

## CASE REPORT

## IMPROVEMENT IN SYMPTOMS OF GAUCHER'S DISEASE BY ENZYME REPLACEMENT THERAPY

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Gaucher's disease is the most common lysosomal storage disease which occurs due to a deficiency of the enzyme glucocerebrosidase. This enzyme deficiency leads to accumulation of glucocerebrosidase in the cells of macrophage-monocyte system. It is inherited as an autosomal recessive mutation and has three clinical subtypes. The disease presents with anaemia, hepatosplenomegaly, skeletal disorders and organ dysfunction. We present the case of an 18-month old male child who had presented to Civil Hospital, Karachi with fever, progressive pallor, abdominal distention for 6 months and was diagnosed as a case of type 1 Gaucher's disease on the basis of low leukocyte glucocerebrosidase activity, raised plasma chitotriosidase and the presence of Gaucher cells on bone marrow biopsy. The disease was treated with Intravenous replacement of the enzyme Imiglucerase (cerezyme) and the patient was followed. An informed Consent of the parents was taken prior to the writing of the manuscript.

**Keywords:** Gaucher Disease; Imiglucerase; Enzyme Replacement therapy.

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## INTRODUCTION

Gaucher's disease is a lysosomal storage disease, caused by a deficiency in the activity of the enzyme glucocerebrosidase, which results in insufficient degradation of glucosylceramide and its accumulation in lysosomes of macrophages, so called Gaucher cells. This is due to more than 350 different mutations in the GBA1 gene, out of which L444P mutations are most common globally. Other mutations include N370S, which is the most common allele of GD in North America, Israel and Europe. Gaucher's disease usually involves the liver, spleen, lungs, bone (cortex and marrow both). These organs are involved in the majority of the cases since the Gaucher cells, which are the hallmark of the disease are derived from macrophages.

The primary enzyme defect, acid - glucosidase, leads to the accumulation of an excess indigestible substrate, glucosylceramide. This leads to hepatosplenomegaly and bone marrow expansion, producing more macrophages and further increase in Gaucher cells causing irreversible tissue damage.<sup>1</sup> Before 1980, patients with Gaucher's disease were offered symptomatic treatment.

Now patients with type I Gaucher disease are treated with cerezyme (enzyme replacement therapy) for more than a decade. This enzyme differs from the human enzyme sequence by a single amino-acid substitution that does not appear to affect catalytic activity.<sup>2</sup> In this case report, we have studied the effects of cerezyme therapy in treatment of type 1 Gaucher's disease.

## CASE REPORT

We present a case of an 18-month-old male infant weighing 10 kg completely vaccinated according to the WHO's "Expanded program on Immunization", who presented to the Paediatric outpatient department of Civil Hospital, Karachi in January 2015 with complaints of on and off fever along with progressive pallor and abdominal distention for 6 months. Fever was high grade, intermittent, gradual in onset, not associated with rigors and chills along with sweating and lethargy while playing or feeding. Gradual, progressive abdominal distention was also noticed by parents. The parents denied any history of bleeding from any site or bruises. His birth history was unremarkable. It was a full-term pregnancy with the child being born by a normal vaginal delivery and didn't require any resuscitation. He was exclusively breastfed till 6 months of age. Weaning was started at 6 months of age. Since the beginning of symptoms his appetite had reduced and was able to take only 30-40% of his required calories. All his developmental milestones were achieved at appropriate ages.

He was the 2<sup>nd</sup> child of a consanguineous marriage. Elder sibling died with similar complains at the age of 3 and used to have multiple blood transfusions. On examination, he was a pale looking child with average height and built lying comfortably in bed, conscious and oriented. His weight was 10 kg, height 78 cm, occipito-frontal circumference 47 cm and mid upper arm circumference 13 cm. He was found to be severely anaemic. Abdomen was distended, soft and non-tender with central umbilicus. Liver was palpable 5 cm below the right costal

margin, firm in consistency with smooth surface and regular margins. Spleen was also palpable 11 cm below left costal margin, firm in consistency with smooth surface and regular margins. Respiratory, cardiovascular and CNS examinations were unremarkable.

