INTRODUCTION

Lysosomal storage disorders (LSDs) are a heterogeneous group of large molecule inborn errors of metabolism due to deficiency of lysosomal enzyme and defect in the transport membrane or activator proteins. This results in accumulation of undigested carbohydrates, proteins, fats and nucleic acids within the cell and produce diverse phenotype of LSD. To date there are nearly 50 different enzyme deficiencies causing 40 known storage diseases. Although individual disorder is rare but collectively group of LSD have a frequency of 1 in 5000 live births worldwide. The most common LSD among known LSDs is Gaucher disease (GD), Mucopolysaccharidosis (MPS), Pompe disease, Niemann-pick disease, and Gangliosidosis. The progressive accumulations of these products lead to cellular dysfunction and produce a variety of clinical phenotype. The LSDs are classified primarily based on the character of stored material. Early diagnosis or identification through the clinical presentation is essential for better outcome.

A few Indian studies have been available to address incidence, clinical features, and mutation spectrum of LSDs in India. Prevalence of LSDs is likely to be higher in India because of higher frequency of consanguinity in few communities and large population in India. Most of the published literature for diagnosis and management of LSD are from genetic centers and diagnostic laboratories in India. There are barriers such as limited diagnostic facilities and lack of awareness among clinician for the early diagnosis of LSD in a resource poor set up like India. This study aims to identify the type, frequency clinical spectrum and their outcome of LSDs at Pediatric rare disease centre, Rajasthan.

MATERIAL AND METHODS

This study was a retrospective study of 65 children, visited to centre of Rare Disease, Department of Pediatrics, J K Lon hospital, SMS medical college, Jaipur, Rajasthan in a period from December 2016 to Dec. 2019. Our hospital is a tertiary care institute; patients are referred from all over the state and from neighboring state also. All relevant clinical history such as three generation pedigree, history of affected family members or sibling, consanguinity, age of onset of symptoms, age of presentation, were documented in performa. Examination included clinical observation, anthropometry.

Keywords: Gaucher disease, lysosomal storage disease, mucopolysaccharidosis, splenomegaly
measurement, facial dysmorphism assessment by medical geneticist, and general as well as systemic examination. All children diagnosed to have LSD on the basis of their clinical features and laboratory findings were included in this study. The details of the baseline investigations and screening as well as enzyme analysis results were noted in the performa. Screening test included skeletal survey for dysostosis multiplex, fundus examination for cherry red spot, neuro-imaging for leukodystrophies, glucosaminoglycans (GAGS) toluidine blue spot test for MPS, chitotriosidase (Gaucher and Niemana Pick disease) or P- Purocatechol sulphate for I-Cell Disease. Confirmation was done by definitive enzyme analysis on dried blood spot or whole blood from diagnostic laboratories. Molecular analysis was done wherever feasible. The collected data was statistically analyzed.

RESULTS

Our cohort comprised 65 children with different type of LSDs including 54 males and 11 females. The average age of presentation of the LSD patients was 3.5 years (range 6 months to 13 years). Consanguinity was present in 16 families (24%). Twenty-four patients (36%) had history of sibling affected with similar features; most of them were expired without establishing the diagnosis. Gaucher disease was the most commonly found LSD (46.1%) followed by mucopolysaccharidosis (35.3%). The distributions of different type of LSD are depicted in Table 1.

The most common features at presentation were coarseness of face, abdominal distention, short stature, skeletal dysplasia, developmental delay, neuroregression, seizures, hearing, and vision loss.

Among GD patients group (n = 30; male = 26 female = 4), common presentation was anemia, thrombocytopenia and splenohepatomegaly/hepatomegaly. Most of them had Beta glucocerebrosidase enzyme activity between 0 to less than 10% of the normal reference range. Molecular studies were performed in fourteen patients, revealed pathogenic mutation L444P in twelve cases [Table 2].

