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# ROLE OF LIVER BIOPSY IN GAUCHER DISEASE – A CASE SERIES PRESENTATION AT A SINGLE TERTIARY CENTRE

Pathology

**Dr.Prachi*** Senior Resident, Dharamshila Narayana superspeciality hospital, New Delhi-110092. *Corresponding Author

**Dr. Gaurav Sharma** Senior Consultant, Dharamshila Narayana superspeciality hospital.

## ABSTRACT

Gaucher Disease being the most common lysosomal storage disorder ,shows heterogeneity in geographic and ethnic distribution. Our study includes 6 cases in south- Asian population presenting with varying symptoms but without neurological and skeletal involvement and all were evaluated with the aid of liver biopsy. All were diagnosed as type I Gaucher Disease having better prognosis as compared to other Gaucher disease subtypes and increased survival rate. The line of management is intravenous administration of enzyme replacement therapy and also oral administration of glucosylceramide biosynthesis inhibitor is recommended.

## KEYWORDS

Gaucher , Type I, Enzyme Replacement Therapy

## INTRODUCTION –

Gaucher disease (GD), is a rare autosomal recessive lysosomal storage disorder first described in 1882 by Philippe Charles Ernest Gaucher and the storage of glucocerebroside in the cells was first recognized by Epstein in 1924.The metabolic defect, which is due to the deficiency of the lysosomal hydrolase β-glucosidase, or β-glucocerebrosoidse, was identified by Brady et al. [1] Incidence is 1 per 50,000 to 1 per 1,00,000 population. It is more common in Ashkenazi Jewish ethnicity with an incidence of 1 per 850 births.[2,3]. Due to the tradition of consanguinous marriage in India , its incidence has increased.

It is caused due to the deficiency of the enzyme acid β-glucosidase (GBA), results in an accumulation of glucocerebroside in the lysosomes of different cells in various organs.

There are three types of Gauchers disease- Type 1- Adult non-neuronopathic is the most common form, with incidence of 1: 40000 and 1:800 in Ashkenazi Jews, showing variable manifestations, and without CNS involvement; Type 2 is acute neuronopathic, infrequent, and is usually fatal after birth and with CNS involvement; and Type 3 is subacute or chronic neuronopathic,[4] begins in childhood, adolescence or adulthood, with involvement of the CNS, symptoms include seizures and myoclonus.

The main signs and symptoms of Gauchers disease include hepatosplenomegaly, anaemia, thrombocytopenia, bone deformities and pain, osteonecrosis, restrictive pulmonary disease, and neurological compromise in patients with GD type II and III.

Liver involvement in Gauchers disease is not well characterised and ranges from hepatomegaly to focal fibrosis to cirrhosis and hepatocellular carcinoma. Liver involvement in Gauchers disease is common, in type 1 ,especially in splenectomised patients.

Here we report a case series of 6 patients who presented with massive hepatomegaly with few cases also showing splenomegaly, cytopenia, prolonged fever, failure to thrive and vomiting. We are evaluating the patients with liver biopsy and histopathological examination in all the 6 cases, which aids in the early and prompt diagnosis of this rare genetic disorder, which were further evaluated and confirmed by genetic studies and were then administered definitive management.

## MATERIALAND METHODS –

In our present study, we have included 6 cases from January 2017 to January 2021who visited our single tertiary centre in the Department of Pediatric Gastro-enterology. 4 were males and 2 were females. The age of onset ranged from 3 months to 10 years with an average of 4 years. The following baseline demographic characteristics were recorded for each patient in the study: age, sex, ethnicity, parental consanguinity, as well as the clinical, analytical, therapeutic and follow-up data, blood investigations, liver biopsy was done to establish diagnosis. Sample size is 6 of our study, inclusive of pediatric age group (from 1 month to 18 years) only and excluding children suffering from any other chronic illness or any other genetic disorder. According to the clinical presentation and examination, all were included under Type 1 Gaucher's Disease, having better prognosis as compared to its other subtypes i.e. type II and type III.[ Table 1 , 2 ]

