Original Article

Metabolic Storage Disorders at a Tertiary Care Hospital, Pakistan

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ABSTRACT

OBJECTIVE: To determine the clinical spectrum of metabolic storage disorders presenting to a public sector tertiary care hospital in Karachi, Pakistan.

METHODOLOGY: This retrospective, cross-sectional study was conducted at the Department of Pediatrics, Dr. Ruth K.M Pfau Civil Hospital Karachi, in 2021. We reviewed the medical records of patients from January 2015 to December 2020. We included all pediatric patients admitted with suspicion of metabolic storage disorders based on two or more: visceromegaly, developmental delay, regression of milestones, fits without fever, family history of similar illness, and family history of expiry of children due to unknown reasons. Patients of malaria, enteric fever, epilepsy and cerebral palsy were excluded. We noted the demographic and clinical variables and applied descriptive statistics using SPSS version 22.

RESULTS: Out of n=140 suspected children, n=40 (28.5%) patients were diagnosed with metabolic storage disorder. Among these, 26 (65%) were Lysosomal, and 14 (35%) were Glycogen storage disorders (LSDs and GSDs). The most common clinical feature of LSDs was faltering growth in 23 (88.4%), while for GSDs, it was abdominal distention and hepatomegaly in 100% of patients. Mucopolysaccharidoses were the most common type of LSD identified in 9 (34.6%). Interestingly, family history of similar illness was not a standard feature (19.2% for LSDs and 7% for GSDs).

CONCLUSION: Metabolic storage disorders are an emerging concern to pediatric health in our population. Physicians need to keep a high index of suspicion for patients with faltering growth and visceromegaly, with or without a significant family history.

KEYWORDS: Glycogen storage diseases; Lysosomal storage diseases; Metabolic diseases; Inborn errors of metabolism; Hepatomegaly; Genetic diseases

INTRODUCTION

Inborn errors of metabolism (IEM) are genetic disorders, defined as any condition that disrupts a metabolic pathway, irrespective of being associated with abnormalities in biochemical laboratory tests. According to the recent classification by Ferreira et al., IEM is classified into nine major groups based on the distinct metabolic pathway involved[1]. Those IEMs in which enzyme defects lead to the storage of incompletely metabolised substrates in multiple tissues and body organs are termed Metabolic storage disorders, which can be broadly categorised into Lysosomal and Glycogen storage disorders[2].

Lysosomal storage disorders (LSDs) are caused by mutations in genes encoding lysosomal hydrolases, membrane proteins and transporters, leading to the intra-lysosomal storage of substrates in multiple tissues and organs[2,3]. The site(s) of storage and type of substrate stored varies, which is used to group these disorders into broad categories, including Sphingolipidosis, Mucopolysaccharidoses (MPSs), Lipid storage disorders, Mucolipidoses, Oligosaccharidosis, Neuronal ceroid lipofuscinoses and Pompe's disease[3]. Glycogen storage disorders (GSDs), on the other hand, are a group of inborn errors of glycogen metabolism that primarily affect the liver and/or muscle, the main sites of glycogen storage. They are classified into many types based on specific enzyme deficiency and affected tissue[4].

Metabolic storage disorders, as a group, are rare in Western countries, with incidence of 1 per 10,000 live births for GSDs[4] and 1 per 4,800 live births for LSDs[3]. However, due to the genetic nature of transmission, they are comparatively common in countries with high consanguinity rates, like Saudi Arabia, where the reported incidence of LSDs is 1 in 2236 live births[5]. A similar situation is expected in Pakistan, as we also have a high consanguinity rate of 63.6%[6]. Unfortunately, due to the lack of screening programs, the incidence and prevalence in Pakistan are unknown[7]. Only a few observational studies have been published where screening of high-risk patients has been done, showing varying frequencies of various inherited metabolic disorders.