MPS type 2 (Hunter syndrome) was the most common (39.1%) type, followed by MPS type 1(Hurler syndrome) (30%) and MPS type IVA (Morquio syndrome) (17.3%) in MPS patients group (n = 23), [Table 3]. Facial Coarseness was depicted in all type 1 and 2 MPS patients. Dysostosis multiplex was encountered in all except MPS type 3. Mutation confirmation was done in 12 patients.

The non GD, non-MPS group (n = 12), comprising most common GM1 Gangliosidosis (n = 4) followed by Pompe disease (n = 2), Tay-sachs disease (n = 2), Metachromatic Leucodystrophy (n = 2), Mucolipidosis type II (I-cell disease) (n = 1), and Sandhoff disease (n = 1) [Table 4].

Mutation analysis was available in 7 out of 12 non-GD non-MPS patients. All were known pathogenic mutations. Sanger confirmation was done where mutation was detected by exome sequencing. Parental testing was not possible due to financial constrain.

Enzyme replacement therapy (ERT) is instituted for two GD patients and two type 1 patients. All other patients are provided with symptomatic and supportive treatment including correction of anemia, prevention of osteoporosis or bone complications. Preconceptional genetic counseling was done to prevent risk of recurrence.

DISCUSSION

Patients with LSDs are most commonly presented in pediatric age group (<18 group). The age of presentation and severity of symptom depends on the level of residual functional enzyme and rate of intracellular substrate accumulation.[11]

The suspicion of LSD is made according to clinical symptoms, given in Table 5. Since most LSD is not apparent at birth and has multi-organ involvement, diagnosis by the enzyme activity assays and molecular examination is advised. Sanofi Genzyme India did enzyme assay for Gaucher disease, Pompe disease, MPS type I, Niemann Pick B disease, and Fabry disease free of cost. Molecular confirmation was also done of positive cases.

We divided LSDs patients into three groups: GD group, MPS group, and non-GD non MPS group.

GD was the most commonly diagnosed LSD (46.1%) similar to that observed worldwide and in India.[10,12-16] A study by Sheth J. et al., included 432 children with clinical symptoms suggestive of LSD showed 50.2% with glycolipid storage disorders including Gaucher disease followed by mucopolysaccharidosis in 21.7% cases.[10] Another study by Pradhan et al., diagnosed a total of 55 cases; of these 24 cases were GD and 31 cases were non-Gaucher disease.[12] Retrospective study by Agarawal et al., showed LSD in 119 cases (2.03%) of all referrals. Among them GD was the most common type (31.93%) followed by MPS (20.16%).[17]

Visceromegaly was the most common reason for referral. Bicytopenia (anemia and thrombocytopenia) was present in 14/30 cases, while anemia in 9/30 cases at the time of presentation. Rest had pancytopenia. The cause for both anemia and thrombocytopenia in most patients with GD is the

| Disorder              | Number of cases (N = 65) |
|-----------------------|--------------------------|
| Gaucher disease       | 30 (46.1%)               |
| MPS                   | 23 (35.3%)               |
| GM1 gangliosidosis    | 4 (6.1%)                 |
| Pompe disease         | 2 (3%)                   |
| Tay Sach’s            | 2 (3%)                   |
| MLD                   | 2 (3%)                   |
| I-Cell Disease        | 1 (1.53%)                |
| Sandhoff disease      | 1 (1.53%)                |

References:
1. Pradhan et al., 2018
2. Sheth et al., 2019
3. Agarawal et al., 2020

