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RESEARCH ARTICLE

Pattern of Presentation of Lysosomal Storage Disease in Tertiary Care Hospital of Bangladesh

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ABSTRACT

Lysosomal storage disorders (LSD) are a family of genetic diseases that have a devastating impact on the patient and family with a concomitant health burden. These are inherited in an autosomal recessive or, in some cases, in an X-linked manner. Due to the variability of LSD phenotypes, the clinical characteristics of LSD are also heterogeneous. A hospital-based cross-sectional study was conducted at Department of Pediatric Neurology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka from July 2022 to June 2022 to explore clinical & laboratory profile of various forms of childhood Lysosomal storage disorders. A total of 59 suspected children of Lysosomal storage disorders (LSD), admitted to hospital during the study period, were included in this study. Among them, 55 cases were diagnosed as Lysosomal storage disorders on the basis of clinical suspicion, biochemical testing and neuroimaging study, and in few cases bone marrow study and molecular genetic testing. Mucopolysaccharidosis 24 (43.64%) and metachromatic leukodystrophy 12 (21.82%) were the most common among all lysosomal storage disorders in our study. Neuroregression 26 (47.27%), microcephaly, and dysmorphism were predominant clinical features. Abnormal neuroimaging changes were found in two-thirds 37 (67.27%) of the cases. Among them, periventricular demyelination 12 (21.82%) and cerebral atrophy 6 (10.91%) were common imaging changes in this study.

Keywords: Clinical profile, Laboratory profile, Lysosomal storage disorders.

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1. Introduction

Lysosomal storage disorders (LSD) are a family of genetic diseases that have a devastating impact on the patient and family with a concomitant health burden. Although each disorder is rare, per se, with estimated incidences ranging from 1 in 50,000 to 1 in 250,000 live births, LSDs as a group are relatively common disorders (1:5000 live births) [1]. LSD are grouped depending on the substrate involved as lipid storage disorders (sphingolipidoses, gangliosidoses, leukodystrophies), mucopolysaccharidoses (MPS), glycoprotein storage disorders, mucolipidoses, and cystinosis [2]. These are inherited in an autosomal recessive or, in some types, in an X-linked manner [3].

Age of onset varies from early childhood to late adulthood [4]. Due to the variability of LSD phenotypes, the clinical characteristics of LSD are also heterogeneous. Among the broad spectrum of clinical manifestations, symptoms can be divided into 3 categories: 1) storage abnormalities (facial dysmorphisms, visceromegaly, and cardiopulmonary dysfunctions), 2) bone-related changes (short stature, severe joint abnormalities, spinal dysmorphisms, and bone pain), and 3) neurologic symptoms (including seizures, dementia, blindness, developmental delay, ataxia, and progressive encephalopathies) [5]. In cases of LSDs involving the brain, the most common clinical characteristics are hepatosplenomegaly, skeletal anomalies, and EEG abnormalities (disorganized background and/or generalized epileptiform discharges) [3].

There is a dearth of studies regarding the pattern of presentation of patients with LSD. Even a wide variability of clinical profiles and laboratory findings encountered in different studies [4], [5]. The findings of such studies may clarify the knowledge about LSD. In addition, this study may provide future insights to potential candidates for genetic counseling and modern treatment both at home and abroad [6]–[8]. So our objective was to explore clinical

& laboratory profile of various forms of childhood Lysosomal storage disorders.

2. Methodology

This hospital-based cross-sectional study was done to explore clinical & laboratory profile of various forms of lysosomal storage disorders in Bangladesh. It was conducted in the Department of Pediatric Neurology in Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka from July 2020 to June 2022.

Children (<10 years) with clinically suspected lysosomal storage disorders were enrolled consecutively in this study. 59 children were included in this study on the basis of a high index of clinical suspicion after evaluating appropriate history and performing relevant clinical examination. Demographic characteristics, age at onset of disease, clinical presentations, and family history with parental consanguinity were recorded. Informed written consent was taken from their legal guardian or caregiver. Organomegaly was assessed clinically by a standardized approach. Additionally, ophthalmologic evaluation was done in all cases with the support of ophthalmological department of the same institute. Then diagnosis of fifty five (55) lysosomal storage disease was supported by biochemical test including blood ammonia, blood lactate, and urine for ketone body in the biochemistry department of BSMMU with appropriate standard precaution. Neuroimaging study was done in all cases. Bone marrow study was done whenever it was necessary. In addition, some biochemical tests including MPS spot urine test, acylcarnitine profile, and clinical exom sequencing were done from abroad due to a lack of logistics in our country. Data were collected from their parents in structured predesigned questionnaire. Data analysis was performed by Statistical Package for Social Science (SPSS), version-24. Results were presented as the frequency of different variables and expressed in %.

