

CASE REPORT

IMIGLUCERASE TREATMENT IN GAUCHER'S DISEASE

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Gaucher's disease is an inherited lysosomal storage disorder with a deficiency of the enzyme glucocerebrosidase that manifests with clinical features of anemia, hepato-splenomegaly, skeletal destruction and organ dysfunction due to the accumulation of glucocerebrosides. There are several types of Gaucher's disease with varying prognosis and clinical progression of disease. We describe two cases followed at the Aga Khan University, Karachi, Pakistan, with different forms of the disorder. The enzyme Imiglucerase (Cerezyme, Genzyme) has been used to treat Type 1 Gaucher disease while the neuronopathic type has been resistant to therapy. We used Imiglucerase 60 µg/kg every 2 weeks in one patient with Type 1 Gaucher disease and followed hepatic, splenic volumes and blood counts. Treatment with Imiglucerase resulted in a decrease in splenic size, reduced requirements for transfusions and an improvement in cardiopulmonary symptoms.

Keywords: Gaucher, Imiglucerase

INTRODUCTION

Gaucher's disease is an inherited lysosomal storage disorder^{1,2} due to deficiency of the enzyme glucocerebrosidase. It manifests with clinical features of anemia, hepato-splenomegaly, skeletal destruction and organ dysfunction. We are describing two types of Gaucher's disease and the use of the enzyme Cerezyme (Imiglucerase, Genzyme) in the management of one type.

CASE 1

BA, a 14 month old male child, presented with inconsolable crying and irritability. On clinical examination, he was found to have pallor and massive hepatosplenomegaly. Rest of his systemic examination was normal. Initial laboratory values indicated anemia with a hemoglobin of 6.9 g/L, a white blood cell count of $6.9 \times 10^9/L$ with a normal differential count and a platelet count of 74,000. The possibility of a storage disorder was entertained and he underwent a bone marrow biopsy that demonstrated the presence of Gaucher cells. A liver biopsy was also done and showed Kupfer cell hyperplasia with cells that had a striated appearance consistent with those of Gaucher cells.

He was subsequently admitted to the hospital numerous times for the treatment of pneumonia, sepsis, and for transfusions of blood and platelets. Over the following year he developed cardiac disease with cardiomegaly, pulmonary edema, mitral regurgitation and tricuspid regurgitation. He was managed with bronchodilators, diuretics and antibiotics.

His condition deteriorated and by the age of 2 years and 4 months he had life threatening disease with cardiac failure, respiratory compromise and hypersplenism. He was then fortunately included in

the International Gaucher's Initiative (a humanitarian service provided by Genzyme) and was started on replacement with Imiglucerase (Cerezyme). The drug was infused at a dose of 60µg/kg every two weeks in an inpatient setting. A pre-treatment, volumetric CT evaluation demonstrated a liver volume of 4461 ml and a splenic volume of 5529 ml. Plain radiograph of pelvis demonstrated decreased bone density over the femoral heads. Hematology revealed; platelet count of 28,000, hemoglobin of 7.4 g/L, serum white blood cell count of $3.3 \times 10^9/L$ with 33% neutrophils, serum alanine aminotransferase (ALT) was 21 IU/L, alkaline phosphatase 203 IU/L, prothrombin time 16.8 seconds, partial thromboplastin time 33.8, INR 1.28, calcium 7.9 mg/dl, phosphorus 2.9 mg/dl, acid phosphatase 24.7 mg/dl, total protein 7.2 g/dl and serum albumin 2.9 g/dl.

Six months after the initiation of therapy his respiratory compromise resolved and the need for transfusions decreased. On a repeat evaluation at 9 months of therapy, a volumetric CT showed a decrease in splenic size by 2156 ml and hepatic size by 856 ml. An increased density of the femoral head was also noted on plain films of the pelvis. The platelet count improved to 34,000 as did the hemoglobin to 10.4g/L, with an increase in the white blood cell count to $4.5 \times 10^9/L$. After a year on therapy the liver size had decreased further by 560 ml to 3045 ml and the splenic size had decreased a further 827 ml to 2495 ml. His platelet count improved to 95,000 with no further requirements for transfusion and his cardiac and pulmonary issues resolved.

CASE 2

WA, presented at 7 months of age with a history of recurrent vomiting and difficulty in feeding since

birth. She was irritable and had developmental delay. Her birth history was unremarkable and she was born to a consanguineous marriage. At the time of admission she was found to be opisthotonic with inconsolable crying and developmental delay. On clinical examination, she had pneumonia with hepatomegaly of 2 cm below the right costal margin. An initial work up demonstrated a serum hemoglobin of 10.6g/L, white blood cell count of $8.7 \times 10^9/L$ and platelet count of 150,000. A presumptive diagnosis of Sandifer's syndrome was made. She was readmitted at the age of 9 months with aspiration pneumonia and evaluation of hepatosplenomegaly. At this time she was found to have a liver palpable 3 cm below the right costal margin with a spleen palpable 6 cm below the left costal margin. She was opisthotonic with exaggerated motor reflexes. She had hemoglobin of 9.8 g/l, white blood cell count of $12.7 \times 10^9/L$, platelet count of 88,000, normal liver function tests and a normal coagulation profile. Her serum albumin was 2.9 g/dl. Abdominal ultrasound showed an enlarged liver with increased echogenicity, ascites and massive splenomegaly. A bone marrow biopsy demonstrated the presence of histiocytes with a crumpled tissue paper appearance consistent with Gaucher's cells. A liver biopsy was deferred because of the presence of ascites.

DISCUSSION

Gaucher's disease is an inherited lysosomal storage disorder^{1,2} due to the deficiency of the enzyme glucocerebrosidase that leads to the accumulation of the lipid glucocerebroside within the lysosomes of the monocyte-macrophage system.

