Unusual case of Gaucher's disease in an infant - a rare case report

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ABSTRACT
Gaucher’s Disease (G.D) is a rare, inherited, autosomal recessive systemic disease. It is a lysosomal storage disorder caused by a deficiency of the lysosomal glucocerebrosidase enzyme leading to accumulation of glucocerebroside substrate in the cells of monocyte/macrophage system. There is a wide spectrum of its clinical presentation having an overall incidence of 1 in 40,000 individuals with 3 variants, Type I (Adult, non neuropathic) Type II (Infantile, neuropathic) and Type III (Sub acute neuropathic). Due to its rarity, it is often initially misdiagnosed. We present a case of a 10 month old boy presenting with jaundice, hepatosplenomegaly and thrombocytopenia as major features. Clinical examination and history pointed to a lysosomal storage disease. Final diagnosis was done on the basis of histopathological examination of liver biopsy as Gaucher’s disease (Infantile form)

Key words: Gaucher’s disease, lysosomal storage disorder, autosomal recessive, liver biopsy

INTRODUCTION
Gaucher’s disease, a lysosomal storage disorder is caused by defective glucocerebrosidase hydrolysis leading to its accumulation in histiocytes of the reticuloendothelial system (RES). Thus it leads to transformation of cells having foamy glycolipid laden cytoplasm known as Gaucher’s cells. Infiltration of Gaucher’s cells in tissue results in the varied systemic manifestation such as hepatosplenomegaly, pancytopenia, skin pigmentation, neurologic symptoms, severe bony pain etc.

Gaucher’s disease has an overall incidence of 1 in 40,000 individuals. Depending upon the age of onset and neurological symptoms, Gaucher’s disease has three phenotypes. Type I (Most common, usually adults, predilection for Ashkenazi Jewish descent individuals, non neuropathic) Type II (Rarest, most severe form occurring in 1/100,000 to 1/500,000 live births without ethnic predisposition, Infantile, neuropathic) and Type III (Early adolescents, Sub acute, neuropathic)

We report a case of type II Gaucher’s disease in an infant who presented with hepatosplenomegaly, thrombocytopenia and jaundice as major features without any neurological symptoms but died due to delayed diagnosis.

Early diagnosis is important because the disease is rare and the diagnosis may be delayed, leading to severe complications or even patient death. Although leucocyte glucocerebrosidase enzyme assay is the diagnostic test, but its higher cost and availability in only fewer advanced laboratories makes it unaffordable for the majority of the poor population. So we emphasize the importance of clinical examination and comparatively affordable and easily accessible histopathological finding in early diagnosis of such a rare disease.

CASE REPORT
10 month old boy presented with jaundice, persistent thrombocytopenia and massive hepatosplenomegaly since last 4 months. He was the first child born to Sunni Muslim parents having consanguinous marriage. He was a low birth weight child (2 kg) born after full term normal vaginal delivery. Then he had history of umbilical bleeding at 15 days of life with gradually increasing jaundice for which he got admitted and received phototherapy. Then he had a history of blood stained clots from right ear on and off since 6 months of life. His developmental milestones were normal. He had normal dietary history feeding 6-8 times / day. There was no history of similar complaints in other family members. However there is no sign of ocular motor problem / any neurological abnormalities / skeletal deformity / skin pigmentation/ lymphadenopathy. Rest of the systemic examination was normal.

Investigations:
CBC showed Normocytic normochromic anemia and thrombocytopenia (30,000).
Liver function tests showed raised Total serum bilirubin (25.6mg / dl) with raised direct serum bilirubin (15.9mg/dl) and raised indirect serum bilirubin (9.7 mg/dl). Serum SGOT (1083.3 IU / ml) and SGPT (468.3 IU /L) and serum alkaline phosphatase (448.3 IU / L) was also raised. Coagulation profile was deranged and showed raised APTT (45.6 seconds), raised PT (26.7 sec) with raised INR (International normalized ratio = 2.2).

Figure 1: H and E Stain, 10X ,showing Gauchers cells having abundant, granular, fibrillar cytoplasm resembling crumpled tissue paper

Figure 2: PAS Stain, 10X, showing Gauchers cells with intensely PAS positivity USG showed hepatosplenomegaly

Histopathological examination of liver biopsy was done for confirming the diagnosis of Gaucher’s disease. On H&E stain, it showed characteristic large phagocytic cells called as Gaucher’s cells having abundant, granular, fibrillar cytoplasm resembling crumpled tissue paper appearance and eccentrically placed 1-3 nuclei (Figure 1). These cells showed intensely PAS positivity (Figure 2) ruling out other storage disorders like Niemann Pick’s Disease (PAS negative).

Final diagnosis was Gaucher’s disease (Type II, Infantile form but having no neurological symptoms yet.)

He got admitted in three hospitals previously but initially clinician’s did not suspected Gauchers disease due to its rarity and diagnostic difficulties. So at 10 months of patient age, final diagnosis was made. Patient died at 1 year of age.

