

Type I (Non-neuronopathic) Gaucher's Disease with Bone Marrow Involvement: A Rare Case Report

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ABSTRACT

Gaucher's disease is an uncommon autosomal recessive sphingolipid lysosomal storage disease characterized by the deposition of glucocerebroside in cells of the macrophage-monocyte system from the deficient activity of the lysosomal hydrolase β -glucosidase (glucocerebrosidase). In the absence of the enzyme, glucosylceramide accumulates in lysosomes of macrophages of tissues with multisystem organ involvement viz. liver, spleen, bone marrow, lungs and central nervous system. Serum β glucosidase levels <15% of mean normal activity confirm the diagnosis, enzyme replacement being the only definitive treatment. We report this case of a 1 year 6 month male child who presented with delayed milestones, purpuric rashes and massive hepatosplenomegaly. Hematological workup revealed pancytopenia. Bone marrow study showed characteristic Gaucher cells and liver biopsy also showed evidence of Gaucher's disease. Hence diagnosis of Type I (non-neuronopathic) Gaucher disease was given. With the advent of enzyme replacement therapy and substrate reduction therapy the natural history of the disease has been changed with a marked decrease in morbidity. The incidence of Type I Gaucher's disease is 1 in 60,000 births but this non-neuronopathic type presenting with pancytopenia due to bone marrow involvement is a rare entity with very few cases in India.

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Introduction

Gaucher's disease is a lysosomal storage disorder characterized by the accumulation of glucosylceramide in cells of the macrophage/monocyte system. It results from a hereditary deficiency of the lysosomal acid β -glucosidase enzyme. Gaucher's disease is due to mutations involving the β -glucosidase gene, localized in the large arm of chromosome 1.^[1] Gaucher's disease was first described by Gaucher in 1882, and the storage of glucocerebroside was first recognized by Epstein in 1924.^[2]

The metabolic defect, which is the deficiency of the lysosomal hydrolase β -glucosidase, or β -glucocerebroside, was identified by Brady et al. There are three clinical subtypes, which are delineated by the absence or presence and progression of neurologic involvement. Type 1 or non-neuronopathic form; Type 2, the infantile-onset, acute neuronopathic form; and Type 3, the juvenile-onset neuronopathic form. All three subtypes are inherited as autosomal recessive traits. Type I is the most common form of Gaucher's disease with an incidence of approximately 1/40–60,000 in the general population. The incidence varies between 1/40,000 in Central Europe and 1/2,000 in some non-European countries, such as Israel. It is most prevalent in the Ashkenazi Jewish population (1/450).^[3] This Non-neuronopathic type presenting with bone marrow involvement is rare entity with very few cases reported in India.

Case Report

A one and half year old male child born of second degree consanguinity presented with chief complaints of poor appetite, poor feeding orally, poor weight gain and failure to thrive. Patient also had persistent intermittent low grade fever since birth as informed by the mother and she noticed distension of abdomen of the child since 2 months. Child had birth weight of 3 kg and immunization was complete for age. Developmental history revealed delayed milestones. On examination, heart rate was 106/minute, respiratory rate was 24 breaths/minute and child was afebrile. Child was moderately nourished. Pallor was present with no edema or cyanosis. Purpuric rash was present on left thigh. On CNS examination, child was conscious and playful. Per abdomen examination findings included hepatomegaly with liver span of 7 cm and moderate splenomegaly. Hematological investigations including bone marrow examination, biochemical tests, Ultrasonography abdomen and liver biopsy was performed with due consent. Investigations revealed hemoglobin – 10.2 gm% ; RBC count – 4.74 million/cumm, Reticulocyte count 0.4 %, Total leucocyte count - 6460 / cumm, Platelet count - 82000/cumm. Peripheral smear examination showed

