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Characterization of 42 Egyptian Children with Lysosomal Storage Disorders

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ABSTRACT

Background: Lysosomal storage disorders (LSDs) are a heterogeneous family of genetic diseases with a broad phenotypic spectrum. There is a paucity of data on LSDs from developing countries.

Objective: We aimed to study the pattern, relative frequency, and phenotypic spectrum of LSDs in children at an Egyptian medical center.

Patients and Methods: This study included children < 18 years with LSDs diagnosed and followed up at an Egyptian medical center from January 2018 to December 2021. Data were collected on patients' demographics, clinical features, characteristic metabolites, specific enzyme assay, and genetic testing.

Results: Forty-two children (62% males, 74% parental consanguinity and 26% positive family history) were diagnosed with 10 different LSDs, representing 14% of all cases with inborn errors of metabolism (IEMs). The most frequent LSDs groups were mucopolysaccharidosis (MPS) (52.4%) and sphingolipidosis (40.8%). The most common individual diseases were MPS I (26.2%), Gaucher disease (23.8), MPS III (16.7%), and acid sphingomyelinase deficiency (11.9%). The median age at presentation was two years with a median diagnostic delay of 12 months. The most common clinical manifestations were delayed development, intellectual disability, visceromegaly, coarse facial features, and skeletal abnormalities. Finally, genetic data were available for only 12 patients (8 Gaucher disease, 3 MPS-III, and 1 MPS-VI).

Conclusion: LSDs (most commonly MPS and Gaucher disease) represent an important part of IEMs at our medical center, and the diagnosis seems challenging and often delayed.

Keywords: Lysosomal storage disorders, Mucopolysaccharidosis, Gaucher disease, Enzyme assay, Gene analysis.

INTRODUCTION

Lysosomal storage disorders (LSDs) are a heterogeneous family of inborn errors of metabolism (IEMs), which causes lysosomal dysfunction with devastating consequences on patients, their families, and health systems. To date, more than 70 different monogenic LSDs have been described, most of which have autosomal recessive inheritance, except for three X-linked entities (Fabry Disease, Hunter syndrome, and Dannon disease) [(1)]. LSDs are caused by pathogenic mutations in genes encoding for lysosomal proteins (e.g., lysosomal hydrolases), lysosomal membrane proteins, lipid and ion transporters, and enzyme modifiers/activators). These diseases are classified based on the nature of accumulated intralysosomal macromolecules, such as mucopolysaccharidosis (MPS), sphingolipidosis, oligosaccharidosis, mucolipidosis, and lysosomal membrane proteins defects [(2)].

LSDs are characterized by a broad phenotypic spectrum of nonspecific and overlapping clinical manifestations, disease severity, and age at presentations, which depends, at least in part, on the degree of residual enzyme activity and rate of intracellular macromolecule accumulation. They frequently manifest as pediatric neurodegenerative diseases that are oftentimes associated with visceromegaly. Nevertheless, based on the specific genetic problem and accumulated macromolecules, LSDs can affect multiple organ systems with many other manifestations [(3)]. Early diagnosis and management of LSDs have become quite important with the advent of therapies for more diseases (e.g., enzyme replacement therapy, hematopoietic stem cell transplantation, small molecules, and gene therapies), but this remains highly challenging, particularly in developing countries [(2)].

LSDs are individually rare but collectively have an estimated prevalence of 1 in 5,000 live births, but these diseases are likely more frequent among populations with a high percentage of consanguineous marriage, such as the Middle East and North Africa [(1)]. The most commonly reported individual LSDs are Fabry disease, Gaucher disease, MPS, metachromatic leukodystrophy, Pompe disease, and neuronal ceroid lipofuscinosis (NCL). However, the prevalence and relative frequency of LSDs vary among studies from different regions and ethnicities. For instance, NCL is relatively common in the Finnish population, Gaucher disease type I, Tay-Sachs disease, and acid sphingomyelinase deficiency (ASMD) in Ashkenazi Jewish, and Hermansky-Pudlak syndrome in northwestern Puerto Rico. This underscores the need for specific regional and ethnic studies on the pattern and characteristics of LSD [(1, 3, 4)].

