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Gaucher Disease: A Case Series

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Abstract

Gaucher disease (GD) is the commonest lysosomal storage disorder (LSD). We report a case series of GD from a single centre of North India. Over a 2-year period, 21 children referred with chronic splenohepatomegaly, after ruling out hemolysis and portal hypertension, were screened for GD. GD was diagnosed in 13 of them. Initial screening was done on a dried blood spot sample. Nine of them underwent molecular genetic testing and all 9 had the homozygous mutation c.1448 T>C; p.Leu483Pro (previously named as p.Leu444Pro).

Keywords: Gaucher disease, splenohepatomegaly, *GBA* mutation.

Introduction

Gaucher disease (GD) is the commonest lysosomal storage disorder (LSD) with an estimated global incidence of 1: 40,000 to 1: 60,000 live births (Mistry et al., 2007). Globally, type I GD accounts for around 95% of cases. Interestingly, type III GD is relatively more common in India as compared to the western population (Puri et al., 2018). We report a case series of GD from a single center of North India.

Patients and Methods

Children less than 16 years of age, with predominant complaints of splenohepatomegaly of more than 6 months duration and no evidence of hemolytic anemia and portal hypertension, were prospectively evaluated from June 2017 to June 2019. Hemolytic screening included complete blood count, reticulocyte count, peripheral blood smear examination and lactate dehydrogenase assay. Portal hypertension screening included a Doppler ultrasound of the abdomen. Children having any abnormality on these tests were evaluated further accordingly.

Patients with no evidence of hemolytic anemia or portal hypertension were initially screened for GD by measuring beta-glucosidase enzyme activity using the dried blood spot (DBS) kit, under the "Disha" diagnostic support service. All children were also referred for a detailed ophthalmology examination for cherry red spot and abnormal eye movements. Skeletal survey was not performed. Of those screened positive for GD on DBS, mutation analysis and plasma chitotriosidase assay were done in 9 and 10 children, respectively. Children having normal beta-glucosidase levels were advised to undergo sphingomyelinase enzyme assay in peripheral blood leucocytes (for Niemann-Pick disease type A/B), followed by clinical exome sequencing test, if the enzyme levels were normal.

Results

Twenty-one children were evaluated during the study period. GD was diagnosed in 13 children and Niemann-Pick disease type B was diagnosed in 3 (**Figure 1**). The remaining 5 children were advised further testing but could not get it done and were lost to follow up.

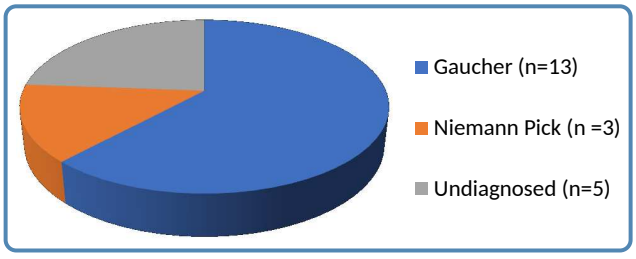

Figure 1 Etiology in patients with splenohepatomegaly of more than 6 months duration (n=21).

Table 1 Characteristics of patients with Gaucher disease in the study cohort.

Sl. No.	Age at diagnosis (years)	Sex	Liver (cm palpable)	Spleen (cm palpable)	Hb gm %	Total leucocyte count/ cu mm	Platelet count/ cu mm	Mutation in *GBA* gene	Plasma chitotriosidase (nmol/ml/hr)	Beta-glucosidase (normal reference range)	ERT sessions during and after study period	Response to ERT
1	8	F	6	23	8.5	3200	14000	NA	NA	1.1 micromol/L of blood/hr (2.3-16)	None	NAP
2	2	M	0	17	7.3	2300	100000	c.1448T>C; p.L483P	59922	0.608 nmol/hr/mg protein (4-32)	6 + 11	CBC: Hb/TLC/ Plt: 9/2.8/1.2; Spleen 12 cm palpable
3	1.5	F	2	8	NA	NA	NA	NA	NA	0.8 micromol/L of blood/hr (2.3-16)	None	NAP
4	1.5	F	5	5	5.6	3000	90000	NA	NA	0.9 micromol/L of blood/hr (2.3-16)	None	NAP
5	3	M	9	0	8.3	4000	170000	c.1448T>C; p.L483P	1041	1.9 micromol/L of blood/hr (2.3-16)	0 + 15	NAP
6	1.1	M	2	8	10.6	5500	230000	c.1448T>C; p.L483P	750	0.75 micromol/L of blood/hr (2.3-16)	None	NAP