**Table 1 – Demographic Characteristic of our cases-**

| Demographic characteristics | Case 1 | Case 2 | Case 3 | Case 4 | Case 5 | Case 6 |
|---|---|---|---|---|---|---|
| Age | 4 years | 6 months | 1 year | 5 year | 2 years | 2.5 years |
| Sex | Male | Female | Male | Male | Female | Male |
| Ethnicity | South – Asian | South-Asian | South-Asian | South-Asian | South – Asian | South-Asian |
| Parental Consanguinity | No | Yes | No | No | No | Yes |

**Table 2 - Clinical manifestation of our Cases-**

| Clinical Signs / symptoms | Case 1 | Case 2 | Case 3 | Case 4 | Case 5 | Case 6 |
|---|---|---|---|---|---|---|
| Fever | Yes | No | No | Yes | No | No |
| Abdominal Distension | Yes | Yes | Yes | Yes | Yes | Yes |
| Anaemia | Yes | No | No | No | No | Yes |
| Thrombocytopenia | No | Yes | No | No | No | Yes |
| Failure to thrive | No | No | Yes | No | No | Yes |
| Hepatomegaly | Yes | Yes | Yes | Yes | Yes | Yes |
| Splenomegaly | Yes | Yes | No | Yes | Yes | No |
| Neurological Manifestation | No | No | No | No | No | No |
| Bone Marrow Involvement | No | No | No | No | No | No |
| Skeletal Manifestation | No | No | No | No | No | No |

**Case 1**- A 4 year-old male child of South- Asian ethnicity presented with a chief complaint of prolonged fever and abdominal distension from past 3-4 weeks. There was no history of paternal consanguinity. On general physical examination, the child had severe pallor. There were no signs of ocular motor problems or other neurological abnormalities. Per abdomen examination revealed hepato-splenomegaly. Rest of systemic examination was essentially unremarkable. Lab investigations revealed hemoglobin=8.5 g/dl, white blood cells=$6.9x10^9$/L and platelets=$175x10^9$/L). Liver enzymes were increased slightly (aspartate aminotransferase = 113IU/ml, alanine aminotransferase =61 IU/ml) but serum proteins and albumin, kidney function test and urine analysis were unremarkable. PT (prothrombin time) was 14sec [International normalized ratio (INR)=1.3] and PTT (partial thromboplastin time) was 42sec. Mantoux (tuberculin sensitivity test or PPD test) viral markers, ANA (antinuclear antibody) and HIV (human immunodeficiency virus) antibody test were negative. Blood and urine cultures were negative. X-ray of the pelvis with lower limbs was found to be unremarkable.

Fundoscopy examination and hemoglobin electrophoresis were also found to be unremarkable. Ultrasound revealed grossly enlarged spleen (140x57mm) but splenic and portal veins had diameter within normal range. Liver span was 108 mm with normal echotexture.

**Case 2-** A 6 month old female child of South – Asian ethnicity presented with chief complaint of abdominal distension from past 1 month. There was a history of paternal consanguinity. On general physical examination, the child was moderately built and nourished. There were no signs of ocular motor symptoms or other neurological abnormalities. Rest of systemic examination was essentially unremarkable. Haematologically, mild thrombocytopenic picture was seen (platelet count – $114x10^9$/ L). Liver enzymes were increased slightly (aspartate aminotransferase= 143IU/ml, alanine aminotransferase=81 IU/ml) but serum proteins and albumin, kidney function test and urine analysis were unremarkable. PT (prothrombin time) was 12sec [International normalized ratio(INR)=1.3] and PTT (partial thromboplastin time) was 32sec. Mantoux (tuberculin sensitivity test or PPD test) viral markers, ANA (antinuclear antibody) and HIV (human immunodeficiency virus) antibody test were negative. Blood and urine cultures were negative. X-ray of the pelvis was normal. Fundoscopy examination and hemoglobin electrophoresis were found to be unremarkable. Ultrasound revealed grossly enlarged spleen (120x47mm) but splenic and portal veins were not dilated. Liver span was 98 mm with normal echotexture.