Egypt is one of the largest countries in the Middle East, spanning over 1 million Km^2, has >100 million population (with around 2 million are added every year), and is characterized by a high prevalence (35.3%) of consanguineous marriage [(5)]. Based on these data, the number of patients with LSDs is expected to be high, but it seems that only a small fraction (around 20%) is actually diagnosed [(6)]. There is a paucity of data on the prevalence, spectrum, and characteristics of LSDs in the

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Middle East and North Africa, particularly in Egypt [6, 7]. In this work, we aimed to elucidate the pattern, relative frequency, and phenotypic spectrum of LSDs in a group of Egyptian children. These data are important for the medical community as well as public health authorities to enhance timely diagnosis and management of LSDs.

SUBJECTS AND METHODS

The present study included children < 18 years with LSDs who were diagnosed and followed up at the Center of Inherited Metabolic Diseases of Sohag University Hospital (CIMD-SUH) from January 2018 to December 2021. The CIMD-SUH has been established in 2017 as the main referral center for children with suspected/confirmed IEMs in Sohag governorate (southern Egypt; surface area 1,547 km^2; population >5 million) as well as neighboring areas. Our medical center follows diagnostic flow charts for the detection of LSDs [6, 8].

Children were suspected of having LSD based on the presence of the following features: mental/motor developmental regression, developmental delay, neurological abnormalities (e.g., hypotonia, spasticity, seizures), skeletal problems (e.g., kyphosis, scoliosis, chest deformities, rickets), coarse facial features, ocular abnormalities (e.g., corneal clouding, macular cherry-red spots), hepatosplenomegaly, recurrent upper respiratory tract infections, unexplained cardiomyopathy, and Fanconi syndrome. All patients underwent thorough clinical assessment, including demographic data, parental consanguinity, family history of LSDs, age at presentation and diagnosis, main symptoms, anthropometry measurement, dysmorphology assessment (by two independent experts), and detailed clinical examination.

Investigations varied according to the patients' clinical presentations and included brain imaging (CT, MRI), skeletal survey, abdominal ultrasound, echocardiography, ECG, fundus examination, neurophysiologic studies (e.g., EEG, EMG), bone marrow aspiration, and laboratory tests, such as complete blood count, liver and kidney function tests, coagulation studies, serum electrolytes, blood gases, lactate, creatine kinase, thyroid function tests, and lipid profile. Patients suspected of having MPS underwent urinary analysis of glycosaminoglycans (GAGs). Assay of specific enzyme activities was guided by clinical and laboratory findings, including specific enzymes for different subtypes of MPS, β-glucosidase for Gaucher disease, acid sphingomyelinase for ASMD, acid ceramidase for Farber disease, and acid α-1,4-glucosidase for Pompe disease. Molecular studies were available for only some patients (due to logistic and financial constraints) using CentoMetabolic® panel (Centogene, Rostock, Germany).

Ethical consent:

This study was approved by the Research Ethics Committee of Faculty of Medicine, Sohag University and was carried out in accordance with the ethical principles of the Declaration of Helsinki (2013 revision). Informed consents were obtained from parents or authorized legal guardians of all children enrolled in this study.

Statistical analysis

Patients' data were collected through Excel 2015 for Windows and were analyzed using IBM SPSS Statistics, version 20 (IBM Corp., Armonk, NY, USA). Qualitative data were presented as numbers and percentages, while quantitative data were presented as medians and range (Shapiro-Wilk test showed that quantitative data are not normally distributed). P value ≤ 0.05 was considered significant.

RESULTS

Over four years (2018 – 2021) at our medical center, 102 children were suspected of having LSDs based on their clinical manifestations. Out of these, 42 children from 39 unrelated families were diagnosed with 10 different LSDs, which constitutes 14% of all cases with IEMs detected during this period.

A summary of the pattern of LSDs and patients' demographic and clinical features is provided in **table (1)**. There were 26 males and 16 females with a median age of 6 years (range 7 m – 12 y). Parental consanguinity and having at least one sibling with the same illness were present in 31 (73.8%) and 11 (26.2%) cases, respectively. The median age at presentation was 2 years (range 1 m – 7 y), and the median time from presentation to diagnosis was 12 months (range 1 wk – 7 y). The most frequently diagnosed groups of LSDs were MPS (22 cases) and sphingolipidosis (17 cases), while the most commonly diagnosed individual LSDs were MPS I (11 cases), Gaucher disease (10 cases), MPS III (7 cases), and ASMD (5 cases). The most common clinical manifestations were delayed development, intellectual disability, visceromegaly, coarse facial features, and skeletal abnormalities. Genetic analysis was available for 13 cases.