Considering the minimal published literature on this topic, this study aims to determine the clinical

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spectrum of metabolic storage disorders presented to a public sector tertiary care hospital in Karachi, Pakistan. Knowledge of standard clinical features will help identify and manage these disorders, which may impact the patient's outcomes.

METHODOLOGY

This retrospective, cross-sectional study was conducted at the Department of Pediatrics of Dr. Ruth K.M Pfau Civil Hospital Karachi, Pakistan, in 2021. Medical records of patients from January 2015 to December 2020 were reviewed. All patients, one month to 12 years of age, of either gender, in whom metabolic storage disorder was clinically suspected as a differential diagnosis based on history and examination during the five-year study period, were included in the study by convenience sampling. The clinical features leading to suspicion of metabolic storage disorder included a varying combination of two or more of the following: visceromegaly, developmental delay, regression of milestones, fits without fever, family history of inherited metabolic disorders and/or family history of expiry of children less than ten years of age due to unknown reasons. Patients of malaria, enteric fever, leishmaniasis, epilepsy and cerebral palsy were excluded. All suspected patients had undergone investigations per institutional protocols to lead towards diagnosis. Baseline hematologic investigations included complete blood count (CBC) and liver function tests (LFTs). Then, specific tests were done per the clinical suspicion of a particular storage disorder type. For Glycogen Storage Disorders (GSDs), fasting blood sugar, serum triacylglycerol, serum uric acid and liver histopathology were performed. For Lysosomal Storage Disorders (LSDs), for Mucopolysacchraidoses (MPSs), the skeletal survey was done; lipid storage disorders for, bone marrow biopsy was done and for Metachromatic Leucodystrophy (MLD), Magnetic Resonance Imaging (MRI) of the brain with contrast was done. All investigations were performed at the study centre's Central Laboratory and Radiology department, and informed consent was taken before invasive procedures. In some cases, where possible, a dried blood sample on filter paper was sent to a laboratory in India for enzyme analysis.

Patients' demographic and clinical variables were collected on a predesigned proforma, and data was stored on a password-protected computer. Data was analyzed in SPSS version 22.0. Descriptive statistics were used for computing frequencies and percentages.

RESULTS

Out of the sample of 140 suspected cases, n=40 (28.5%) were confirmed to have metabolic storage disorder. Of these 40 patients, LSDs were found in 65% (n = 26), while GSDs were found in 35% (n=14) of patients. Male gender was predominant (57.6%) among LSDs, with the mean age at presentation being 3.5 years (range 5.5 months to 13 years). The mean duration of symptoms was 15.54 months (**Table I**).

Table I: Demographic features of patients with Metabolic Storage Disorders

Demographic features	LSDs n=26 (65%)	GSDs n=14 (35%)
Predominant Gender	Male 15 (57.6%)	Female 8 (57.1%)
Mean age of presentation in months (Mean ± SD)	41.75±39.64	33.43±36.04
Mean duration of symptoms in months (Mean ± SD)	15.54±22.01	7.57 ± 6.50
Residence in urban areas	19 (73.0%)	9 (64.3%)
Consanguinity	23 (88.4%)	13 (92.9%)

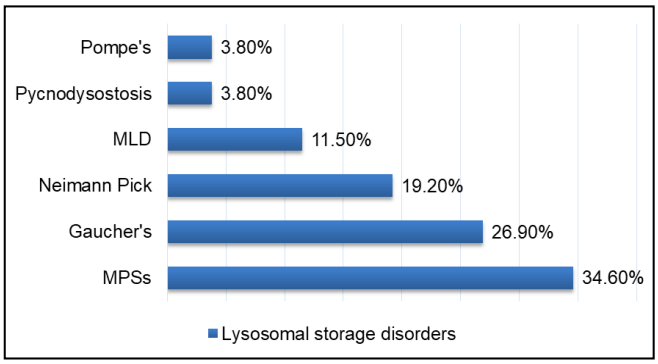
The most common clinical feature of LSDs was poor growth with growth parameters below the 50th centile in n=23 (88.4%), followed by abdominal distention due to hepatosplenomegaly in 21 (80.7%), developmental delay in 14 (53.8%) and eye findings in 13 (50%). Eye findings included corneal opacity in 6 (23%), Cherry red macula in 4 (15.3%), Optic atrophy in 2 (7.6%) and oculomotor apraxia in 1 (3.8%) (**Table II**).