Among 59 suspected Lysosomal Storage Diseases cases, 55 confirmed cases were included and 4 cases were excluded due to incomplete investigation.

3. Results

Most of the children with LSD 39 (70.91%) were within 1–5 years of age. Male 29 (52.73%) are outnumbered than female 26 (47.27%). About half of the patients 25 (45.45%) had parental consanguinity followed by sib death 7 (12.73%) and affected sib 6 (10.91%) (Table I).

Here most common LSD were MPS 24 (43.64%) and MLD 12 (21.82%) followed by NCL 6 (10.91%), Krabbe 4 (7.27%), NPD 3 (5.45%), Mucolipidosis 3 (5.45%), Farber 2 (3.64%) and Gaucher disease 1 (1.82%) (Table II).

In this study, LSD frequently presented with neuroregression 26 (47.27%), behavioral abnormality 20 (36.36%), and Seizures 10 (18.28%) (Table III).

Common physical finding encountered in the study were dysmorphism 25 (45.45%), microcephaly 24 (43.64%), organomegaly 10 (18.18%), and macrocephaly 18 (32.73%) (Table IV).

Neuroimaging changes were found in the majority 37 (67.27%) of the cases. About one-fourth 12 (21.82%) cases had perentricular demyelination, followed by cerebral atrophy 10 (18.28%) and white matter hyperintensities 10 (9.14%) (Table V).

Abnormally high ammonia and lactate were found in 10 (18.18%) and 6 (10.91%) respectively followed by positive ketone body 8 (14.55%), acycarnitine deficiency 5 (9.09%), urinary organic acid 4 (7.27%) and MPS spot urine test 4 (7.27%) (Table VI).

Common eye findings in our study were corneal clouding 18 (33.73%), optic atrophy 8 (14.55%), cherry red spot 6 (10.91%) followed by cataract 2 (3.64%), and retinitis pigmentosa in 1 (1.82%) patients (Table VII).

TABLE I: Baseline Distribution of Study Population (n = 55)

Variable	Number	Frequency (%)
Age at onset		
<1 year	05	9.09
1–5 year	39	70.91
>5 year	11	20
Sex		
Male	29	52.73
Female	26	47.27
Family history		
Consanguinity	25	45.45
Sib death	07	12.73
Affected sib	06	10.91

TABLE II: Distribution of Study Cases of LSG by Types (n = 55)

Patterns of lysosomal storage disease	Number	Frequency (%)
Mucopolysaccharidosis (MPS)	24	43.64
Metachromatic leukodystrophy (MLD)	12	21.82
Neuronal ceroid lipofuscinosis (NCL)	06	10.91
Krabbe	04	7.27
Niemann pick disease (NPD)	03	5.45
Mucolipidosis	03	5.45
Farber	02	3.64
Gaucher	01	1.82

TABLE III: Distribution of Study Cases by Clinical Presentation of LSD (n = 55)

Presentation	Number	Frequency (%)
Neuroregression	26	47.27
Behavior abnormality	20	36.36
Seizures	10	18.28
Failure to thrive	07	12.73
Scholastic performance deterioration	05	9.09
Ataxia	04	7.27

4. Discussion

Lysosomal storage disorders (LSDs) represent a group of Neurodegenerative disorders that include at least 41 distinct genetic diseases. Each LSD results from a deficiency

TABLE IV: Distribution of Study Cases of LSD by Physical Findings (n = 55)

Physical findings	Number	Frequency (%)
Dysmorphism	25	45.45
Microcephaly	24	43.64
Organomegaly	10	18.18
Macrocephaly	18	32.73
Visual impairment	06	10.91
Hearing impairment	02	3.64
Subcutaneous nodule	01	1.82

TABLE V: Distribution of Study Population by Neuroimaging Findings (n = 55)

Neuroimaging	Number	Frequency (%)
(MRI of brain)		
Normal	18	33.73
Abnormal	37	67.27
Periventricular demyelination	12	21.82
Cerebral atrophy	10	18.28
White matter hyperintensity	05	9.14
Cerebellar atrophy	06	10.91
Thalamic hyperintensity	04	7.27

TABLE VI: Distribution of Study Populations by Biochemical Profile (n = 37)

