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Case Report

Unexplained hepatosplenomegaly: a storage disorder

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ABSTRACT

Gaucher's disease (GD), a lysosomal storage disorder is caused by defect in the housekeeping gene lysosomal glucocerebrosidase which is present on the first chromosome (1q22). It was first described by a French physician, Philippe Gaucher in 1882. The metabolic defect is the deficiency of the lysosomal hydrolase β-glucosidase, identified by Brady et al. Hereby we reported a 3 year 6-month-old male child presenting with mass per abdomen. Peripheral smear showed bicytopenia and bone marrow aspiration revealed normal erythropoiesis and Gaucher's cells in a background of normal erythroid, myeloid, and megakaryocytic lineage cells. An impression of lysosomal storage disorder was given and child was evaluated further by genetic analysis. Therefore, we emphasized the importance of early recognition by clinical manifestation and histological findings. The practicing paediatrician should have an index of suspicion for storage disorders as a differential diagnosis of children with unexplained hepatosplenomegaly. Early diagnosis of GD would lead to initiation of effective treatment with enzyme replacement which can decrease morbidity.

Keywords: Hepatosplenomegaly, Lysosomal storage disorder, Gaucher's disease, Enzyme replacement therapy

INTRODUCTION

GD, a lysosomal storage disorder is caused by defect in the housekeeping gene lysosomal glucocerebrosidase which is present on the first chromosome (1q22). It was first described by a French physician, Philippe Gaucher in 1882. The metabolic defect is the deficiency of the lysosomal hydrolase β-glucosidase, identified by Brady et al.[1] The gene GBA1 encodes for enzyme glucocerebrosidase that converts glucosylceramide (GlcCer) into ceramide and glucose.[2] Decreased activity of glucocerebrosidase affects in accumulation of undegraded glucocerebrosides in lysosomes of macrophages in the liver, spleen, and bone marrow, transforming macrophages to Gaucher cells.

Based on the severity of neurological manifestations, GD is categorized into three types. Type 1 is the most common and not associated with neurological damage. Type 2 and type 3 are more severe with acute and subacute neuropathic symptoms, respectively with early involvement of the nervous system.[3]

Glucocerebroside accumulation contributes to fatigue, bleeding and easy bruising, distended abdomen, diffuse infiltrative pulmonary disease and pathologic fractures. Bone marrow aspiration may be performed in patients without a diagnosis accompanied with isolated thrombocytopenia and/or hepatosplenomegaly moreover it can help when Gaucher cells are found.[4]

The prevalence of GD is approximately 1/40,000 to 1/60,000 births; however, a higher prevalence of 1/800 has been reported in Ashkenazi Jews.[5]

CASE REPORT

We presented a case of a 3 year 6 months old male child, first born to a non-consanguineously married couple was brought with complaints of abdominal distension and

mass per abdomen noticed since 1 month, on the left side, gradually increasing in size. The child was developmentally normal. There was no history of easy bruising or prolonged bleeding on trauma, hematemesis, fever, night sweats, weight loss or bone pains. On examination, there was pallor but no lymphadenopathy or pedal edema. Anthropometry was normal for age. There were no signs of ocular or neurological abnormalities. He had firm, nontender massive splenomegaly, 14 cm below left costal margin and hepatomegaly 10 cm below right costal margin.

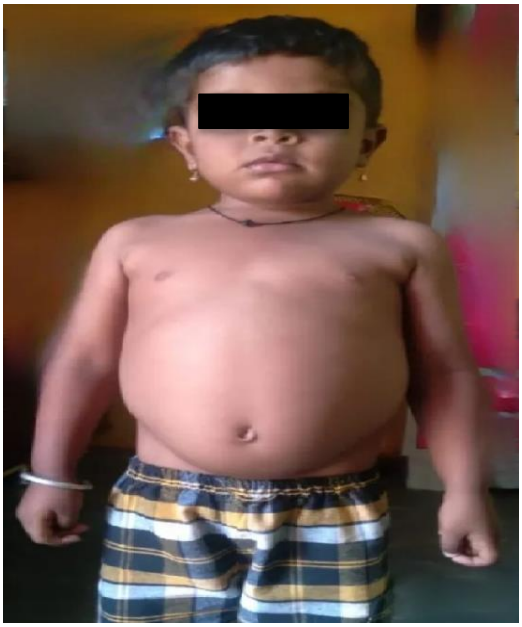

Figure 1: Image showing massive hepatosplenomegaly in the patient.

Laboratory investigation revealed bicytopenia (haemoglobin=7.9 g/dl, white blood cells=2.60×10^3 /l, and platelets=217×10^3 /l). Liver function tests, kidney function test, thyroid function tests coagulation profile and urine analysis were unremarkable. Peripheral blood smear revealed moderate microcytic hypochromic anaemia with poikilocytosis, tear drop elongated cells, acanthocytes, target cells and pancytopenia.

