regarding optimal dosage regimens, at a recommended dose in children of 60 units imiglucerase per kilogram body weight, every two weeks, the therapy can range from $70,000USD to $90,000USD or P 4 to 5 million pesos annually for each child (this estimate is for a child of 10-15 kg maximum, and for a 70 kg adult the cost per annum would be 4x60x70x26 = $436,000USD). Patients 2, 3 and 4 were able to access ERT through a compassionate program. Patients 2 and 3 improved significantly with ERT; Patient 4's early demise did not allow us to properly document the significant changes in quality of life with ERT.

Patients with severe Gaucher disease, primarily those with chronic neurologic involvement (Type 3), can benefit from bone marrow transplantation (BMT). Successful engraftment can correct the metabolic defect, improve the blood count, and lead to a reduction of the hepatomegaly. In a few patients, stabilization of bone disease and neurological disease has occurred; however, the morbidity and mortality associated with BMT limits its use in patients with type 1 and type 3 Gaucher disease.[4]

Another approach to the treatment of Gaucher disease currently under clinical investigation is "substrate reduction therapy": orally administered inhibitors of the synthesis of glucocerebroside (the substrate of the deficient glucocerebrosidase), thus allowing a better balance of residual enzyme activity and substrate, and gradual clearance of accumulated glucosylceramide from the lysosomes. Gene therapy involving the introduction of the *GBA* gene into hematopoeitic stem cells is likewise under investigation.[2]

Although ERT has changed the natural history of Gaucher disease, patients not receiving ERT and certain other patients may still require symptomatic treatment such as partial or total splenectomy for patients with massive splenomegaly with significant areas of infarction and persistent severe thrombocytopenia, transfusion of blood products, analgesics for bone pain, and joint replacement therapy. Patient 5 underwent splenectomy due to the massive splenomegaly, severe anemia and thrombocytopenia. While the initial response to splenectomy is usually satisfactory, concern has been expressed about the possible effect of the removal of the spleen on progressive deposition of glycolipid in other organs.[2] Splenectomy can be a predisposing factor to pulmonary hypertension[9] and severe bone disease,[10] thus unless there is a medical urgency, splenectomy should not be undertaken due to the availability of ERT.

Genetic counseling is an important aspect of management and was provided to all families. Since Gaucher disease is transmitted in an autosomal recessive manner, there is a 25% chance of producing an affected child each pregnancy.

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References

1. Mankin HJ, Rosenthal DI, Xavier R. Current Concepts Review: Gaucher Disease. J Bone Joint Surg Am. 2001;83 :748-762.
2. Beutler E, Grabowski GA. Gaucher disease. In Scriver CR, Beaudet AI, Sly WS, Valle D, eds. The metabolic and molecular basis of inherited disease, 8th ed. New York: McGraw-Hill, 2001:3635.
3. Gaucher Disease Current Issues in Diagnosis and Treatment. NIH Technology Assessment Conference. JAMA 1996:275; 548-553.
4. Pastores GM. Gaucher Disease. Available at http:// www.geneclinics.org. Accessed July 3, 2004.
5. Charrow J, Esplin JA, Gribble TJ, et al. Gaucher Disease, Recommendations on Diagnosis, Evaluation and Monitoring. Arch Intern Med. 1998;158:1754-1760.
6. Hruska KS, La Marca ME, Scott CR and Sidransky E. Gaucher disease: mutation and polymorphism in the glucocerebrosidase gene (GBA). Hum Mutat. 2008: 29(5):567-83.
7. Elstein D, Abrahamov A, Dweck A, Hadas-Halpern I, Zimran A. Gaucher Disease: pediatric concerns. Pediatr Drugs. 2002;4 :417-426
8. Cerezyme Product Monograph. Genzyme Therapeutics, Mass., USA, 1999.
9. Elstein D, Klutstein MW, Lahad A, Abrahamov A, Hadas-Halpern I, A. Echocardiographic assessment of pulmonary hypertension in Gaucher disease. Lancet. 1998; 351:1554-1556.
10. Schiffmann R, Mankin H, Dambrosia JM, Xavier RJ, Kreps C, Hill SC, et al. Decreased bone density in splenectomized Gaucher patients receiving enzyme replacement therapy. Blood Cell Mol Dis. 2002:28:228-296.