DISCUSSION

Gaucher’s disease was first described by Gauchers in 1882 and the metabolic defect of enzyme deficiency was identified by Brady et al in 1962. It manifests with broad phenotypic variations typical of many metabolic disorders ranging from asymptomatic octogenarians to neonatal lethargy.

A Mutation in the β glucocerebrosidase gene located on chromosome 1q 21 - 22 leads to deficiency in lysosomal enzyme glucocerebrosidase (GBA, glucosylceramidase acid β glucosidase) which normally cleaves glucocerebroside. The main sources of glucocerebroside in phagocytic cells are the membrane glycolipid of old leucocytes and erythrocytes, while the deposits in the neurons consist of gangliosides.

Presently nearly 300 mutations have been identified in Gaucher’s disease. These mutations...
are classified as Null, mild or severe with respect to levels of glucocerebrosidase production. Null mutation such as C. 84 dup G (84GG) does not direct any enzyme production. Mild mutations such as C226A>G are those associated with Type I disease. Severe mutations such as C1448T>C (2444P) produce enzyme but when inherited with null or another severe mutation leads to Type II or Type III disease.

Patients with unexplained hepatosplenomegaly, anemia, thrombocytopenia, neurological degeneration, renal dysfunction or cutaneous abnormalities must be evaluated for Lysosomal storage disorders. But like many other Lysosomal storage disorders, Gaucher’s disease patients do not have dysmorphic features.

In the current presented case hepatosplenomegaly, anemia and thrombocytopenia were predominant features leading to jaundice, pallor, abdominal distension and bleeding manifestations. Although there was no evidence of either cardiovascular or neurological disease given the early age of presentation, these and other manifestations may still develop later.

In our case differential diagnosis was neonatal cholestasis, obstructive jaundice which was ruled out by Hepatobiliary scan report (HIDA scan). TORCH infection was ruled out due to negative serological test results. Hematological abnormalities like sickle cell disease, myeloproliferative disorders etc. (one of the causes of hepatosplenomegaly) were ruled out because of absence of other key features such as painful crisis and Abnormal peripheral smear and hemoglobin electrophoresis.

Malignant neoplasm’s like leukemia, lymphoma and primary splenic tumors were rejected as they usually present with acute rapidly developing symptoms unlike the slow progression in our case. Moreover patient lacked other characteristic symptoms of such cancers like loss of weight and appetite. Peripheral smear and Histopathological examination were also not supportive.

Many histiocytic disorders were ruled out as it was unlikely for patient age and lack of other associated symptoms such as rapid clinical deterioration, wasting, skin rash and irritability along with negative histopathological findings. Several metabolic storage disorders commonly present with hepatosplenomegaly but they were ruled out on basis of histopathological findings and PAS staining.

Niemann Pick Disease shows storage of cholesterol and sphingomyelin within the lysosomes of the cells of RES. But on histopathology examination, the cells of Niemann-Pick disease are smaller than Gauchers cells and their cytoplasm is foamy and vacuolated instead of wrinkling which stains positively with fat stains and are PAS negative. Tay-Sachs disease was rejected as it showed involvement of retina and neurons in the central and autonomic nervous system clinically with histopathopathology showing neurons ballooning with cytoplasmic vacuoles staining positive with fat stains oil red O and Sudan black B but were PAS negative (unlike our case).

Mucopolysaccharidoses (MPS) are progressive disorders showing coarse facial features, joint stiffness, cornea clouding, skeletal deformities which were not seen in our case. Mucopolysaccharides also get deposited in cells of RES. Although Liver Biopsy in MPS also shows PAS positivity but it has distended affected cells having cytoplasmic clearing known as balloon cells instead of crumpled tissue paper appearance of Gauchers cells. So MPS was also ruled out.

Pseudo-Gaucher cells are reported in the lymph nodes and bone marrow in plasmacytoid lymphoma, thalassemia, Hodgkin lymphoma, multiple myeloma, acute lymphoblastic leukemia and AIDS etc. Morphological differentiation of pseudoGaucher cells from Gauchers cells is required and the diagnosis should be made in an appropriate clinical context. Pseudo-Gaucher cells are smaller than Gauchers cells, PAS negative and lack the characteristic “wrinkled tissue paper appearance” that is seen in Gauchers cells.

Although serum lysosomal enzyme assay revealing decreased leucocyte glucocerebrosidase activity helps in confirming the diagnosis but it was not done in our case due to reluctance of patient’s family to pay for such a costly test as they belonged to lower socioeconomic status.

Gaucher’s disease was first to be successfully treated with enzyme replacement therapy.
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But, their high expenses has led to search of alternate treatment options such as substrate reduction/ inhibition therapy, Chaperone therapy and gene therapy 8.

CONCLUSION
Gaucher’s disease is a rare systemic metabolic disorder. We speculate that heightened awareness of the association of Gaucher’s disease with visceromegaly and its early diagnosis may lead to its early treatment, thus decreasing the morbidity and reducing as far as possible the neurological and skeletal involvement. Gauchers disease can mimic many other diseases and can be a diagnostic challenge. Thus, in addition to clinical examination, we highlight the role of histopathological findings in its early diagnosis due to its affordability and easy accessibility for majority of the population.

REFERENCES