

Gaucher Disease: A 10 Year Old Girl with Anemia and Huge Splenomegaly (A Case Report)

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Abstract: Gaucher's disease is a rare lipid storage disorder, affecting one in 40,000-200,000 people and results from a genetic deficiency of the enzyme glucocerebrosidase (glucosylceramidase). We report a 10-year old Iranian girl with chief complaint of anemia from 8 years ago, managed for iron deficiency anemia. The patient had hepatomegaly associated with huge splenomegaly which was confirmed by sonography. No skeletal disorder was found. Bone marrow aspiration revealed typical Gaucher cells. Low level of β -glucocerebrosidase enzyme activity confirmed the Gaucher disease. The patient is now under treatment with CERESIME, a recombinant DNA modified form of glucocerebrosidase with good condition.

Key words: Anemia, huge splenomegaly, Gaucher disease, β -glucocerebrosidase

INTRODUCTION

Gaucher's disease is the most common lipid storage disorder known and results from a genetic deficiency of the enzyme glucocerebrosidase (glucosylceramidase). Enzyme deficiency results in accumulation of glucocerebroside within the reticuloendothelial system. It may present with delayed stanturoponderal growth, a cutaneomucous pallor hepatosplenomegaly, bone marrow suppression and bone lesions (Rachid *et al.*, 2005; Morales, 1996). The blood count formula showed anemia with major thrombocytopenia. The myelogram was poor and the osteomedullar biopsy showed the presence of Gaucher's cells. The diagnosis has been confirmed by enzymatic dosage (Leucocytar β -glucosidase). Gaucher's disease is classified into three types: type 1 (non-neuronopathic), type 2 (acute neuronopathic) and type 3 (subacute neuronopathic). Of the three, type 1 is the most common, affecting one in 40,000-200,000 people and having a high prevalence among Ashkenazi Jews, affecting one in 450-1500 (Fumić *et al.*, 2004). In 1991, enzyme treatment became available with the marketing of alglucerase, a placentally derived modified form of glucocerebrosidase. In 1994, a recombinant DNA modified form of glucocerebrosidase, known as imiglucerase, was developed to replace alglucerase. Most published data on enzyme therapy are with alglucerase in patients with type 1 disease. A dosage regimen of 60 units kg^{-1} every

2 weeks for moderate to severe ill patients has been effective in reducing hepatosplenomegaly, improving anemia and thrombocytopenia, as well as improving weight gain and growth in children and increasing vigor and self-esteem in adults. Bone involvement is often slow to respond to therapy although pain is frequently improved. Controversy exists as to whether lower dosage regimens are as effective. The role of enzyme therapy in the rarer neuronopathic subtypes remains to be determined, but initial reports have been disappointing (Morales, 1996; Butters, 2007; Starzyk *et al.*, 2007).

CASE REPORT

The patient was a 10 year old girl, third child of her family, result of C/S. Their parents were non-consanguineous and healthy. Their ethnic was KORD, non-jewish and other child are healthy. Her mother didn't use any drug during this pregnancy. The patient managed for iron deficiency anemia for the first two years of her life. Easy bruising and paleness with decreased appetite were her chief complaint on her first visit to oncologist on 1385/8/24. CBC was taken, revealed WBC = $4300 \mu\text{L}^{-1}$ (N = 45%, L = 52%, E = 3%), RBC = $4,190,000 \mu\text{L}^{-1}$, Hb = 10.9 mg dL^{-1} , MCV = 78.28 fl , Plt = $52,000 \text{ mL}^{-1}$. Biochemistry revealed calcium = 9.1 mg dL^{-1} and normal liver function. On physical examination, pale conjunctiva, clear lungs, NI heart sound