Table (1): Summarized features of 42 Egyptian children with lysosomal storage disorders

Category	Patients No, (male/female)	Age (years) median (range)	Age (years) at presentation median (range)	Age (years) at diagnosis median (range)
MPS	22 (13/9)	5 (1.4 – 10)	2 (0.5 – 6)	3 (0.9 – 6.5)
MPS I	11 (4/7)	3 (1.5 – 8)	1.5 (0.5 – 4)	2 (0.9 – 5)
MPS II	2 (2/0)	6	2	3
MPS III	7 (5/2)	6 (1.4 – 10)	2 (1.4 – 2.5)	4 (1.4 – 4.5)
MPS IV	1 (1/0)	7	6	6.5
MPS VI	1 (1/0)	4.5	2	4.5
Sphingolipidosis	17 (11/6)	6 (0.7 – 12)	2.5 (0.1 – 7)	4 (0.3 – 12)
Gaucher disease I	10 (6/4)	8 (5.0 – 12)	4 (1.5 – 7)	7 (4 – 12)
ASMD	5 (4/1)	1 (0.7 – 3.2)	0.2 (0.1 – 0.4)	0.6 (0.3 – 1)
Farber disease	2 (1/1)	1.1 (0.7 - 1.5)	0.4 (0.3 – 0.4)	0.5 (0.4 – 0.6)
GSD				
Pompe disease	1 (0/1)	8	1	2.3
Transporters defects				
Cystinosis	2 (2/0)	10	4.25 (4 – 4.5)	5
Total	42 (26/16)	6 (0.7 – 12)	2 (0.1 – 7)	3.8 (0.3 – 12)

ASMD, acid sphingomyelinase deficiency; GSD, glycogen storage disease; MPS, mucopolysaccharidosis;

The demographic, clinical, and laboratory features of 22 (13 males and 9 females) children with MPS are provided in **table (2)**. Parental consanguinity and positive family history of MPS were present in 15 (68.2%) and 7 (31.8%) cases respectively. Patients presented at a median age of 2 y (range 5 m – 6 y) with a median diagnostic delay of 12 months (1 wk – 4 y). The most frequent clinical features were intellectual disability, coarse facies, visceromegaly, corneal clouding, and skeletal abnormalities. Among seven cases underwent echocardiography, four had mitral regurgitation and one had pulmonary hypertension. All cases showed excessive urinary excretion of GAGs and low enzymatic activities. Genetic analysis was available for four cases. Case M12 was homozygous for c.1031G>A (p.Arg344His) variant in *SGSH* gene. Cases M13 and M18 were homozygous for c.2190del (p.Phe731Serfs*76) and c.587C>T (p.Prol196Leu) variants, respectively, in *NAGLU* gene. Last, case M19 was homozygous for exons 3-8 deletions in *ARSB* gene.