normocytic hypochromic anemia with thrombocytopenia. Liver function tests showed raised enzymes with AST - 102 IU/L, ALT – 150 IU/L, ALP – 326 IU/L . Blood urea and serum creatinine were within normal limits. USG abdomen showed hepatomegaly with increased echotexture and gross splenomegaly with no focal lesions/collaterals at hilum. Bone marrow examination and liver biopsy was advised based on the above clinical findings and basic investigations. Bone marrow aspiration showed cellular smear which was satisfactory for evaluation. Myeloid series were normal in morphology and distribution. Moderate erythroid hyperplasia was noted and megakaryocytes were increased in number 5-7/ lpf in marrow particles. Many megakaryocytes were hypolobated. Scattered good number of foamy histiocytes were seen amidst marrow particles having abundant wrinkled 'tissue paper like' cytoplasm resembling gaucher cells which are highly characteristic of Gaucher's disease were present [Figure 1A and 1B]. Hence an opinion of Megakaryocyte hyperplasia with erythroid hyperplasia and probable Gauchers disease was given. Subsequently liver biopsy was performed which showed sheets of gauchers cells disrupting the liver architecture [Figure 2A and 2B]. Periodic Acid Schiff (PAS) stain was intensely positive. [Figure 3]. The patient was diagnosed with Lysosomal storage disorder, Type I(Non neuronopathic) Gauchers disease based on clinical examination, bone marrow examination and liver biopsy. Parents were advised further confirmation by enzyme studies. But due to financial constraints of parents, further evaluation and confirmation of this case was not possible.

Discussion

Gaucher's disease results from deficiency of a lysosomal enzyme glucocerebroside also known as acid beta-glucosidase. The glucocerebroside gene is located on chromosome 1q21. The enzyme acts on the substrate glucocerebroside which is a component of the cell membrane. In the normal lysosome, protein Saposin C presents glucocerebroside to GBA which activates the enzyme. This enzyme is responsible for hydrolytic breakdown of glucosylceramide to glucose and ceramide. Deficiency of the enzyme leads to accumulation of glucosylceramide and other glycolipids in the lysosomes of macrophages, primarily in the spleen, liver, bone marrow, brain, osteoclasts and less often the lungs, skin, kidneys, conjunctiva and heart. The deacylated form of glucosylceramide, glucosylsphingosine, is elevated in neuronopathic disease and correlates more with phenotype severity compared to glucosylceramide.^[4]

Three types of Gaucher's Disease (GD) have been described based on the clinical features, ethnicity and

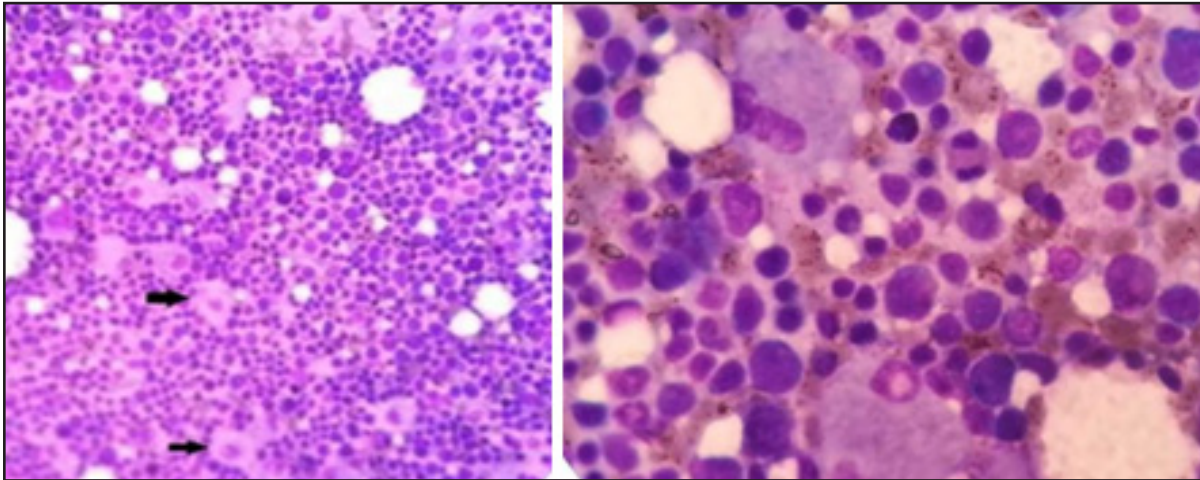


Fig. 1A and 1 B: Bone marrow aspiration smear shows numerous Gauchers cells (Wright Stain ,100 X, 400 X)