7	2	M	5	0	9.5	5000	170000	c.1448T>C; p.L483P	1361	1.58 micromol/L of blood/hr (2.3-16)	None	NAP
8	2.5	M	0	11	9.4	2750	125000	c.1448T>C; p.L483P	1178	1 micromol/L of blood/hr (2.3-16)	None	NAP
9	1.5	M	2	12	8	2600	90000	c.1448T>C; p.L483P	2.79	1.8 micromol/L of blood/hr (2.3-16)	None	CBC: Hb/TLC/Plt: 9.5/2.9/1.1; Spleen 8 cm
10	3.5	M	2	10	8.3	7000	190000	c.1448T>C; p.L483P	1350	0.74 micromol/L of blood/hr (2.3-16)	0 + 12	NA; ERT & FU with nearby pediatrician
11	1.5	F	2	7	9.3	7500	210000	c.1448T>C; p.L483P	600	0.94 micromol/L of blood/hr (2.3-16)	0 + 12	NA; ERT & FU with nearby pediatrician
12	1.5	M	2	8	NA	NA	NA	NA	12947.3	0.43 nmol/hr/mg protein (4-32)	None	NAP
13	2	M	8	12	9	3750	115000	c.1448T>C; p.L483P	1232	1.38 micromol/L of blood/hr (2.3-16)	None	NAP

NA - Not available; NAP - Not applicable; M - Male; F - Female; CBC – Complete blood counts; Hb- Hemoglobin; TLC – Total leucocyte count; Plt – Platelet count; ERT – Enzyme replacement therapy; FU – Follow-up

The features of the GD patients are shown in **Table 1**. Eleven of the 13 children belonged to the Muslim community and history of parental consanguinity was present in 4 of them. There were 2 pair of siblings with GD (patient nos. 4 & 5, and 10 & 11) in this series. Apart from these, two children had a positive family history of sib death (patient nos. 1 & 2) with GD. The most common presenting symptom in our series was abdominal distension. The age of presentation ranged from 6 to 36 months and the median was 12 months. The age at diagnosis ranged from 13 months to 96 months with a median of 24 months.

Four patients had history of receiving blood transfusion and two of them had undergone splenectomy before referral. None had history of any bleeding manifestations or any significant bone pain or fracture.

Eight patients of GD hailed from a single district i.e., the Churu district of Rajasthan (**Figure 2**). Ophthalmological evaluation records were available in 10 children and none of them had cherry red spot or any abnormal eye movements. Hence all our patients were categorized as GD type I. Three children (patient nos. 1, 4 and 9) succumbed to the disease, due to inability to get enzyme replacement therapy (ERT).

There was anemia in all (100 %) with a mean hemoglobin of 8.65 gm/dl and platelets were low (< 1.5 lac/µL) in 4 (30%).

The beta-glucosidase enzyme level in the dried blood spot sample was low in all patients (mean level in patients 1.07 nmol/hr/mL; normal reference range of 2.3-18.4 nmol/hr/mL) suggesting the diagnosis. Out of the 10 patients in whom plasma chitotriosidase assay was done, nine had raised levels and one (patient no. 9) had a normal value, with a mean value of 8931 nmol/ml/hr (range in patients 600 – 59922 nmol/ml/hr; normal reference range of 0-90 nmol/ml/hr).

All nine patients had the same homozygous mutation c.1448 T>C; p.Leu483Pro (previously named as p.Leu444Pro). Though the phenotype of our patients is suggestive of type 1 GD, the genotype i.e., p.Leu483Pro is expected to cause the type III GD phenotype, as per existing data about the mutation. Four patients (patient nos. 2, 5, 10, and 11) are on ERT under the temporary bridging therapy program and have shown improvement in general well-being and spleen size. Complete blood counts were available in two of them and it showed improvement in all parameters. Of the remaining nine patients, three (patient nos. 1, 4, and 9) have succumbed due to inability to get ERT, and the rest are not motivated enough for regular follow up.