Table 1: Distribution of the confirmed LSD cases
| Sr. No. | Age at presentation | Gender | Clinical features at the time of diagnosis | Organomegaly | Enzyme Level (β-glucocerebrosidase activity $n>(2\text{ nmol/hr/ml})$) | MOLECULAR |
|---------|---------------------|--------|-------------------------------------------|--------------|------------------------------------------------|------------|
| 2 Year  | M                   | H,S,A  | Liver-11.47 cm, Spleen -10.65 cm          | 0.35         | Homozygous L444P (c.1448T>C)                  |            |
| 13 Year | M                   | H,S,B  | Liver-13.9 cm, Spleen -17.5 cm            | 1.2          | Homozygous L444P (c.1448T>C)                  |            |
| 2.5 Year| M                   | H,S,P,GR | Liver 12 cm, Spleen 14 cm | 1.5          | Homozygous L444P (c.1448T>C)                  |            |
| 1 Year  | M                   | H,S,A  | Liver-10.7 cm, Spleen -11.7 cm            | 0.88         | Homozygous L444P (c.1448T>C)                  |            |
| 15 Months| M                 | H,S,B  | Liver-16.7 cm, Spleen -14.6 cm           | 1.9          | Homozygous L444P (c.1448T>C)                  |            |
| 11 Months| F                  | H,B,Sx | Liver-13.5 cm                             | 1.7          | Compound heterozygous L444P and RecNcil of exon 10 |            |
| 6 Months| M                   | H,S,P, | Liver-16.5 cm, Spleen -19 cm              | 1.01         | Homozygous L444P (c.1448T>C)                  |            |
| 6 Year  | M                   | H,S,A  | Spleen -11.5 cm                           | 1.31         | Homozygous L444P (c.1448T>C)                  |            |
| 3 Year  | M                   | H,S,P  | Liver 12.5 cm, Spleen -16.4 cm            | 0.5          | Homozygous c.1603C>T (R496C)                  |            |
| 4 Year  | M                   | H,S,A  | Liver 11 cm, Spleen -1.5 cm               | 0.6          | Homozygous L444P (c.1448T>C)                  |            |
| 2 years | M                   | H,P,Sx | Liver-10 cm                               | 0.608        | Homozygous L444P (c.1448T>C)                  |            |
| 2 yrs   | M                   | H,B,Sx | Liver-11.2 cm                             | 0.46         | Homozygous L444P (c.1448T>C)                  |            |
| 7 Year  | F                   | H,B,Sx | Liver-12.5 cm                             | 0.8          | Homozygous L444P (c.1448T>C)                  |            |
| 2 Year  | M                   | H,S,P,GR | Liver-10.21 cm, Spleen -10.07 cm        | 1.38         | Homozygous L444P (c.1448T>C)                  |            |
| 7 Year  | M                   | H,B,Sx | Liver 11.6 cm                             | 1            | Homozygous L444P (c.1448T>C)                  |            |
| 3 Year  | M                   | H,S,P,O| Liver 10.8 cm, Spleen -12 cm              | 1.4          | Homozygous L444P (c.1448T>C)                  |            |
| 6 Year  | M                   | H,S,A  | Liver 12 cm, Spleen 11 cm                 | 0.4          | Homozygous L444P (c.1448T>C)                  |            |
| 11 Months| M                 | H,S,B,GR | Liver 10.4 cm, Spleen 14 cm             | 1.25         | Homozygous L444P (c.1448T>C)                  |            |
| 3 Year  | M                   | H,S,A  | Liver-9.8 cm, Spleen -11.6 cm             | 0.92         | Homozygous L444P (c.1448T>C)                  |            |
| 5 Year  | M                   | H,S,B  | Liver 11 cm, Spleen 13.4 cm               | 1            | Homozygous L444P (c.1448T>C)                  |            |
| 4 Year  | M                   | H,B,Sx | Liver-12.36 cm                            | 1.54         | Homozygous L444P (c.1448T>C)                  |            |
| 18 Months| M               | H,S,P  | Liver 12 cm, Spleen 14 cm                 | 1            | Homozygous L444P (c.1448T>C)                  |            |
| 8 Year  | F                   | H,S,A  | Liver 10 cm, Spleen -15.15 cm             | 1.47         | Homozygous L444P (c.1448T>C)                  |            |
| 14 Months| M                 | H,S,B  | Liver-12 cm, Spleen -14 cm                | 0.91         | Homozygous L444P (c.1448T>C)                  |            |
| 18 Months| M               | H,B,Sx | Liver 11 cm, Spleen 12 cm                 | 1.8          | Homozygous L444P (c.1448T>C)                  |            |
| 20 Months| M                 | H,S,B  | Liver 12 cm, Spleen 13 cm                 | 0.74         | Homozygous L444P (c.1448T>C)                  |            |
| 10 Months| M                 | H,S,B  | Liver-12 cm, Spleen -15 cm                | 1.63         | Homozygous L444P (c.1448T>C)                  |            |
| 16 Months| M                 | H,S,A  | Liver-8 cm, Spleen -10 cm                 | 1.58         | Homozygous L444P (c.1448T>C)                  |            |
| 10 Months| M                 | H,S,B  | Liver-8.1 cm, Spleen -12.1 cm             | 1.97         | Homozygous L444P (c.1448T>C)                  |            |
| 2 Year  | F                   | H,S,A  | Liver 11 cm, Spleen 14 cm                 | 0.69         | c.1504C>T/exon 4-10 del                       |            |