**Case 3 -** A 1 year-old male child of South – Asian ethnicity presented with a chief complaint of abdominal distension and failure to thrive from past 6-7 weeks. There was no history of paternal consanguinity. On general physical examination, the child appeared sick. There were no signs of ocular motor symptoms or other neurological abnormalities. Rest of systemic examination was essentially unremarkable. Lab investigations revealed bicytopenia (hemoglobin=8.5 g/dl, white blood cells=$6.9x10^9$/L and platelets =$114x10^9$/L). Liver enzymes were mildly increased (aspartate aminotransferase= 93IU/ml, alanine aminotransferase=61 IU/ml) but serum proteins and albumin, kidney function test and urine analysis were unremarkable. PT (prothrombin time) was 14sec [International normalized ratio (INR) =1.3] and PTT (partial thromboplastin time) was 32sec. Mantoux (tuberculin sensitivity test or PPD test) viral markers, ANA (antinuclear antibody) and HIV (human immunodeficiency virus) antibody test were negative. Blood and urine cultures were negative. X-ray revealed no skeletal manifestation. Fundoscopy examination and hemoglobin electrophoresis were found to be normal. Ultrasound showed increased Liver span was 118 mm with normal echotexture.

**Case 4-** A 5 year-old male child of South – Asian ethnicity presented with a chief complaint of fever and abdominal distension from past 4-5 weeks. On general physical examination, the child looks ill. There were no signs of ocular motor symptoms or other neurological abnormalities. Per abdomen examination revealed mild hepatomegaly. Rest of systemic examination was essentially unremarkable. Lab investigations revealed normal haemogram. Liver enzymes, serum proteins and albumin, kidney function test and urine analysis were unremarkable. PT (prothrombin time) was 14sec [International normalized ratio (INR) =1.3] and PTT (partial thromboplastin time) was 32sec. Mantoux(tuberculin sensitivity test or PPD test) viral markers, ANA (antinuclear antibody) and HIV (human immunodeficiency virus) antibody test were negative. Blood and urine cultures were negative. X-ray revealed no skeletal manifestation. Fundoscopy examination and hemoglobin electrophoresis were found to be normal. Ultrasound showed increased Liver span was 96 mm with normal echotexture.

**Case – 5**
A 2 year-old female child of South – Asian ethnicity presented with a chief complaint of abdominal distension from past 6-7 weeks. On general physical examination, the child was moderately built and nourished. There were no signs of ocular motor symptoms or other neurological abnormalities. On Per abdomen examination, there was spleen and liver enlargement. Rest of systemic examination was essentially unremarkable. Lab investigations revealed bicytopenia (hemoglobin=7.5 g/dl, white blood cells=$6.9x10^9$/L and platelets=$120x10^9$/L). Liver enzymes were increased (aspartate aminotransferase= 103IU/ml, alanine aminotransferase=91 IU/ml) but serum proteins and albumin, kidney function test and urine analysis were unremarkable. PT(prothrombin time) was 12sec [International normalized ratio(INR)=1.3] and PTT (partial thromboplastin time) was 22sec. Mantoux (tuberculin sensitivity test or PPD test) viral markers, ANA (antinuclear antibody) and HIV (human immunodeficiency virus) antibody test were negative. Blood and urine cultures were negative. X-ray revealed no skeletal manifestation. Fundoscopy examination and hemoglobin electrophoresis were found to be normal. Ultrasound showed increased Liver span (128mm) and enlarged spleen (108x75mm) with normal portal vein diameter.