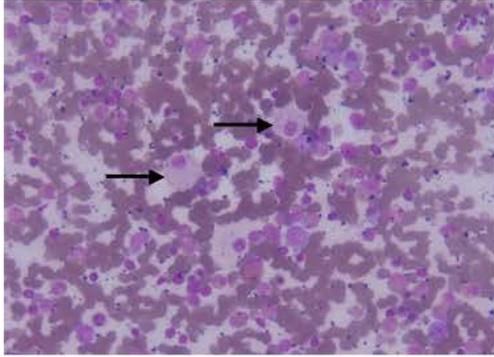


Fig. 1: Bone marrow aspirate shows typical Gaucher cells → 40 x view

were found. No abnormal ophthalmoscopic findings were found. Neurologic exam was normal. Anthropometric measures were: wt = 25 kg (< 25th percentile), Ht = 133 cm (< 10th percentile) and Hc = 50.5. The liver edge was palpable 6 cm below the subxiphoid process and 4 cm below the right costal margin. Huge splenomegaly was also found. Other findings were normal. Liver parenchyma was normal in ultrasonography (US) and the liver size was 10 mm which was larger than normal. Also, homogenous and normal echo spleen was found with 184 mm length which was categorized as huge splenomegaly. Based on clinical and US findings, Bone Marrow Aspiration (BMA) was done for ruling out malignancy. BMA revealed moderate cellularity with normal erythroid, lymphoid and myeloid series, but increased number of megakaryocytes and large lipid storage cells resembling Gaucher cells (Fig. 1). The diagnosis was established by β -glucocerebrosidase activity level assay (1.4 mcmol/L/h, normal: 2.1-5.3) in peripheral leukocytes which was done by the help of UNESCO organization in Argentina. The patient is now under Enzyme Replacement Therapy (ERT) by CERZYME with good condition.

DISCUSSION

Our case was referred by anemia and complete blood count showed bicytopenia and hepatosplenomegaly, confirmed by abdominal sonography. Splenomegaly and bicytopenia were two important signs with multiple differential diagnosis. Reticuloendothelial system hyperplasia, immune hyperplasia, extramedullary hematopoiesis, intra or extracellular depositions and benign or malignant cellular infiltrations are the most causes of splenomegaly. On the other hand, primary bone marrow disease such as myelofibrosis, leukemia and lymphoma, also systemic disease such as hypersplenism,

sarcoidosis, SLE and folate deficiency can potentially lead to cytopenia with cellular bone marrow. So, in order to approach to our case and rule-in causes, bone marrow aspiration was done, showed typical Gaucher cells (Kasper *et al.*, 2005; Barton *et al.*, 1991).

Gaucher disease is mainly due to mutations in the gene-encoding acid β -glucosidase (GBA), located on chromosome 1 at position q21 (Phillip and Poplack, 1998). This disease severely impairs quality of life because of hematologic or skeletal complications, physical limitations and psychosocial problems for both patients and their families (Barnevel *et al.*, 1983). Gaucher's disease, type 1 should be considered when unexplained spleno- and hepatomegaly, anemia, thrombocytopenia, or skeletal disease are present, particularly in combination. In our case, all of the so called signs except skeletal problems were found.

Lack of awareness and of widespread availability of the enzyme assay has as yet limited its application in clinical practice and led to many cases of Gaucher's disease being diagnosed by bone marrow and liver biopsy (Charrow *et al.*, 2000).

The diagnosis of Gaucher disease is established by an assay for β -glucocerebrosidase enzyme activity in peripheral leukocytes (Niederau and Häussinger, 2000). In our case, enzymatic diagnosis in dried blood spots on filter paper which has been previously discussed by Chamoles *et al.* (2002), showed serum level of 1.4 mcmol/L/h (Normal range: 2.1-5.3) for the β -D-glucosidase activity, which was lower than normal range.

The treatment of type 1 Gaucher disease has dramatically improved with the development of Enzyme Replacement Therapy (ERT) (Chamoles *et al.*, 2002). In previous studies, ERT has been shown to prevent progressive manifestations of Gaucher disease, as well as ameliorating specific features of the disease (Lin *et al.*, 2006; Zimran *et al.*, 1995; Weinreb *et al.*, 2002). The study by Weinreb *et al.* (2002) found a 20-30% decrease in liver volume within 1-2 years after beginning ERT, with a reduction of 30-40% by 5 years.

A case report describes an experience of using recombinant enzyme by Masood and Ali (2006) in a child who was diagnosed as a case of Gaucher disease at the age of 3 years. Regular enzyme replacement therapy has resulted in marked improvement in his hemoglobin level, absolute neutrophil count, platelets and physical growth.

In the study of Grigorescu Sido *et al.* (2007), enzyme replacement therapy administered for 18 months in Romanian patients with Gaucher disease type I led to a marked improvement in haematological parameters and hepato- and splenomegaly. In the majority of patients no further progress of bone disease was observed.

Our patient suffered from hepatomegaly, with the liver edge palpable 6 cm below the subxiphoid process and 4 cm below the right costal margin before ERT, which we expect to decrease after treatment initiation.

CONCLUSION

Enzyme replacement therapy is available for the treatment of type 1 Gaucher's disease, resulting in clinical improvement with enhanced quality of life within the first year of treatment, although improvement in bone disease can take longer. Doses of 60 units kg⁻¹ every 2 weeks are of clinical benefit to patients with moderate to severe disease. A number of lower dosage regimens have been evaluated in small groups of patients, with satisfactory clinical responses occurring in some of these patients.

ACKNOWLEDGMENTS

We appreciate the laboratory of Dr. Mariana Blanco, Argentina, for enzyme assay. We are indebted to Mr. Rahim Davarian and Mrs. O. Shirinbeik Mohajer for their leading suggestions.

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