Metabolic screening	Number	Frequency (%)
Blood		
Elevated ammonia	10	18.18
Elevated lactate	06	10.91
Acylcarnitinedeficiancy	05	9.09
Urine		
Positive ketone body	08	14.55
Organic acid	04	7.27
MPS spot urine test	04	7.27

TABLE VII: Distribution of Study Populations by Ophthalmologic Findings (n = 55)

Presentation	Number	Frequency (%)
Corneal clouding	18	33.73
Optic atrophy	08	14.55
Cherry red spot	06	10.91
Cataract	02	3.64
Retinitis pigmentosa	01	1.82
Normal	20	36.36

of a particular lysosomal protein or, in a few cases, from non lysosomal proteins. Most LSDs are inherited in an autosomal recessive manner, with the exception of Fabry disease and mucopolysaccharidosis (MPS) type II, which show X-linked recessive inheritance. These disorders are devastating for individuals and their families and result in considerable use of resources from health care systems; however, the magnitude of the problem is not well defined. To date, no comprehensive study has been done on the pattern of presentation of these disorders as a group.

In the current study, most of the patients among 55 patients were between 1 to 5 years (39/55, 70.9%). Male (29/55, 52.73%) outnumbered female in this study. In a hospital-based study among 65 children, the observed average age of presentation was 3.5 years ranging from 6 months to 13 years with a male predominance [9]. The findings of the aforementioned study corroborate with that of the current study.

In this study, the total number of MPS (24/55, 43.64%) and Metachromatic leukodystrophy (MLD) (12/55, 21.82%) among 55 patients was more common than other LSD. Goyal and Gupta conducted a retrospective cohort study among 65 admitted children from 2016 to 2019 and found Gaucher disease was the most commonly found LSD (46.1%) followed by mucopolysaccharidosis (35.3%) [9]. Poupětová *et al*. reported that more than half of all LSD patients had a lipidosis, about one-quarter mucopolysaccharidosis, and the remaining quarter suffered from NCL, GSD II, mucolipidoses, or glycoproteinoses [10]. Mehta *et al*. reported Fabry disease to be the second most prevalent disease after Gaucher disease [11]. Though these studies had a clinical spectrum similar to our findings, the incidence of different LSD varies probably due to geographical variation and limited resources for diagnoses.

In our current study, about half of the patients 25 (45.45%) had parental consanguinity followed by sib death 7 (12.73%) and affected sib 6 (10.91%). A similar hospital-based study in India by Goyal and Gupta reported consanguinity was present in 16 families (24%) and twenty-four patients (36%) among a total of 65 cases of LSDs had a history of siblings affected with similar features, most of them died before diagnoses [9]. The increased prevalence of consanguinity may be explained by cultural and religious differences among 2 different geographical areas.

In the present study, most of the LSD patients clinically demonstrated features of Neuroregression (26/55, 47.27%), followed by behaviour abnormality (20/55, 36.36%) and developmental delay (10/55, 18.28%) patient followed by deterioration of scholastic performances and ataxia. However, Parenti *et al*. stated that about 2/3 rd of LSD patients presented with neurological, behavioural and psychiatric manifestations with a wide range of clinical variation in their study [12]. Pearl *et al*. reviewed the clinical features of LSDs.They stated that most of them presents with a subacute or chronic encephalopathy. Myoclonic seizures occur in fucosidosis, Gaucher disease types II and III, GM2 gangliosidosis, Schindler disease (α-N-acetylgalactosaminidase deficiency), and sialidosis type 1 [13]. These two different studies have some similarities and disparities with our current study regarding neurological findings. However, the geographical variability and type of study may be the attributing factor.

Extensive clinical heterogeneity is seen in lysosomal storage disorders, regarding the age of onset and severity of symptoms, and the organs involved. Extra CNS menifestations like organomegaly, macrocephaly, and dysmorphism are seen in MPS, Gangliosidosis and mucolipidosis, Skin manifestation in farber disease, renal and acroparesthesia in fabry disease [1], [12], [14], [15]. Among other features in addition to neurological manifestation dysmorphism (25, 45.45%), microcephaly (24/55, 43.64%), organomegaly in (20/55, 36.36%), macrocephaly (18, 32.73%), visual problem (6/55, 10.91%), hearing impairment (2/55, 3.64%), subcutaneous nodule (01, 1.82%) was found in the current study. However, some variable clinical expression of the

same enzyme defect is not clearly understood in other studies as well as the current study. Other mechanisms, for example, the effect of specific activators, may also have an influence on phenotype [12]. The variability of methodology along with single-centred study may contribute to additional possible explanations.