**Case – 6**
A 2.5 year-old male child of South – Asian ethnicity presented with a chief complaint of abdominal distension and failure to thrive from past 3-4 weeks .On general physical examination, the child looks ill and malnourished. There were no signs of ocular motor problems or other neurological abnormalities. On per Abdomen examination, Rest of systemic examination was essentially normal. Lab investigations revealed bicytopenia (hemoglobin=6.5 g/dl, white blood cells =$6.9x10^9$/L and platelets=$94x10^9$/L). Liver enzymes were increased mildly increased (aspartate aminotransferase= 133IU/ml, alanine aminotransferase=101 IU/ml) but serum proteins and albumin, kidney function test and urine analysis were unremarkable. PT (prothrombin time) was 11sec [International normalized ratio (INR) =1.3] and PTT (partial thromboplastin time) was 34sec. Mantoux (tuberculin sensitivity test or PPD test) viral markers; ANA (antinuclear antibody) and HIV (human immunodeficiency virus) antibody test were negative. Blood and urine cultures were negative. X-ray revealed no skeletal manifestation. Fundoscopy examination and hemoglobin electrophoresis were found to be normal. Ultrasound showed increased Liver span was 128mm with normal echotexture and enlarged spleen (120x54mm), with normal portal vein diameter.

Percutaneous liver biopsies were obtained under local anaesthesia and were sent in formalin to histopathology department for evaluation. The biopsy was a linear core measures 1.0 to 1.5 cm in size. After processing it was stained with routine Haematoxylin and Eosin and special stains like PAS, PAS with Diastase, Masson Trichrome, Reticulin, Copper & Iron stains.

Microsections showed deranged liver architecture with focal disruption of Hepatic Plates. Portal tracts are markedly expanded by enlarged macrophages along with Portal fibrosis. Sinusoids are filled with enlarged kupffer cells which show marked hyperplasia and are lighter stained on PAS with cytoplasmic striations. Stains for Iron and Copper were Negative showing no deposition. There was no evidence of steatosis, cholestasis, lobular inflammation, granuloma, cirrhosis and malignancy seen. Histomorphological features were consistent with kupffer cell hyperplasia and portal fibrosis consistent with storage disorder, Gaucher's disease type 1. [Figure 1- 3]

**DISCUSSION -**
Gauchers Disease is a pan-ethnic , autosomal recessive , rare genetic disorder. It is caused due to the mutation of GBA gene encoding the enzyme glucocerebrosidase located on the chromosome 1q21.31 resulting in the accumulation of glucocerebroside inside the cells , giving vacuolated appearance to the cells, named as Gauchers cells. These subset of cells are seen in other conditions also apart from this lysosomal storage disorder. It is multisystem involvement disorder involving skeletal , neurological ,liver , marrow and ocular involvement . neurological manifestation are common in type II and III type of Gauchers Disease.

According to the study by Nagral,[4], liver involvement includes hepatomegaly (63% of GD type 1 patients) and ranges from mildly elevated liver enzymes to fibrosis to cirrhosis and portal hypertension. In the work by James,[5]24 of 25 GD patients had hepatomegaly and the majority had serum transaminases and alkaline phosphatase abnormalities.

In the Baris study [6] hepatomegaly was almost universally present in GD type 1 but not usually massive unless massive splenomegaly was also present. In splenectomised patients advanced liver disease with portal hypertension and hepatopulmonary syndrome may occur.

Haematologically it may show pancytopenia or bicytopenia and rarely leucopoenia, clinically hepatosplenomegaly, changes in the central nervous system (CNS) and skeletal manifestations.

The most common signs and symptoms present in Gauchers Disease

are splenomegaly, hepatomegaly, radiological bone disease, thrombocytopenia, anaemia, growth retardation, bone pain and bone crisis, hepatosplenomegaly being the most common sign and skeletal manifestation is found more often in older children.[7]

The pathologic hallmark of GD is the presence of Gaucher cells in the macrophage-monocyte system, particularly in the bone marrow or in liver biopsy samples. These cells have a characteristic wrinkled-paper appearance, resulting from intracytoplasmic substrate deposition, and stain strongly positive with periodic acid-Schiff., enzymatic dosage in our study wasn't always available, and therefore diagnosis was based on histological findings especially the liver biopsy.

Diagnosis can be confirmed through measurement of glucocerebrosidase activity in peripheral blood leukocytes. A finding of less than 15% of mean normal activity is diagnostic. Heterozygotes generally have half-normal enzyme activity, but as much as 20% overlap with activity levels of healthy controls has been reported, rendering enzymatic testing for carrier status.