A = Anemia, B = Bicytopenia(anemia and thrombocytopenia), P = Pancytopenia, S = splenomegaly, H = hepatomegaly, Sx = splenectomy, GR = growth retardation O = osteomyelitis
infiltration of bone marrow with Gaucher cells. Seven patients had history of splenectomy at the time of presentation. All had bicytopenia or pancytopenia. It is reported that splenectomized patients with Gaucher disease continue to suffer from anemia and thrombocytopenia.[13] The number of splenectomized patients are more in our study with the belief that splenectomy may

| Table 3: Profile of MPS patients (n = 23) |
|----------------|----------------|----------------|----------------|----------------|----------------|
| Type of MPS    | No (n = 23)    | Gender         | Clinical features                                      | Blood Enzyme Levels(range) | Molecular                                                 |
|----------------|----------------|----------------|--------------------------------------------------------|-----------------------------|-----------------------------------------------------------|
| MPS I          | 7 (30.43%)     | M = 6 F = 1    | Facial Coarsness 7/7                                    | 0.1-0.6 nmol/hr/ml           | Homozygous or compound heterozygous variation in IDUA gene in all cases |
|                |                |                | Corneal clouding 7/7                                    |                             |                                                           |
|                |                |                | Hernia 7/7                                              |                             |                                                           |
|                |                |                | Hepatosplenomegaly 7/7                                  |                             |                                                           |
|                |                |                | Dysostosis multiplex 7/7                                |                             |                                                           |
|                |                |                | Intellectual disability 3/7                             |                             |                                                           |
| MPS II         | 9 (39.13%)     | M = 9          | Facial Coarsness 9/9                                    | 0-0.8 nmol/4hr/mg            | Case 1 Hemizygous mutation c.1403 G>A p.Arg468Gln in IDS gene |
|                |                |                | Corneal clouding - no                                   |                             |                                                           |
|                |                |                | Hernia- 6/9                                             |                             |                                                           |
|                |                |                | Hepatosplenomegaly 7/9                                  |                             |                                                           |
|                |                |                | Hepatomegaly 2/9                                        |                             |                                                           |
|                |                |                | Contracture 9/9                                         |                             |                                                           |
|                |                |                | Dysostosis multiplex 9/9                                |                             |                                                           |
|                |                |                | Intelligence –normal 7/9                                |                             |                                                           |
| MPSIIIA        | 1 (4.34%)      | F = 1          | Facial Coarsness –mild                                  | Heparan sulphamidase - deficient | -                                                         |
|                |                |                | Contracture - nil                                       |                             |                                                           |
|                |                |                | Dysostosis multiplex - nil                              |                             |                                                           |
|                |                |                | Intellect –severe mental retardation                     |                             |                                                           |
|                |                |                | And hyperactivity                                       |                             |                                                           |
| MPS IVA        | 4 (17.39%)     | M = 2 F = 2    | Facial coarsness – mild in 2/4                          | 0.03-0.06 nmol/17h/ mg protein | Case 1 and case 4 Homozygous mutation p.P125L of GALNS gene |
|                |                |                | Dysostosis multiplex 4/4                                |                             |                                                           |
|                |                |                | Intelligence- normal                                     |                             |                                                           |
|                |                |                | Skeletal – 4/4                                          |                             |                                                           |
| MPS VI         | 2 (8.69%)      | M1 F = 1       | Facial coarsness- nil                                   | 0.3-0.6 nmol/h/mg            | Case 1- Homozygous mutation c.293T>G:p.L98R in ARSB gene |
|                |                |                | Corneal clouding 2/2                                    |                             |                                                           |
|                |                |                | Intelligence- normal                                     |                             |                                                           |
|                |                |                | Dysostosis multiplex 2/2                                 |                             |                                                           |