Complete blood count revealed hypochromic microcytic anaemia with a Haemoglobin level of 5.1 mg, a total leukocyte count of 10,700 with 60% lymphocytes and 34% neutrophils. His platelet count was 75000 and a reticulocyte count of 3.1%. The rest of the baseline investigations were normal.

Ultrasound abdomen revealed hepatosplenomegaly. A liver measuring 11 cm with smooth margins, uniform echotexture. Portal vein was normal measuring 0.5 cm. Spleen measuring 12 cm. Uniform echotexture. No mass or cyst seen. Splenic vein was not dilated. The rest of the scan was normal.

Bone marrow aspiration was done, exhibiting a fair amount of macrophages & few of them showing little wrinkled cytoplasm and eccentric nucleus morphology. Liver biopsy showed hepatocytes admixed at place with numerous Kupffer cells, revealing pale, wrinkled, striated appearance of the cytoplasm. Findings of bone marrow aspiration and liver biopsy were suggestive of Gaucher's disease.

An assay for  $\beta$ - Glucosidase activity in the peripheral blood leukocytes was carried out employing the fluorometry method and revealed decreased enzyme activity (1.42 nmol/ml/HR) which was consistent with the diagnosis of Gaucher's disease. Acid Phosphatase level were also raised (35 U/L). Enzyme Chitotriosidase usually elevated in symptomatic Gaucher's patients. Its levels in this patient were found to be significantly raised (336.97 nmol/HR/ml) and thus a diagnosis of "Type 1 Gaucher disease" was made.

The patient was started on enzyme replacement therapy cerezyme (Imiglucerase) on 19<sup>th</sup> March 2015. It is produced by recombinant DNA technology and is an analogue of the human enzyme  $\beta$ -glucocerebrosidase. The usual dose is 60 units/kg once every two weeks. The child has received 4 doses till date. The cost of a 400 unit vial is 200,000 Pakistani Rupees.

On a follow up visit on 11<sup>th</sup> May 2017, an examination was done on which liver was palpable 3 cm below RCM, span 8 cm, firm in consistency, smooth surface and regular margins. Spleen was palpable 9 cm below LCM, firm in consistency, smooth surface and regular margins. Complete blood count showed marked improvement in haemoglobin level (10.6 mg%) and platelet count (130,000).

## DISCUSSION

GD is classified into type 1 (non-neuronopathic), type 2 (acute neuronopathic), and type 3 (chronic neuronopathic) according to the presence of neurological deterioration, age of identification, and rate of disease progression.<sup>3</sup> GD affects both the genders equally. The National Gaucher Foundation estimated that one in 20,000 live births in the USA is diagnosed with GD1. Individuals with Ashkenazi Jewish ancestry have a high incidence of Gaucher's disease, i.e., 1 in 450 births. The incidence of GD in the general population is 1:20,000 to 1:200,000.<sup>4</sup> According to a study, the frequency of Gaucher's disease in Pakistan is 34.4%.

This may be due to higher incidence of inter-family marriages and larger family size.<sup>5</sup> Gaucher's cells, the hallmark of the disease is found in bone, bone marrow, liver, spleen, and lymph node parenchyma. They increase the production of inflammatory cytokines, which causes hepatomegaly, splenomegaly, bone loss and pancytopenia. Gaucher's Disease type 2 involves the brain, spleen, liver, and lungs. It manifests with neurological complications. There is rapid progression of disease, leading to death within the first 2 years of life. Gaucher's Disease type 3 is a rare form. It affects fewer than 1 in 100 000 people. It has 3 subtypes: 3a, 3b, and 3c. GD3a has only mild visceral manifestations, but causes severe, progressive myoclonic seizures, causing death within first 20 years of life. GD3b has a severe visceral involvement, such as massive visceromegaly involving liver and spleen, stunted growth and gaze palsy. GD3c patients with the D409H allele, a rare cardiac mitral and aortic calcification, usually have a very short lifespan.<sup>6</sup> A large number of patients show skeletal abnormalities on x-ray like, "Erlenmeyer flask" deformity of the distal femur and lytic lesions in long bones like the femur, humerus and tibia. Other affected bones include ribs, pelvis, bones of the feet, mandible and vertebral bodies.<sup>7</sup>