Discussion

GD is the most common lysosomal storage disorder. Type I GD accounts for around 95% of cases. Most published literature is focused on Caucasian patients (Mistry et al., 2015). However, there are a few previous studies available from India. In a large case series of LSD from India, GD was the most common and constituted 16% of the total 387 patients with lysosomal storage diseases reported (Sheth et al., 2013). In a study reported from north India, out of ten cases of GD, eight had type I, and one each had type II and type III (Verma et al., 2012). Another study by Nagral et al. reported type III to be constituting 27% of the total analysed 22 GD patients on ERT (Nagral et al., 2011). Of more than 300 mutations documented in GD, p.Leu444Pro(p.Leu483Pro) appears to be the most prevalent in India (Ankleshwaria et al., 2014).

The metabolic defect in GD is a deficiency of acid beta-glucosidase (also known as lysosomal beta-glucocerebrosidase) enzyme (Cox et al., 1997). The gold standard for diagnosis of GD is acid beta-glucosidase enzyme assay in blood leucocytes. However, dried blood spot (DBS) testing is suggested in India as it overcomes the logistical difficulty in sending blood samples over long distances, in good condition (Verma et al., 2015). Plasma chitotriosidase is commonly employed first as a screening marker for the diagnosis of GD and then as a biomarker for monitoring treatment efficacy. A recent study from India (Kadali et al., 2016) has shown that 22% of our population is deficient in plasma chitotriosidase activity. This could explain the normal chitotriosidase level in one of our patients.

GD is not uncommon in Rajasthan. Geographical clustering of GD in a single district suggests the possible need for population screening in that area. Consanguineous marriage appears to be one predisposing factor. The mutation noted in our series i.e., p.Leu483Pro (p.Leu444Pro) is the most common mutation reported from other studies in India. This mutation is most commonly reported to be associated with the subacute neuronopathic type i.e., type III GD. Thus, though all our patients were phenotypically type I GD, their genotype is consistent with type III GD. It would be interesting to see if some

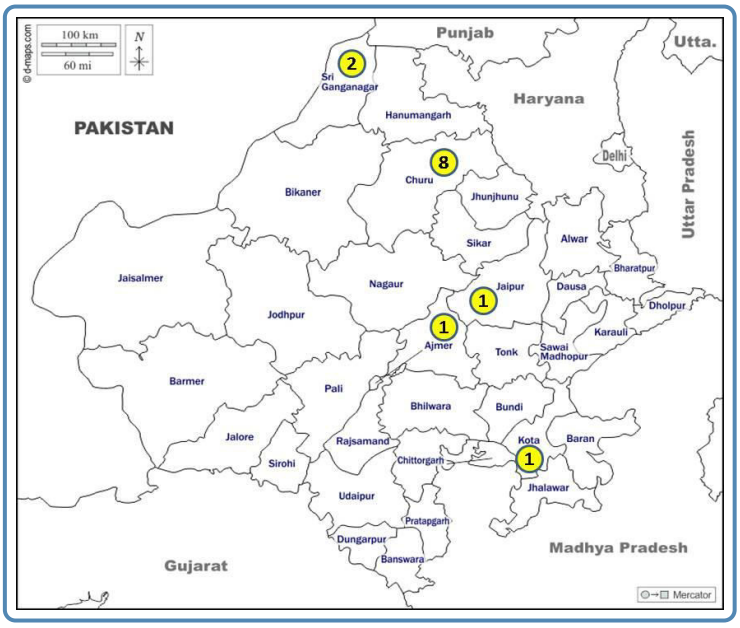

Figure 2 District-wise distribution of patients with Gaucher disease from Rajasthan in our series.

of these patients indeed progress to the type III GD phenotype in the years to come. We plan to do a repeat detailed neurological and ophthalmological evaluation on follow up, to look for subtle abnormalities seen in type III GD.

One of the main limitations of the present study is that being a study from a tertiary referral centre, the results cannot be generalized to the general population.

This article should help improve the awareness of GD when a child presents with splenohepatomegaly of chronic duration when other causes such as infections, portal hypertension and hemolytic anemia have been ruled out.

Acknowledgement: Enzyme replacement therapy for our patients is being provided by Sanofi Genzyme as bridging therapy, on compassionate grounds.

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