In addition to excessive storage, a number of disorders affect the cerebral white matter leading to demyelination, often visible on magnetic resonance imaging (MRI) scanning as central white matter involvement and usually termed "leukodystrophy" such as MLD. Our study showed normal MRI in 18 (33.73%) and abnormal MRI present in 37 (67.27%) patients. Among them periventricular demyelination in 12 (21.82%), cerebral atropy in 10 (18.28) patients, white matter hyperintensity in 5 patients that is (9.14%), cerebellar atrophy in 6 (10.91%) patients, thalamic hyperintensity in 4 (7.27%) patients. D'Arco *et al*. reported most of the LSD subtypes Neuroimaging features are cerebral atrophy, basal ganglia hypointensity in T2 image along with some additional special findings like periventricular hyperintensity in T2 image sparing subcortical U fibre in metachromatic lekodystrophy, asymmetrical dural thickening in MPS and Gaucher disease, vasculopathy in pompe and fabry disease, thalamic hyperintensity in krabbe disease [5]. Most of these findings were present in our study. The type of LSD variability in current study may be attributed to different neuroimaging findings.

McKenna *et al*. reviewed that in LSD there is decreased ATP synthesis in mitochondria due to the accumulation of cholesterol, GAG, Lipofuschin granules [16]. Thereby increase in lactate both in blood and CNS may be seen specially in NPD, MPS and NCL. Wong *et al*. reported contact sites between mitochondria and lysosomes and suggested "mitochondria–lysosome contacts" thus allow bidirectional regulation of mitochondrial and lysosomal dynamics, and may explain the dysfunction [17]. The present study evidenced abnormally high ammonia and lactate found in 10 (18.18%) and 6 (10.91%) respectively followed by positive ketone body 8 (14.55%), acycarnitine deficiency 5 (9.09%), urinary organic acid 4 (7.27%) and MPS spot urine test 4 (7.27%). Tomatsu *et al*. reported MPS spot urine test using a given set of cut-off values: which yields sensitivity around 100% and specificity of 98.5–99.4% in diagnosing MPS I, II, and VII patients [18]. These findings justify the metabolic tests done in our poor resource country. Although specific enzymetic and genetic tests are still required to confirm the different LSD.

Ophthalmological findings comprise corneal clouding due to abnormalities in glycosaminoglycan metabolism is seen in patients with mucopolysaccharidoses types I, IV, VI and VII. In mucolipidosis type IV, corneal opacification is often the presenting feature. Many other disorders such as the oligosaccharidoses and glycoproteinoses will develop some corneal clouding, often at a later stage of the illness and sometimes only visible with a slit-lamp examination. In Fabry disease corneal haziness followed by streak-like opacities occur as the disease progresses and many patients develop a posterior cataract. The most quoted ocular abnormality associated with LSDs is the macular cherry red spot [15]. In our study regarding ophthalmological findings, corneal clouding was present (27/55, 49.09%) in most of the patients, followed by optic atrophy (8/55, 14.55%), cherry red spot (6/55, 10.91%), cataract (2/55, 3.64%) and retinitis pigmentosa (1/55, 1.82%). This wide range of spectrum of ophthalmologic findings may add to an important clue for the diagnosis of LSD.

In our country, there is a lack of logistics for enzyme assay or genetic test, antenatal or post natal diagnosis, or even screening test. Thus, clinician has to rely solely on clinical clues from history, physical examination, neurological findings, ophthalmological evaluation, MRI findings, and some other supportive investigations. Our study covered a wide spectrum of clinical and relevant laboratory findings to add insight into diagnosing different LSDs in limited settings. A definite policy should be made along with stakeholders, different pharma companies, and organizations to make available diagnostic facilities and treatment for improved outcomes of this rare group of diseases.

5. Conclusion

In our study, MPS and MLD were the most common among all lysosomal storage disorders. Neuroregression, microcephaly, and dysmorphism were predominant clinical features. Abnormal neuroimaging changes were found in two-thirds of the cases. Among them, periventricular demyelination, and cerebral atrophy were the common changes in our study. Despite the progress in the group of lysosomal storage disorders, we still cannot fully explain the individual pathologies that lead to a wide spectrum of clinical and investigation findings in our study. So further extensive studies are needed on larger populations to alleviate the shortcomings.

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Conflicts of Interest

There are no conflicts of interest.

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