More than 200 gene mutation are observed in patient with Gauchers Disease , the most frequent pathogenic mutations in the GBA gene are p.N370S .

Genotype testing is more helpful in Ashkenazy patients as more than 6 gene mutation is observed in them (i.e. N370S, c.84insG, L444P, IVS2 + 1g > a, V394L, and R496H).

International Collaborative Gaucher Group reported that 63% of patients have experience with bone pain and 26% develop bone crisis.[8]

In our series of cases , the patients presented with hepatosplenomegaly, failure to thrive and there was no evidence of bone disease even radiologically.

In our study the differential diagnosis includes -anatomical abnormalities, congestion, infection, hematologic disorders, and infiltrative processes .

Hematologic disorders including chronic haemolytic anaemia, disorders associated with extramedullary haematopoiesis, myeloproliferative disorders, and sickle-cell disease were ruled out as there was no sign jaundice, abnormal hemoglobin electrophoresis, painful crisis and leukocytosis.

In the category of infiltrative processes, we consider either malignant neoplasms or histiocytic disorders. Malignant neoplasms having hepatosplenomegaly includes leukaemia, lymphoma and primary splenic tumors. These cancers are acute in onset , and progress rapidly unlike the slow progression course in our study.

In addition, the patient lacked other characteristic symptoms of such cancers, including appearance of illness, loss of appetite and weight loss. Other types of cancer were deemed unlikely for the patient's age .

Histiocytic disorders were excluded with respect to age and other symptoms like muscle wasting, skin rash and irritability. Among other histiocytic disorders, several metabolic storage disorders commonly present with hepatosplenomegaly.

Gaucher disease was unique in its consistent with our study symptoms.

Liver biopsy evaluation is the hallmark for the diagnosis of Gauchers Disease however; all suspects should be confirmed by demonstrating deficient acid β-glucosidase activity in isolated leukocytes.[9]

The extents of liver damage in Gauchers Disease are hepatomegaly, focal fibrosis, cholelithiasis, steatosis, haemosiderosis, overt cirrhosis, and hepatocellular carcinoma (HCC). Recent studieshave shown that liver stiffness is increased in a large proportion of patients with GD, suggesting that fibrosis may be a pervasive process even in patients with apparent controlled disease, and also that it is correlated to disease severity, making it an important cause of morbidity to be addressed in this population.

Gauchers Disease is treated with symptomatic therapies and palliative measures such as transfusion, analgesics and splenectomy. Enzyme replacement therapy (ERT) is now available and includes imiglucerase (Cerezyme), velaglucerase alfa (VPRIV), and taliglucerase alfa (Elelyso). Most patients receive the recombinant enzyme imiglucerase, and the response differs in all the 3 subtypes, with better response in type I GD.[10-12]

Life expectancy at birth in patients with type 1 GD to be 68 years, compared with 77 years in the reference population. The prognosis for symptomatic patients with type 1 or type 3 GD who receive treatment is very good, with a decrease in organomegaly and an eventual rise in hemoglobin levels and platelet counts.

## CONCLUSION –

Gauchers Disease is considered in the differential diagnosis of patients with unexplained hepatosplenomegaly for a prolonged period of time. The early recognition of Gauchers Disease is mandatory which leads to safe and effective treatment with enzyme replacement therapy hence decreasing the morbidity and reducing the visceral and skeletal involvement.

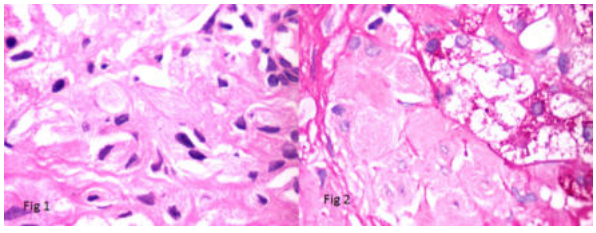


**Fig 1,2: Kupffer cell hyperplasia ,portal fibrosis andenlarged macrophages - consistent with Gaucher Disease**

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