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Study of Clinical Spectrum and Enzyme Replacement EffectinGaucher's disease: Series of 7 Cases

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Abstract
Introduction*: Gaucher's disease is a rare disease with autosomal recessive inheritance. Increased awareness with advent of availability of diagnostic facilities & enzyme replacement therapy for this disease has led to its early diagnosis even in our centre. The purpose of this study was to highlight the clinical features andtreatment challenges observed in our institute.*
Material and methods: *A retrospective study of total 7 cases of Gaucher's Disease was done with cataloguing of their clinical features, method of diagnosis, response to treatment and difficulties in the management.*
Results: *Gaucher's Disease type 1 was the most common finding with abdominal distension as the most common presenting feature with progression to bone marrow involvement.Two siblings were recorded in one family was found. One patient had undergone splenectomy without much relief. Enzyme replacement therapy was initiated in two of the patients showed marked improvement in systemic features. Treatment could not be started in 5 cases due to various constraints.*
Keywords: *Lysosomal Storage Disorder, Gaucher's disease, Enzyme Replacement Therapy*

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I. Introduction

Gaucher's disease is the most common lysosomal storage disorder and mostly prevalent among Ashkenazi Jews. It is autosomal recessive disease with three subtypes delineated by the absence or presence and progression of neurologic manifestations: type 1 or the adult, non-neuronopathic form; type 2, the infantile or acute neuronopathic form; and type 3, the juvenile or subacute neuronopathic form. [1,2,4]

Gaucher's disease results from the deficient activity of lysosomal hydrolase, acid β-glucosidase, resulting in accumulation of undegraded glycilipid substrates, the glycosulceramide, in calls of reticuloendothelial system. The progressive deposition results in infiltration of the bone marrow, progressive hepatomegaly, and skeletal complications. [2,4,5]

All suspected cases are confirmed by determination of the acid β-glucosidase activity in isolated leukocytes or cultured fibroblasts, and specific β-glucosidase gene mutation analysis.[2,6]

Treatment includes enzyme replacement therapy which reverses most symptoms like organomegaly, hematologic indices and bone pain. Enzyme replacement doesnot alter the neurologic progression. [1,2,3,5]

II. Material And Methods

We performed a 3 years (2016-2019) retrospective study of 7 patients with Gaucher's disease,followed-up in the Department of Pediatrics, Rajendra Institute of Medical Sciences (RIMS), Ranchi, India.

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 with the relevant blood investigations. Enzyme assay of β-glucosidase and chitotriosidase with dry blood spot was done to establish diagnosis.

III. Results

Table1: Symptoms in patients with Gaucher's disease type 3

SYMPTOMS	NUMBER	%
Abdominal Distension	7	100%
Abdominal Pain	3	43%
Fatigue	7	100%
Breathing Difficulty	3	43%
Failure to thrive	7	100%

Table2: Signs in patients with Gaucher's disease type 3

SIGNS	NUMBER	%
Splenomegaly	7	100%
Hepatomegaly	7	100%
Pallor	7	100%
Bone Marrow involvement	4	57%
Lower Respiratory Tract Infection	2	29%
Cholelithiasis	2	29%
Lower limb swelling	1	14%
Bleeding	1	14%

Table3: Enzyme Level at time of diagnosis

CASES	B-GLUCOSIDASE	CHITOTRIOSIDASE	MUTATION ANALYSIS
Cases 1	3.14 nmol/hr/ml	40795.66 nmol/hr/ml	Not Available
Cases 2	4.29 nmol/hr/ml	27382.99 nmol/hr/ml	Not Available
Cases 3	1.54 nmol/hr/ml	1203.3 nmol/hr/ml	homozygous p.Leu483Pro[c.(1448T>C)]
Cases 4	0.54 nmol/hr/ml	43,391.66 nmol/hr/ml	homozygous p.Leu483Pro[c.(1448T>C)]
Cases 5	0.85 nmol/hr/ml	1225.0 nmol/hr/ml	Not Available
Cases 6	1.25 nmol/hr/ml	13459.42 nmol/hr/ml	Not Available
Cases 7	0.7nmol/hr/ml	8495.3 nmol/hr/ml	homozygous p.L483P(c.1448T>c)

7 patients with Gaucher's Disease reported in our unit out of these 4 were males and 3 females. The age at onset ranged from 1 year to 5 years with an average of 2.8 years. 4 cases were Hindu and 3 cases were Muslims. Parental consanguinity was noted in 2 out of 7 (28%) cases.6 out of 7 cases was type 1 & one case was type 3 Gaucher's Disease. Two cases were siblings (one male and 1 female) with similar presentations.