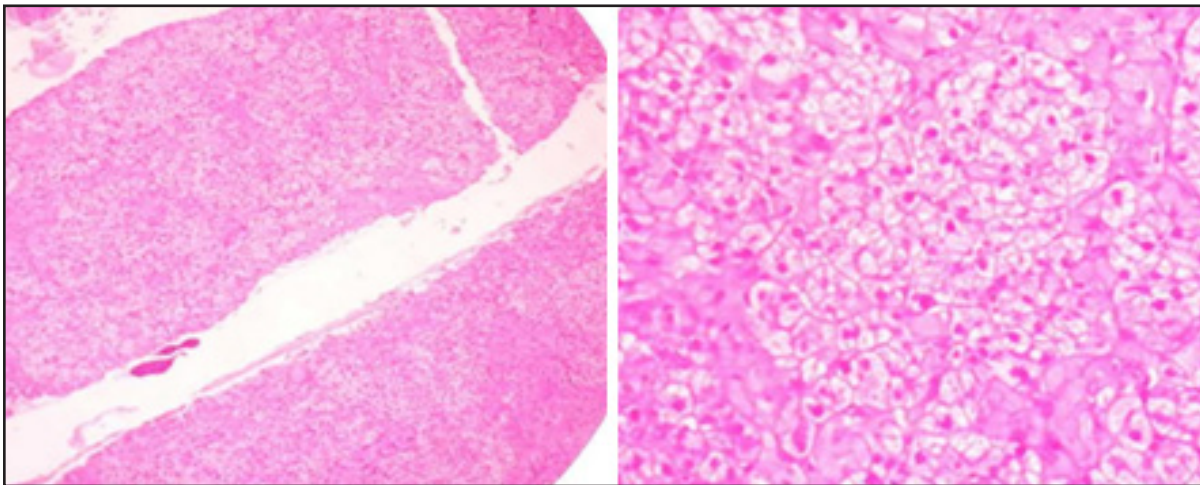


Fig. 2 A and 2 B : Liver biopsy showing sheets of Gauchers cells (H&E stain :100 x and 400x)

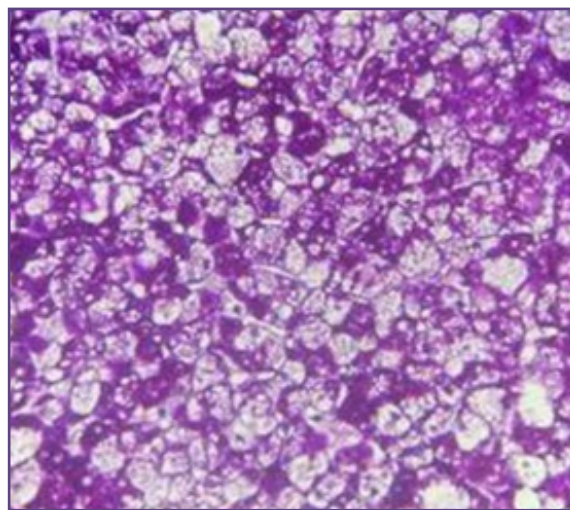


Fig. 3 : Liver biopsy showing sheets of Gauchers cells with PAS positive material (PAS stain, 400x).

the natural history of the disease. Type 1 GD patients do not have neurological involvement, Type 2 is the acute neuronopathic and Type 3 is the chronic neuronopathic type. Type 3 is further subdivided in to 3 subtypes a, b and c depending on the clinical features. Gaucher disease can also present as hydrops in the perinatal period which is often lethal.