Table II: Clinical features of patients with Lysosomal Storage Disorders (LSDs)

Clinical feature	No. of patients n (%)
Growth parameters below the 50th percentile	23 (88.4%)
Abdominal distention due to hepatosplenomegaly	21(80.7%)
Developmental delay	14 (53.8%)
Eye signs	13 (50%)
Anemia	12 (46.1%)
Coarse facies	11 (42.3%)
Family history of childhood expiries	7 (26.9%)
Umbilical hernia	7 (26. 9%)
One or more fits without fever	6 (23.0%)
Family history of the same illness	5(19.2%)
Regression of achieved milestones	4(15.3%)
Recurrent vomiting	3(11.5%)
Bleeding	1 (3.8%)
Jaundice	1 (3.8%)

Various types of LSDs identified were Mucopolysaccharidoses (MPSs) n=9 (34.6%), Gaucher's disease 7 (26. 9%), Neimann Pick Disease 5 (19.2%), Metachromatic Leucodystrophy (MLD) 3 (11.5%), Pycnodysostosis and Pompe's Disease both in 1 (3.8%) (**Figure I**).

Figure I: Types of Lysosomal storage disorders



Among GSDs, a female predominance was found n=8 (57.1%). The mean age of presentation was 2.8 years, ranging from 7 months to 12 years. The majority were from Urban areas, 9 (64.3%), and consanguinity was found in 13 (92.8%). The mean duration of symptoms was 7.57 months, ranging from 1 to 24 months (**Table I**). Abdominal distention and hepatomegaly were the most consistent clinical features in 100% of patients, with an average liver span of 11.57±2.36 cm. Other standard clinical features were: Growth parameters below the 50th centile in 13 (92.9%), and doll-like facies were present in 12 (85.7%) (**Table III**).

Table III: Clinical features of patients with Glycogen Storage Disorders (GSDs)

Symptoms and Signs	No. of patients n (%)
Abdominal distention and hepatomegaly	14 (100.0%)
Growth parameters below the 50th percentile	13 (92.9%)
Doll like facies	12 (85.7%)
Developmental delay	11 (78.5%)
One or more fits without fever	5 (35.7%)
Recurrent vomiting	5 (35.7%)
Family history of childhood expiries at an early age due to unknown reasons	5 (35.7%)
Anemia	4 (28.5%)
Voracious appetite	3 (21.4%)
Bleeding/bruising	2 (14.2%)
Family history of similar illness	1 (7%)

DISCUSSION

Inborn errors of metabolism (IEM) are increasingly being recognised in the Pakistani population as the awareness is increasing, though slow, and few centres are providing enzyme analysis and genetic diagnostic facilities in collaboration with foreign laboratories[8,9]. The knowledge regarding the suspicion, diagnosis and management of these disorders is still not up to the mark, consequent not only to the lack of testing facilities in government institutes[10] but also due to the considerable burden of infectious diseases in our population, which keeps the minds of the clinicians occupied while making the differentials. This study aimed to highlight the common clinical presentations of metabolic storage disorders, thus raising awareness and knowledge and highlighting these disorders as an emerging concern in our population.