| Table 4: Profile of non GD non MPS patients (n = 12) |
|----------------|----------------|----------------|----------------|----------------|----------------|
| Type of LSD    | No. (n = 12)   | Gender         | Blood Enzyme levels                                      | Mutation identified         |
|----------------|----------------|----------------|--------------------------------------------------------|-----------------------------|
| GM1 gangliosidosis | 4             | M = 3 F = 1    | β-galactosidase 0- 2.5 nmol/hr/mg                        | GLB1 gene: - case 1 Homozygous missense variation in exon 3 (c.385G>C) case 2- Homozygous variation intron 1, c.65_75+1del case 3- compound heterozygous intron1 splice site variation and exon deletion 7-9 |
| Pompe disease   | 2             | M = 2          | Ratio of Lysosomal alpha-glucosidase to total alpha glucosidase case 1 - 0.06 Case 2 - 0.19 | Case 1 -GAA gene: Homozygous nonsense variation (c.[2431 dupC]) |
| I-Cell Disease  | 1             | F = 1          | -----                                                   | GNPTAB gene: Homogygoustwo base pair deletion exon 19 |
| Tay Sachs       | 2             | M = 1 F = 1    | Case 1-0.4 nmol/h/ml Case 2 – 0.8 nmol/h/ml             | Case 1 -HEXA gene: homoygous missense variation in exon 8 (c.964G>T) |
| MLD             | 2             | M = 2          | aroylsulfatase A case 1- 6.6 nmol/17 hr/mg case 2- 7.8 nmol/17 hr/mg |                                |
| Sandhoff disease| 1             | M = 1          | Total Hexosaminidase: 79 nmol/mm/hr/mg protein          | HEXB gene: Homogygous deletion exon 4 and exon 5 |
The clinical symptoms of Lysosomal storage disorders (LSDs) are presented in Table 5.

**Table 5: Clinical symptoms of Lysosomal storage disorders (LSDs)**

| Disorder name               | Clinical symptoms                                                                 |
|-----------------------------|----------------------------------------------------------------------------------|
| Gaucher Disease             | Visceral enlargement, splenomegaly, hepatomegaly, thrombocytopenia, anemia,       |
| Type 1 (Non-neuronopathic form) | pancytopenia, coagulation abnormalities and bone pain                        |
| Gaucher Disease             | Hematological complications similar to type 1 and with involvements of the       |
| Type 2,3 (Neuronopathic form) | central nervous system (myoclonus, seizures, ataxia, cognitive impairment, and   |
| Mucopolysaccharidosis       | supranuclear gaze palsy)                                                        |
| Pompe Disease Infantile form | Hypertrophic cardiomyopathy, hypotonia, hepatomegaly, and poor prognosis due to |
| Pompe Disease Late-onset form | cardiorespiratory failure                                                        |
| GM1 Gangliosidosis          | Facial coarseness, hepatosplenomegaly, hypotonia, seizures, profound intellectual |
| Niemann-Pick Disease        | disability, Loss of vision                                                       |
| Tay Sachs Disease           | Psychomotor regression, startle reaction to loud noises, seizures, vision and   |
| Sandhoff Disease            | hearing loss, Dysarthria, dysphagia, and hypotonia followed by spasticity         |