Type 1 GD or the non-neuronopathic type presents with symptoms which may first present in infancy to late adulthood. It is characterized by painless hepatosplenomegaly, which often leads to massive abdominal distension with anemia and thrombocytopenia. Fatigue, nose bleeds, and easy bruising are a manifestation of the cytopenias. Some patients are transfusion dependent. Cytopenias are secondary to hypersplenism, bone marrow infiltration by Gaucher cells and an intrinsic haemopoietic defect in cells. These patients with Type 1 GD are at increased risk of bleeding tendency which is related to thrombocytopenia, defective platelet function and coagulation abnormalities.^[4]

Differential Diagnosis include hematological malignancies and storage disorders like Niemann–Pick disease. Most of these disorders have characteristic clinical, radiographic, or laboratory features that distinguish them from GD. Atypical Gaucher disease or a variant of GD is known which is severe disorder due to deficiency of Saposin C.^[5]

Diagnosis of Gaucher disease is made on the basis of clinical history, physical examination, laboratory test and confirmed by a blood test showing deficient glucocerebrosidase enzyme which was not possible in this case and genetic mutation studies when the diagnosis is doubtful. History of consanguinity and family history of suspected or proven GD will support the diagnosis.

Gaucher's cells are large, round or oval, and have pale blue cytoplasm with a wrinkled appearance due to the presence of many fibrillar structures. The cytoplasm is Sudan Black B- and PAS-positive. Gaucher cells also stain positively for nonspecific esterase and tartrate-resistant acid phosphatase. Stains for iron give weak positive reactions. In histologic sections, Gaucher cells are often found in clumps or sheets and their abundant cytoplasm has a crumpled appearance. The affected marrow may show an increase in reticulin and collagen. The gold standard for diagnosing Gaucher disease is measurement of glucocerebrosidase enzyme activity in leucocytes or skin fibroblasts on a skin biopsy^[6] The specific acid β -glucosidase gene mutation may be determined for possible genotype/phenotype correlations. Electron microscopy reveals that the cytoplasm is packed with large elongated sacs containing characteristic tubes, 30–40 nm wide, each of which is made up of spirally

arranged fibrils. Imaging studies for organomegaly and skeletal survey for long bones is done. Other additional tests include Chest X-ray and 2D echo are also desirable to rule out lung parenchymal involvement and pulmonary hypertension. Prognostic biological marker Chitotriosidase correlates with the disease burden and is useful in monitoring therapy. It is a chitinase and reflects “alternative” type macrophage activation that is overexpressed by the Gaucher cell.^[7] Prenatal diagnosis is performed by enzyme analysis of fetal cells obtained by chorionic villous sampling or amniocentesis at 16 weeks of pregnancy.^[8]

The treatment of Gaucher disease is by Enzyme Replacement Therapy (ERT) and has now become the standard of care. Administration of the enzyme reduces splenomegaly, hepatomegaly, improvement of anemia and thrombocytopenia. Severely ill patients with Type 1 Gaucher disease are generally started with a dose of 60 Units (U) of enzyme per kg of body weight every other week. As patients improve, the dose may be reduced to 30 U per kg of body weight, and in many cases to 20 U per kg of body weight every other week. The frequency of administration of enzyme has been extended to every 3 weeks in a number of patients who have been maintained in good condition with this regimen. Long term benefit of ERT in patients with type 1 GD has been clearly documented.

Velaglucerase alfa, a newer enzyme therapy has been approved for treatment in Type 1 GD in both adults and children. Oral drugs as substrate reduction therapy with Miglustat and Eliglustat tartrate are used for milder disease where treatment with ERT is not possible.^[9] These drugs are best used as maintenance therapy after the therapeutic goals have been achieved with ERT. The potential for cure of GD is Bone marrow transplantation. Future therapies include Enzyme enhancement therapy with chaperones, gene therapy, retroviral vector transfer of the GBA gene into cultured bone marrow cells of Gaucher patients results in expression of physiologic levels of enzyme.^[4]

Conclusion

Gaucher's disease may be under-diagnosed in India due to the paucity of the sources for performing the genetic evaluation and analysis. Hematologists need to have greater awareness of Gaucher disease because they have a unique opportunity to make an early diagnosis and provide optimal treatment for this disease. This increase in diagnosis is also related to the availability of ERT. ERT is profoundly expensive and virtually beyond the means of any patient. However, with increasing number of patients

being diagnosed, it is becoming difficult to support all patients with the disease. Hence, the government should intervene in assisting this group of patients in diagnosis and therapy.

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Competing Interests

None Declared

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