Our study found a predominance of LSDs, affecting 65% of the sample population; this is consistent with findings by Afroze et al.[7] from a private sector hospital in Karachi, who also found LSDs to be more prevalent than GSDs amongst other IEMs. Interestingly, another research by Cheema et al. [8] from a public sector hospital in Lahore, Pakistan, documented GSDs as the predominant disorder, contributing 67.4% to all IEMs in their sample population. This discrepancy can be attributed to the latter centre specializing in Hepatology and Gastroenterology, thus receiving more patients with hepatomegaly and, hence, a higher frequency of GSDs. Our study's mean age of presentation was 3.4 years for LSDs and 2.7 years for GSDs, and this varies in different research papers from Pakistan, where mean age is reported from 1.3 years[11] to 2 years[12] and 3 years[9], but the age group is identical in all which is 1 to 5 years of age. In studies from India, the mean age of presentation for LSDs is 3.6 years[13], the same as our results. As expected of our societal norms, more than 88% consanguinity rate was found in our data. Hafeez et al. [14] reported a consanguinity rate of 70%, Afroze B et al. [7] reported 78%, and Cheema et al. [8] reported 97% in their datasets from various cities in Pakistan.

We found a male predominance for LSDs, supported by findings from other authors from India and Pakistan[8,11,13]. For LSDs, the mean duration of symptoms was 15 months, with the most common presenting feature being faltering growth and abdominal distention due to hepatosplenomegaly in 88.4% and 80.7% of patients, respectively. Researchers from India[15] have also reported these manifestations as the most typical manifestations of LSDs. Kariyappa P 2022[16] also reported generalized weakness and easy fatigability as a standard presentation. Other common manifestations in our patient population, including developmental delay, anemia, coarse facies and eye manifestations, are consistent with reports by other authors[15,16,17]. Family history of similar illness or childhood expiries at an early age due to unknown reasons were found in only 19.2% and 26.9% of our patients, respectively, which was against expectations considering the autosomal recessive nature of these diseases. Goyal M 2021[17] also show a positive family history in only 36% of cases, though more than ours, but still lower than expected. This reflects the possibility of new mutations occurring in the population. Thus, it can be summed up from our data that while making differential diagnoses for any patient with a chronic history of growth failure and visceromegaly, LSDs should be kept on the list, may it be lower down, irrespective of

the family history. The most common type of LSDs identified in our data set were Mucopolysaccharidoses (MPSs), followed by Gaucher's disease, with similar observations reported by Afroze B et al.[7]. Still, other researchers found Gaucher's disease to be the most common LSD type followed by MPSs[8,13]. So, the published data shows these two LSDs are the most common in our population.

For GSDs, we found a slight female predominance (57.1%), similar to findings by Bilal H 2019[19], who reported a large cohort of GSDs from Lahore, Pakistan. Shah I 2020[18] from India said a 1:1 male to female ratio in their patients with GSDs. The mean duration of symptoms for GSDs was 7.57 months, with abdominal distention due to hepatomegaly in 100% of the cases and faltering growth in 92.9%. Other researchers have reported Abdominal distention as the most common presentation in patients with GSDs too[12,18-20]. Other common manifestations in our data were doll-like facies and developmental delay in 85.7% and 78.5% of patients, respectively. Similar results were reported by Bilal H 2019[19], with doll-like facies in 31.5% and developmental delay in 69% of patients. Fits due to hypoglycemia were found in only 35.7% of children, though hypoglycemia is considered a cardinal metabolic derangement in this disorder. Other researchers observed similar findings where hypoglycemic fits were present in only 22.8% of the patients and 14% of patients[12,19]. As observed for LSDs, family history of similar illness and childhood expiries due to unknown reasons was found in only 7% and 35.7%, respectively, giving rise to suspicion for new onset mutations. Ahmed S 2022[9] performed a molecular analysis of 33 Pakistani patients with GSDs, revealing 19 variants in eight genes causing GSDs, out of 5 were novel variants. Thus, our results suggest that any child with chronic hepatomegaly, faltering growth with doll-like facies, and developmental delay should be worked up for GSD, even without positive family history and hypoglycemic fits.