Generalized osteopenia, decreased bone mineral density (BMD) and pathological fractures are very common. A study showed, treatment with eliglustat results in improved lumbar spine BMD, improvements in platelet count and haemoglobin level, decreases in spleen volume and liver volume, and decreased or stabilized bone marrow infiltration by Gaucher cells.<sup>8</sup> Other rare manifestations of GD include gallstones, functional abnormalities of the immune system, increased incidence of certain malignancies (multiple myeloma), Neurological diseases like early onset parkinsonism, cardiac valve calcification and pulmonary hypertension.<sup>9</sup> This led to the introduction of newer agents like velaglucerase

Alfa, which were better tolerated because of fewer hypersensitivity reactions. Moreover, the use of velaglucerase Alfa has led to safe conceptions, good health during pregnancy with reduced incidence of postnatal complications. Prior to (ERT), the missed abortion rate was 25%, with anaemia, thrombocytopenia, increased incidence of postpartum haemorrhage, puerperal fever and bone crises during pregnancy. A study showed the live birth rate of 84%, with rare postpartum complications and improved haemoglobin and platelet counts with the use of velaglucerase Alfa.<sup>10</sup> Another study reported the use of plant cell derived taliglucerase Alfa, which showed a significant reduction in spleen volume by all patients.<sup>11</sup> Despite of availability of a large variety of ERTs available, if patients with GD do not show improvement, they can undergo arthroplasty and other orthopaedic surgeries for skeletal abnormalities. Though Splenectomy is usually not required after the advent of ERT, it can be done in patients resistant to ERT and with massive splenomegaly.

## REFERENCES

1. Grabowski GA. Gaucher disease and other storage disorders. *Hematology Am Soc Hematol Educ Program* 2012;2012(1):13–8.
2. Bin Turkia H, Gonzalez DE, Barton NW, Zimran A, Kabra M, Lukina EA, *et al.* Velaglucerase Alfa enzyme replacement therapy compared with imiglucerase in patients with Gaucher disease. *Am J Hematol* 2013;88(3):179–84.
3. Lee JY, Lee BH, Kim GH, Jung CW, Lee J, Choi JH, *et al.* Clinical and genetic characteristics of Gaucher disease according to phenotypic subgroups. *Korean J Pediatr* 2012;55(2):48–53.
4. Bennett LL, Turcotte K. Eliglustat tartrate for the treatment of adults with type 1 Gaucher disease. *Drug Des Devel Ther* 2015;9:4639–47.
5. Cheema HA, Malik HS, Parkash A, Fayyaz Z. Spectrum of Inherited Metabolic Disorders in Pakistani Children Presenting at a Tertiary Care Centre. *J Coll Physicians Surg Pak* 2016;26(6):498–502.
6. Bennett LL, Mohan D. Gaucher disease and its treatment options. *Ann Pharmacother* 2013;47(9):1182–93.
7. Wenstrup RJ, Bailey L, Grabowski GA, Moskovitz J, Oestreich AE, Wu W, *et al.* Gaucher disease: alendronate disodium improves bone mineral density in adults receiving enzyme therapy. *Blood* 2004;104(5):1253–7.
8. Kamath RS, Lukina E, Watman N, Dragosky M, Pastores GM, Arreguin EA, *et al.* Skeletal improvement in patients with Gaucher disease type 1: a phase 2 trial of oral eliglustat. *Skeletal Radiol* 2014;43(10):1353–60.
9. Zimran A. How I treat Gaucher disease. *Blood* 2011;118(6):1463–71.
10. Elstein D, Hughes D, Goker-Alpan O, Stivel M, Baris HN, Cohen IJ, *et al.* Outcome of pregnancies in women receiving velaglucerase Alfa for Gaucher disease. *J Obstet Gynaecol Res* 2014;40(4):968–75.
11. Zimran A, Brill-Almon E, Chertkoff R, Petakov M, Blanco-Favela F, Muñoz ET, *et al.* Pivotal trial with plant cell-expressed recombinant glucocerebrosidase, taliglucerase Alfa, a novel enzyme replacement therapy for Gaucher disease. *Blood* 2011;118(22):5767–73.

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