Correct the severe anemia, leukopenia, and thrombocytopenia and sometimes life-threatening splenic infarcts.[14]

One of the patients in GD group was presented with painful movement of the left hip along with pancytopenia and splenohepatomegaly. On evaluation, diagnosed with GD and osteomyelitis. Incision and drainage were done for osteomyelitis. The orthopoeic manifestations are common in GD including abnormal bony remodeling, osteopenia and increased risk for pathologic fracture, osteomyelitis and bone crisis also called Gaucher crisis.[15] Approximately 80% of patients with GD develop classic, typical deformity known as “Erlenmeyer flask deformities of the distal femur and proximal tibia. Decreased bone density can be seen and most apparent in patients who have undergone splenectomy.[16] It is important to recognize osteomyelitis earlier to begin prompt treatment. A bone scan may be an effective means of differentiating osteomyelitis from a Gaucher crisis.[17] Risk factors include male gender, high platelet counts, and osteonecrosis.

In our cohort, mutation c.1448T>C (p.Leu483Pro) was identified in 12 out of 14 molecular confirmed cases. Mutation p.Leu483Pro in GBA gene has been identified as the most prevalent mutation in the Indian population; irrespective of the ethnic group and consider as hot spot for mass screening.[18,19] The given study reports one patient with p.Leu483Pro/RecNcil and one patient with homozygous mutation c.1603C>T (p.Arg535Cys) in exon 12. Sheth J. et al., reported the same mutant complex in their study with GD type 1 and type 2.[18]

MPS was the second most common LSD in our study group, which is comparable to other studies.[9,20,21] The common presentations were facial coarseness and skeletal finding. All MPS type 4 cases were type 4 A, concordance with other reported study.[21] All MPS type 4 had normal IQ and facial coarseness was not present.

A case of MPS type 3 A was presented with severe hyperactivity and had mild facial coarseness. Skeletal survey suggested oval shape vertebrae with normal metacarpals and phalanges. GAG study showed marked disturbance of heparan sulphate. MPS 3 type patients may be misdiagnosed due to mild phenotype and radiological features and lack of awareness in rural set ups.

Two patients were diagnosed with Pompe disease in our study group. Both had severe degree of hypotonia and referred for respiratory distress. Both detected with biventricular hypertrophy and hepatomegaly. Molecular conformation was done in one case. We could not save the children in absence of definitive management; however, we could offer prenatal diagnosis in further pregnancy. The treatment initiated before lysosomal integrity cascade can cure the disease. Treatment of the infants should be started as early as within days after birth, not months.

Case of Mucolipidosis type 2 (I-cell disease) was presented with coarse facies, short stature, stiffness of hands, and dysostosis multiplex complex on radiographs as similar to MPS patients’ group. Additional finding of gingival hyperplasia was seen. Thin layer chromatography for oligosaccharides and urinary GAGs levels was normal and confirmed by molecular study. Now at 3 years of age she could sit without support, stand with support for few seconds. She can speak bisyllabous words with good recognition. I-cell disease remains a severely life-limiting condition with respiratory failure and airway problems including sleep-disordered are common. Strategies should focus upon breathing management, maintaining quality of life and palliation. The finding of severe dysostosis multiplex in I- cell disease resemble like mucopolysaccharidosis I-H (Hurler’s disease). In I-cell disease, the abnormalities are observed in the neonatal period itself whereas in Hurler’s syndrome the radiology becomes characteristic after several months.[22] It should be suspected in the presence of MPS like features with negative toluidine blue dye test.