Unfortunately, we don't have enzymatic or molecular diagnoses available freely in Pakistan for these patients, and diagnosis in most patients is histopathology-based[19]. For definite management, the scenario is even worse as of yet in Pakistan; one option is enzyme replacement therapy (ERT) available for only a few LSDs, namely Gaucher's disease, Pompe's disease, MPS Type 1 and Fabry's disease, which is too expensive for the patient to bear themselves. Stem cell transplantation is an alternative to lifelong ERT[21,22], but it has its own cost and risks vs benefits. Dietary management is being done for GSDs, and for LSDs, supportive management is given to the patients.

The study has some limitations. This retrospective, hospital-based study focuses only on the clinical spectrum of patients. We need further prospective, population-based studies examining these patients' morbidities, outcomes and long-term survival.

CONCLUSION

Metabolic storage disorders are commoner than anticipated in our population. Clinicians need to keep a high index of suspicion for these disorders in patients with chronic visceromegaly, faltering growth, developmental delay and doll-like or coarse facial features, even in the absence of family history and seizures.

RECOMMENDATIONS

The health authorities and government should take steps to make diagnostic and treatment modalities for these disorders available, as these are an emerging challenge to child health along with other infectious diseases. Steps should be taken to increase physicians' awareness regarding the clinical manifestations of these disorders so that the patients are picked and worked up appropriately.

Ethical Considerations: The study was approved by the institutional review board of Dow University of Health Sciences (IRB-2044/DUHS/EXEMPTION/ 2021/647).

Conflict of interest: The authors declare no conflict of interest.

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Data Sharing Statement: The corresponding author can provide the data proving the findings of this study on request. Privacy or ethical restrictions bound us from sharing the data publically.

AUTHOR CONTRIBUTION

Nasir S: Conceived the idea, acquired and analysed data and drafted the article.
Mehnaz A: Contributed to study design, interpretation of data, and critical article review.
Jamal A: Contributed to the interpretation of data and revised the article critically.
Rafique M: Contributed to data acquisition and analysis and drafting of the article.
Yahya Y: Contributed to data acquisition and interpretation, critical article review.
Kamran A: Contributed to acquiring and interpreting data and article drafting.
All authors approved the final version to publish and agree to be accountable for all aspects of the work.

REFERENCES

1. Ferreira CR, van Karnebeek CD, Vockley J, Blau N. A proposed nosology of inborn errors of metabolism. Genet Med. 2019 Jan; 21(1): 102-106. doi: 10.1038/s41436-018-0022-8. Epub 2018 Jun 8.
2. Goebel HH, Müller HD. Storage diseases: diagnostic position. Ultrastruct Pathol. 2013 Feb; 37(1): 19-22. doi: 10.3109/01913123.2012. 670060.
3. Chin SJ, Fuller M. Prevalence of lysosomal storage disorders in Australia from 2009 to 2020.