Fundoscopy, hearing evaluation and 2D Echo were normal. Bone marrow aspiration revealed normal erythropoiesis and Gaucher's cells in a background of normal erythroid, myeloid, and megakaryocytic lineage cells. These cells contained hyperplasic macrophages and had crumbled tissue paper-like appearance. An impression of lysosomal storage disorder was given and child was evaluated further by genetic analysis.

The beta glucosidase enzyme assay by fluorometry method revealed low beta glucosidase enzyme with elevated chitotriosidase enzyme levels. GBA gene analysis for pathogenic variants in GBA gene was conducted which showed likely compound heterozygous variant in the GBA gene.

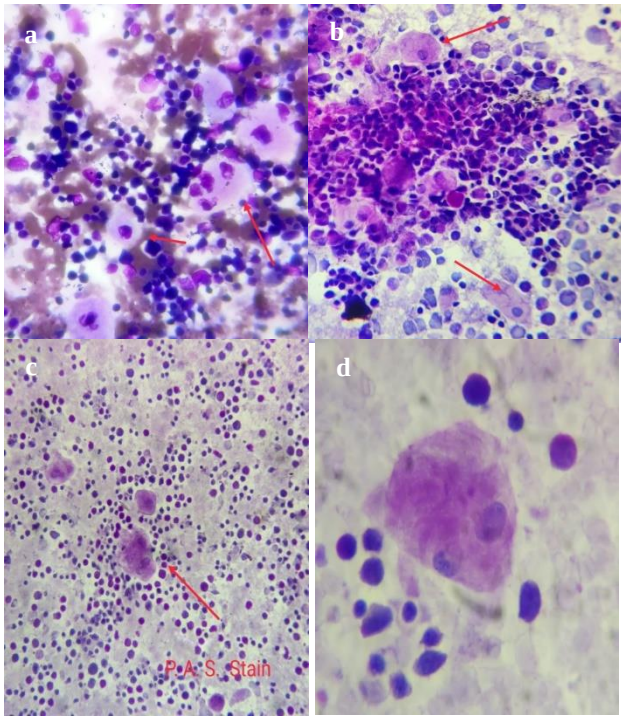

Figure 2 (a-d): Bone marrow smear picture.

A heterozygous missense variation(V414M) in exon 10 of GBA gene that results in amino acid substitution of Methionine for Valine at codon 414 was detected. The observed variation lies in protein kinase domain of GBA protein and a different missense mutation affecting the same codon has been previously reported in patients affected by GD. Genetic counselling was done and child was planned for enzyme replacement therapy (ERT).

DISCUSSION

The GD is genetic disorder that is inherited in an autosomal recessive pattern. It has been reported to affect all races with an occurrence of approximately 1:40,000 individuals.[6] Among the several LSDs known, GD is the most common. The disorder is characterized by diverse clinical manifestations including splenomegaly (95%), hepatomegaly (87%), radiological bone disease (81%), thrombocytopenia (50%), anaemia (40%), growth retardation (34%) and bone crisis (9%).[7] B. M. examination is the hallmark for the diagnosis of GD, confirmed by demonstrating deficient acid β-glucosidase activity in isolated leukocytes.[8]

Macrophage directed ERT had been the most accepted form of treatment for GD. Therapeutic goals for patients with GD on ERT involves, changes in size of liver and spleen, improvement in haematological parameters and bone crises.[9] Many patients would require surgical treatment in the form of splenectomy to correct their pancytopenia.

It was recommended to start early treatment in symptomatic children with GD to avoid irreversible bony

and visceral damage as well as other long-term growth and development issues. Short stature or growth retardation are frequent problems. When treated, these children had normalized onset of puberty and corrected growth curve, both in stature and lean body mass. However, treated patients may not fully reach expected height.[10,11]

Substrate reduction therapy (SRT), a newer form of therapy uses agents that inhibit glucosylceramide synthetase and decrease biosynthesis of glucocerebrosidase.[12] The major advantage of SRT was its ability to cross the blood brain barrier and improve the neurological symptoms of GD. Since the disease was rare, the possibility of a delayed diagnosis was high. An early detection together with treatment using enzyme replacement can considerably reduce the morbidity.

CONCLUSION

The GD is characterized by a wide spectrum of clinical presentations. We describe a case of Gaucher's Disease in a 3 year 6 month old male child who presented with abominal distension. Bone marrow biopsy was suggestive of Gaucher cells and the genetic analysis was confirmatory. It is imperative to have a high index of suspicion while evaluating cases of hepatosplenomegaly and consider storage disorders. Appropriate evaluation, including genetic study can aid in early recognition and prompt initiation of treatment.

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