Apart from the mucopolysaccharidosis, the skeletal findings of dysostosis multiplex were also seen in GM1 gangliosidosis. Four patients were diagnosed with infantile GM1 gangliosidosis.
Prognosis is not good in cases of infantile GM1 gangliosidosis. Death usually occurs during the second year of life because of infection and cardiopulmonary failure. Currently no effective medical treatment is available for infantile GM1 gangliosidosis. Long-term benefit of bone marrow transplantation in infantile GM1 gangliosidosis, are not reported till yet in India.[24]

Cases of GM 2 Gangliosidosis (Tay-sachs and sandhoff) disease were presented with regression of achieved milestones and abnormality in MRI brain. Bilateral fundus cherry red spot were detracted in all cases of Tay-sachs and sandhoff disease and in two out of four GM1 gangliosidosis patients. A complete ophthalmological examination including slit lamp and fundus examination, can provide important clues for the diagnosis of such disorder.[23]

Permanent cure is enzyme replacement therapy (ERT). ERT is currently available for six LSDs (Gaucher disease, Pompe disease, Fabry disease and MPS type 1, 2 and 4 A).[26] ERT comprising of regular intravenous infusion of the recombinant enzyme. It reveres the clinical feature develop from accumulation of substrate such as hematologic, bone and visceral manifestation, and improve the quality of life. In India, very few centers are equipped to treat LSD. They are Sanjay Gandhi Postgraduate Institute of Medical Sciences (Lucknow) Indira Gandhi Institute of Child Health and Center for Human Genetics (Bengaluru), Rainbow Children’s Hospital (Hyderabad), Amrita Institute of Medical Sciences (Kochi), KEM Hospital and Jaslok Hospital (Mumbai), AIIMS and Sir Ganga Ram Hospital (New Delhi). Patients are receiving ERT through various charitable programs of ERT producing companies (Sanofi- Genzyme, Shire). Few patients are receiving ERT through central and state government.

ERT was initiated for four patients, two with Gaucher disease and two with MPS type 1 through the charitable access program on a compassionate basis. There is an increase in weight, height, hemoglobin, and platelets count in both GD patients on ERT. Their liver and spleen had regressed in size and improvement in physical activity. They do not have any serious reactions till date. MPS patients on ERT has shown significant improvement in growth and joint mobility, increase in height and weight, improvement in performing six-minute walk test, reduction in urinary glucosaminoglucon excretion and decrease sleep apnea. There is no change noted in the corneal opacity, facial coarseness, or dysostosis. The currently available forms of ERT cannot cross the blood brain barrier and do not have any effect on the neurological feature of the LSDs.

High cost of ERT emphasizes the need for genetic counseling and prevention by prenatal diagnosis such as chorionic villous sampling. The use of enzyme assay for prenatal diagnosis has limited role and mutation based prenatal diagnosis is more accurate. Accurate diagnosis of the type of LSD is important not only for appropriate line of management but also for prenatal diagnosis to prevent the risk of recurrence in the same family. Prenatal diagnosis is done through targeted mutation analysis in the chorionic willows sample or cultured amniocyte. Enzyme analysis sometime gives erroneous results due to fault in sample transportation, examination, and technical expectation.

The main limitations with molecular genetic testing are the limited availability of centers for such testing and the cost. In the present study, major limitation is a referral bias of children with clinical features suggestive of LSD where previous workup for the cause has been ruled out in the setting of limited availability of diagnostic facility at most of the places in the country.

In resources limited set up like ours, the availability of genetic testing are confined mainly to the few limited genetic centers. There need to facilitate early and accurate diagnosis and increase awareness. The most critical issue would be to sensitize and educate for pediatricians about the diverse clinical feature of LSDs. Lifelong cost of ERT is not bearable hence government should make a definite policy along with stackholders, different pharma company and organization to make available diagnostic facilities and treatment.

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Conflicts of interest
There are no conflicts of interest.

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