Lancet Reg Health West Pac. 2021 Dec 12; 19: 100344. doi: 10.1016/j.lanwpc.2021.100344.
4. Massese M, Tagliaferri F, Dionisi-Vici C, Maiorana A. Glycogen storage diseases with liver involvement: a literature review of GSD type 0, IV, VI, IX and XI. Orphanet J Rare Dis. 2022 Jun 20; 17(1): 241. doi: 10.1186/s13023-022-02387-6.
5. Almuqbil M. Prevalence of neurometabolic diseases in Saudi Arabia. J Biochem Clin Genet. 2020 May 27; 3(1): 14-21. doi: 10.24911/JBC Genetics/183-1585310179.
6. Iqbal S, Zakar R, Fischer F, Zakar MZ. Consanguineous marriages and their association with women's reproductive health and fertility behavior in Pakistan: secondary data analysis from Demographic and Health Surveys, 1990-2018. BMC Women's Health. 2022 Apr 14; 22(1): 118. doi: 10.1186/s12905-022-01704-2.
7. Afroze B, Lakhani L, Naz F, Somani S, Yunus ZM, Brown N. Challenges identified in the management of patients with inherited metabolic disorders–A five year experience from Pakistan. Egypt J Med Human Genet. 2016 July; 17(3): 259 -64. doi: 10.1016/j.ejmhg.2016.03.002.
8. Cheema HA, Malik HS, Parkash A, Fayyaz Z. Spectrum of inherited metabolic disorders in Pakistani children presenting at a tertiary care centre. J Coll Physicians Surg Pak. 2016 Jun 1; 26(6): 498-502.
9. Ahmed S, Akbar F, Ali AJ, Afroze B. Clinical, pathological and molecular spectrum of patients with glycogen storage diseases in Pakistan. J Pediatr Endocrinol Metab. 2022; 35(3): 373-385. doi: 10.1515/jpem-2021-0575.
10. Mansoor S. Trends of congenital hypothyroidism and inborn errors of metabolism in Pakistan. Orphanet J Rare Dis. 2020 Nov 14; 15(1): 321. doi: 10.1186/s13023-020-01602-6.
11. Khan K, Farooq N, Raziq F, Ullah H. Hematological presentation of lysosomal storage disorders. Rawal Med J. 2014; 39(1): 28-31.
12. Saeed A, Arshad H, Alvi A, Suleman H. Clinical presentation and biochemical findings in children with glycogen storage disease type 1a. Pak Armed Forces Med J 2015; 65(5): 682-85.
13. Singh A, Prasad R, Mishra OP. Spectrum of lysosomal storage disorders at tertiary centre: Retrospective case-record analysis. J Pediatr Genet. 2020 Jun; 9(2): 87-92. doi: 10.1055/s-0039 -3402070.
14. Hafeez A, Ijaz A, Chaudhry N, Ali O, Khadim MT. Diagnosis of inherited metabolic disorders by selective metabolite testing: three years experience at a tertiary care center in Rawalpindi. J Pak Med Assoc. 2020 Jan; 70(1): 53-57. doi: 10.5455/JPMA.301908.
15. Verma PK, Ranganath P, Dalal AB, Phadke SR. Spectrum of lysosomal storage disorders at a medical genetics center in Northern India. Indian Pediatr. 2012; 49(10): 799-804. doi: 10.1007/s13 312-012-0192-4.
16. Kariyappa P, Manjunath D, Sarode S, Rao US. Clinical spectrum of lysosomal storage disorders in children. Int J Contemp Pediatr. 2022 Aug; 9(8): 757-761. doi: 10.18203/2349-3291.ijcp20221860.
17. Goyal M, Gupta A. Lysosomal Storage Disorders: Clinical, Biochemical and molecular profile from Rare Disease Centre, India. Ann Indian Acad Neurol. 2021 Sep-Oct; 24(5): 686-692. doi: 10.4103/aian.AIAN_1009_20.
18. Shah I, Tolani D, Shetty NS, Karkare V. Prevalence and clinical profile of glycogen storage diseases in children from Western India. Clin Exp Hepatol. 2020 Feb; 6(1): 9-12. doi: 10.5114/ceh. 2020.93050.
19. Bilal H, Cheema HA, Fayyaz Z, Saeed A, Hamdani SS. Hepatic glycogenosis in children: spectrum of presentation and diagnostic modalities. J Ayub Med Coll Abbottabad. 2019 Jul -Sept; 31(3): 368-71.
20. Kumar TV, Bhat M, Narayanachar SG, Narayan V, Srikanth AK, Anikar S et al. Molecular and clinical profiling in a large cohort of Asian Indians with glycogen storage disorders. PLoS One. 2022 Jul 14; 17(7): e0270373. doi: 10.1371/journal. pone.0270373.
21. Sheth J, Nair A. Treatment for lysosomal storage disorders. Curr Pharmaceut Design. 2020; 26(40): 5110-8. doi: 10.2174/138161282666620101515 4932.
22. Bajaj S, Magar S, Sheth J. Lysosomal Storage Disorders: An Underdiagnosed Metabolic Disorder. Indian Practitioner. 2020 Jul 7; 73(6): 26-32.