The clinical manifestations are summarized in Table 1& 2.

Abdominal Distension was the chief complaint present in all 7 cases, followed by abdominal pain present in 3 out of 7 cases (42%) and recurrent chest infections in 3 out of 7 (42%). One of patient the cases presented with bilateral leg swelling.

Splenomegaly and hepatomegaly were the main clinical symptoms, present in all 7 cases (100%). Splenomegaly was massive in all cases. Hepatomegaly was moderate in all cases. Failure to thrive was prsesnt in all cases. Two patients were having multiple gallstones, One patient was also having additional features like B/L Pelvic ureteric junction obstruction, multiple mesenteric lymph nodes, Obstructive sleep apnea syndrome, dental malocclusion, clubbing grade1& reactive airway disease

The hemogram study revealed pancytopenia in 1 case, anemia in all 7 cases, thrombocytopenia in 3 cases. Renal and hepatic profile was within normal limits in all cases.

The diagnosis was based on **enzyme assay** with dry red blood spot showing low β-glucosidase and high chitotriosidase level in all. **Mutation analysis** was done in 3 out 7 cases. Splenic aspirate and bone marrow examination showed Gaucher's cells in one cases. Dexa scan was done in 2 cases which showed osteopenia.

The treatment was based on symptomatic measures such as red blood cell transfusion for anemia and analgesics for pain. Management of lower respiratory chest infections was done.

Splenectomy was performed in one case presenting with massive spleen, severe abdominal pain,splenic abscesses, cholelithiasis and high blood transfusion requirements along with cholecystectomy. The case was put on prophylactic antibiotics after splenectomy. Post splenectomy there was regression of abdominal distension and improvement in appetite with weight gain.

Only two cases were fortunate enough to get specific treatment (substitutive enzymotherapy) in whom marked improvement in signs & symptoms was noted.The chitotriosidase level showed improvement with ERT therapy indicating good prognosis.

IV. Discussion

Gaucher's Disease is the commonest lysosomal storage disorder with an estimated global incidence of 1: 40,000 to 1:60,000 live births. The metabolic defect is a deficiency of acid β-glucosidase (lysosomal glucocerebrosidase) due to biallelic mutations in *GBA* gene that results in the accumulation of glucocerebroside in lysosomes, classically in tissue macrophages; other cell types involved in disease pathophysiology include immune cells, osteoblasts and hepatocytes. Glucocerebroside-laden macrophages (Gaucher cells) accumulate throughout the body and this is the hallmark of multi-systemic disease manifestations. The severity and pattern of organ involvement is highly heterogeneous and only partly explained by *GBA* mutations.[2,3]

Gaucher disease is a pan-ethnic disorder; although, most published literature is almost entirely focused on Caucasian patients with paucity of any relevant literature from India. Due to the tradition of consanguineous marriages in parts of the country, it seems likely that the frequency of Gaucher disease may be higher in India. Of more than 300 mutations catalogued in Gaucher disease, L444P appears to be the most prevalent in India.[3]

Gaucher's Disease has 3 types based on neurological manifestations and progression of symptoms. The presentation of type 1 Gaucher's Disease is non-neuronopathic with variable age of onset, from early childhood to late adulthood. The patients may present with easy bruising from thrombocytopenia, chronic fatigue secondary to anemia, hepatomegaly with or without elevated liver function test results, splenomegaly and bone pain. Splenomegaly is progressive and eventually becomes massive. They may have growth retardation. [4,6]

Type 2 is rare and characterized by rapid neurodegenerative course with extensive visceral involvement and death within first years of life. It presents in infancy with increased tone, strabismus, organomegaly, failure to thrive and stridor. Death occurs due to respiratory compromise.

Type 3 presents with intermediate manifestations with presentation in childhood and death by 10-15 years.[4,6]

In present series, 6 cases were of type 1 Gaucher's disease while one case was type 3 Gaucher's Disease.

Patients with type 1 Gaucher disease in India present from as early as infancy to late childhood.In the present study, 6 cases were of type 1.This highly aggressive phenotype with spleno-hepatomegaly, cytopenia, irritability, bone involvement and failure to thrive is associated with early mortality without treatment.

The common differential diagnosis of the most prevalent presenting phenotype of splenohepatomegaly in Gaucher disease include hemolytic anemias typically hemoglobinopathies, non-cirrhotic portal hypertension, tropical splenomegaly, lymphoreticular malignancies and other storage disorders.