The disease was first described by a French physician, Phillipa Charles Earnest Gaucher in 1882. He found that cells laden with lipid accumulate to displace healthy cells in various organs of the body such as the bone marrow, liver and spleen. This accumulation leads to anemia, hepatosplenomegaly and eventually skeletal destruction and organ dysfunction. These cells may also get deposited in the brain and lead to neurological disease.

The disease is classified into 3 types depending on the organ involvement. Type 1 is the most common type and usually affects Ashkenazi Jews³⁻⁵. Type 2 and 3 are less common and are characterized by neurological involvement. Type 2 is very aggressive with early demise while Type 3 tends to be slowly progressive.

The disease is inherited in an autosomal recessive fashion and involves 2 mutant alleles of the glucocerebrosidase gene. The broad spectrum of phenotypes can make recognition of the disorder very difficult. Patients with the same mutation may

manifest early in the life or may remain asymptomatic throughout adult life.

Type 1 disease affects several organ systems and therefore has varied signs and symptoms at presentation. Visceral involvement manifests as splenic and hepatic enlargements with sizes that may range from 5 to 75 times of normal volume³. Hepatic size may increase by 1.25 to 2.5 times of normal. The hematological manifestations include anemia, thrombocytopenia, neutropenia, bleeding and bruising. As the abnormal cells accumulate in the bone, they lead to episodes of bone pain with osteoporosis, osteopenia, avascular necrosis and pathological fractures. Pulmonary and renal involvement, fatigue and growth retardations are other features of the disease.

Although Type 1 disease is often referred to as the 'adult' type, the age of onset and the rate of progression of disease varies considerably and the majority of patients are diagnosed before the age of 5 years.³

Gaucher's disease may be difficult to diagnose. A bone marrow examination with the characteristic Gaucher cells or lipid engorged cells is useful. But pseudo-Gaucher cells may be detected in conditions such as chronic granulocytic leukemia, Hodgkin's lymphoma, multiple myeloma and also sometimes in Thalesaemia. Tests measuring the deficient glucocerebrosidase enzyme in leukocytes and skin fibroblasts provide definitive diagnosis but these are not yet available in Pakistan. The disease is confirmed by enzyme values of between 0 and 30% of normal values⁶⁻⁸.

DNA testing for specific gene mutations may be done. The gene encoding glucocerebrosidase has been cloned and mapped to 1q21.1. More than 300 mutations have been identified. Knowledge of the genotype may help in predicting phenotypic expression, although there may be variation in clinical manifestations of the disease. Mutation analysis is useful for the detection of carriers as well as asymptomatic affected individuals. Genotypes 84GG or L444P are typically associated with severe disease and earlier presentation⁹.

Evaluation and monitoring of patients with Gaucher's disease considered for enzyme treatment requires a detailed medical history and a series of investigations that include regular evaluations of hematological parameters, acid phosphatase levels, visceral assessment of splenic and hepatic volumes using volumetric CT or MRI, radiographs of the spine and femoral head and dual energy X-ray absorptiometry (DEXA) scans of the pelvis and spine. Pre-treatment evaluations also include liver function tests, total protein and albumin levels, coagulation profiles and chest radiographs^{10,11}.

Treatment requires replacement of the deficient glucocerebrosidase enzyme. Cerezyme (Genzyme) or imiglucerase is an analogue of the human beta-glucocerebrosidase that is made by recombinant DNA technology and catalyzes the hydrolysis of the glycolipid glucocerebroside to glucose and ceramide. Dosages are individualized to each patient and initial dosages range from 2.5 U/kg of body weight three times a week to 60U/kg once in 2 weeks. Recommendations include the use of ERT (Enzyme replacement therapy) at an initial dose of 30-60 U/kg every 2 weeks and then to be adjusted to the level of response achieved¹²⁻¹⁵.

Patients on therapy achieve a decrease in splenic and hepatic size with normalization of hemoglobin and platelet counts in 2 to 5 years. In anemic patients, hemoglobin levels may rise to normal by 6-12 months of therapy. In thrombocytopenic patients, the most rapid response in platelet recovery is in the first two years of therapy with a slower response later¹⁵. In patients with pre-treatment bone pain, 52% were pain free at 2 years of therapy¹⁵. Enzyme treatment resulted in improved respiratory function as well^{16,17}. We were unable to obtain Cerezyme for the patient with neuronopathic Gaucher's as ERT in these patients may not be as beneficial as that in Type 1 disease. Severe adverse reactions to ERT are rare and include hypersensitivity reactions such as itching, rash and laryngospasm.

A study done on patients who had withdrawn from treatment allowed to study the effects of drug withdrawal. Most patients did not revert to baseline values. It was hence hypothesized that adult patients with stable Gaucher's disease may be withdrawn from treatment for definite periods, restarting therapy when indicated or maintenance at a reduced dosage may be appropriate in some adult patients¹⁸.

Newer drugs such as N-butyldeoxynojirimycin (OGT-918, miglustat) can reduce the production of glycosphingolipids by inhibiting glucosylceramide synthetase and are being studied^{19,20}. Convection enhanced delivery of the deficient enzyme has been used to perfuse areas of the brain and brainstem in neuronopathic Gaucher²¹. In a pilot study with three patients, the glucocerebrosidase gene was transferred into autologous CD34+ cells through a retroviral vector and transduced cells were infused into the patient. However, although the gene marked cells engrafted, levels of the corrected cells were too low²².

CONCLUSION

Imiglucerase treatment in Type 1 Gaucher's disease provides rapid improvement in organ function and

decreases transfusion requirement, in a life threatening disease.

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