Type 3 disease is relatively more common in India as compared to Western populations. The earliest and most common neurological manifestation in these patients includes oculomotor apraxia. This ocular sign must be evaluated in each patient at every clinic visit as it may help to distinguish between Type 1 and type 3 GD. In our study, only one case was of type 3 and was associated with additional features like gall stones and pelviureteric junction obstruction.[1,4,6]

The multisystem involvement in GD may result in complications that involve multiple organ systems. Multispecialty referral is tailored dependent on the manifestations and complications encountered in the patient.[3,5]

Table 4 Complications in Gaucher Disease[3]

1.	Hypersplenism and pancytopenia
2.	Splenic rupture
3.	Bleeding diathesis due to thrombocytopenia and acquired coagulopathy
4.	Fractures and collapsed vertebral bodies, avascular osteonecrosis, chronic bone pain and bone crisis
5.	Hepatic fibrosis, portal hypertension
6.	Hepatopulmonary syndrome
7.	Hematological malignancies - multiple myeloma, hepatocellular carcinoma
8.	Parkinson's disease with Lewy body dementia
9.	Progressive neurodegenerative disease in Gaucher disease type 2 and 3

It is possible to avoid such complications in Gaucher's patients with initiation of Enzyme Replacement Therapy(ERT) at the right point of clinical course. Also, the neurological involvement cannot be reversed back if once occurred due to delay in ERT.[3,5]

Enzyme Replacement Therapy: The development and availability of ERT with Imiglucerase, since 1991 as a treatment modality, has transformed the natural course of the disease in patients affected with Gaucher's Disease. Therapy with ERT significantly ameliorates organomegaly and improves hematological manifestations. Generally, patients with Gaucher disease in India are more severely affected than in the West with earlier onset and more severe disease manifestations, hence need early institution of ERT[1,5]

In setting of progressive neurological symptoms such as seizures and or/ neuroregression, ERT is not recommended, as it cannot cross the blood brain barrier. [1,5]

As the cost of therapy is high, stringent criteria have been formulated and are recommended to identify patients who would best benefit from ERT and optimize the outcome of therapy. **Table5** lists the criteria for initiation of ERT.

Table 5: Criteria for Initiation of Enzyme Replacement Therapy[3]

ERT should be initiated in all symptomatic patients with one or more of the following features:
• Failure to thrive (height and weight less than the 5th centile of age after excluding other causes)
• Splenohepatomegaly causing mechanical discomfort or splenic infarctions
• Severe cytopenia (Bicytopenia at least):-
- Hemoglobin <8 g/dL) due to GD and not to other causes
- Platelets <60,000/µL
- Leucocyte count <3,000/mm3
• Symptomatic bone disease (bone pain, bone crisis), or active bone disease (osteopenia, fractures, marrow infiltration, infarction, osteonecrosis)
• Prior splenectomy (history of splenectomy is a marker for disease severity and such patients carry a high risk of avascular necrosis and osteonecrosis)
• Symptomatic pulmonary involvement (evidence of pulmonary hypertension on 2D echocardiography, or evidence of Infiltrative lung disease on CT chest)

In the present series, only two of the patients were able to receive specific treatment (substitutive enzymotherapy) despite need in all 7 cases.Calculations were based on their body weight (60IU/kg every fortnight). After improvement in one case with ERT, the dose has been reduced to a maintenance dose of 30IU/kg every fortnight.

Chitotriosidase level was monitored in followup as prognostic marker which showed decrement with ERT. In both cases, we observed very good prognosis withdramatic improvement especially on organomegaly. Within first 6 month, the liver and spleen volume decreased significantly, hemoglobin level improved alongwith the platlet count.There was reduced blood transfusion requirement within 1 and half year of enzyme replacement. Growth and development was improved in both cases.

The 5 cases, not under ERT showed progressive deterioration with need of repeated blood transfusion, recurrent and difficult to treat chest infection, recurring episodes of bleeding, progressive organomegaly. Repeated bouts of severe abdominal pain with abdominal distension was the major cause of morbidity and poor quality of life in these cases. Also, it was an issue of serious concern and apprehension among parents forcing them to seek medical consultation from various sites including quacks. Our unit is trying hard to procure enzyme through government or Institutional help.

V. Conclusions

- Gaucher's disease must be considered in the differential diagnosis of unexplained organomegaly with hematological features.
- Dry blood spot is an easy to prepare method by which the Leucocyte acid β-glucosidase activity can be measured for establishing the diagnosis of Gaucher disease.Dry blood spot also makes the mutation analysis possible in patients.
- Enzyme replacement therapy should be initiatedat the earliest , as effective treatment with appropriate doses and regimen, decreases morbidity significantly and reduces the visceral, skeletal and hematological involvement.
- The need for lifelong therapy and high cost makes enzyme replacement therapy unaffordable for majority of patients.

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