Table (2): Characteristics of 22 children with mucopolysaccharidosis

ID	Type	Gender	Age	Age at onset	Age at diagnosis	Consan.	Intel. disability	Coarse facies	Corneal Clouding	Viscero-megaly	Dysostosis multiplex	Echo.	High urinary GAG	Low enzyme activity	Genetic analysis
M-1	MPS IIIB	M	10 y	18 m	4 y	+	+	+	–	+	(+)	N	+	+	NA
M-2	MPS I	M	18 m	6 m	18 m	–	+	+	+	+	+	NA	+	+	NA
M-3	MPS I	F	2 y	9 m	17 m	+	+	+	+	+	+	PHT	+	+	NA
M-4	MPS I	F	3 y	5 m	3 y	+	+	+	+	+	+	NA	+	+	NA
M-5	MPS I	M	5 y	3 y	3.5 y	+	+	+	+	+	+	NA	+	+	NA
M-6	MPS II	M	6 y	2 y	3 y	–	(+)	+	–	+	+	mild MR	+	+	NA
M-7	MPS II	M	6 y	2 y	3 y	–	(+)	+	–	+	+	N	+	+	NA
M-8	MPS III	M	16 m	16 m	16 m	+	+	+	–	(+)	(+)	NA	+	+	NA
M-9	MPS I	F	21 m	18 m	21 m	+	+	+	+	+	+	mild MR	+	+	NA
M-10	MPS III	M	10 y	9 m	9 m	+	+	(+)	–	(+)	(+)	NA	+	+	NA
M-11	MPS I	F	8 y	12 m	5 y	+	+	+	+	(+)	+	NA	+	+	NA
M-12	MPS IIIA	F	6 y	2 y	4 y	+	+	+	–	(+)	(+)	NA	+	+	*SGSH* p.Arg344His*
M-13	MPS IIIB	M	3. 5 y	2 y	3 y	–	+	+	–	(+)	(+)	NA	+	+	*NAGLU* c.2190del*
M-14	MPS I	F	7.5 y	4 y	4.5 y	+	+	+	(+)	+	+	MR	+	+	NA
M-15	MPS I	F	7 y	4 y	4.5 y	–	+	+	+	+	+	NA	+	+	NA
M-16	MPS I	M	3 y	5 m	9 m	+	+	+	+	+	+	NA	+	+	NA
M-17	MPS I	M	3 y	21 m	2 y	+	+	+	+	(+)	+	NA	+	+	NA
M-18	MPS IIIB	M	5 y	2.5 y	4.5 y	+	+	+	–	(+)	(+)	NA	+	+	*NAGLU* p.(Prol196Leu)*
M-19	MPS VI	M	4.5 y	2 y	4.5 y	+	–	+	+	+	+	MR	+	+	*ARSB* exons 3-8 del*
M-20	MPS IV	M	7 y	6 y	6.5 y	–	–	–	(+)	–	+	NA	+	+	NA
M-21	MPS IIIC	F	7 y	2 y	3 y	–	+	+	–	(+)	(+)	NA	+	+	NA
M-22	MPS I	F	2 y	18 m	2 y	+	+	+	(+)	+	(+)	NA	+	+	NA

GAG, glycosaminoglycan; MPS, mucopolysaccharidosis; MR, mitral regurgitation; NA, not applicable; PHT, pulmonary hypertension
Cases M-6 and M-7 are sib pairs. () denotes mild manifestation. * homozygous

Table (3) showed the demographic, clinical, and molecular features of 10 (6 males and 4 females) cases with Gaucher disease. Parental consanguinity and positive family history were present in 8 and 2 cases, respectively. The median ages at presentation and diagnosis were 4 years (range 18 m – 7 y) and 7 years (4 y – 12 y), respectively. The most common clinical manifestations were hepatosplenomegaly, pallor, bleeding tendency, and skeletal abnormalities. All patients showed low acid β-glucosidase enzyme activity. Eight patients underwent *GBA* analysis, five of which were homozygous for c.1226A>G (p.Asn409Ser) and three were homozygous for c.1448T>C (p.Leu483Pro).

Table (3): Characteristics of 10 Egyptian children with Gaucher disease

ID*	Gender	Age (y)	Age at presentation (y)	Age at diagnosis (y)	Consang.	HSM	Pallor	Bleeding tendency	Skeletal involvement	Neurologic involvement	Low acid β-glucosidase activity	*GBA* genetic analysis
GD-1	M	8	4	7	+	+	+	–	+	–	+	NA
GD-2	F	9	4	7	+	+	+	–	–	–	+	NA
GD-3	F	6	1.5	4	+	+	+	+	+	–	+	p.Leu483Pro/p.Leu483Pro
GD-4	F	7	3	5	+	+	+	+	+	–	+	p.Leu483Pro/p.Leu483Pro
GD-5	F	5	3	5	+	+	+	+	+	–	+	p.Leu483Pro/p.Leu483Pro
GD-6	M	6	2.5	4	–	+	–	–	–	–	+	p.Asn409Ser/p.Asn409Ser
GD-7	M	8	5	7	+	+	+	–	–	–	+	p.Asn409Ser/p.Asn409Ser
GD-8	M	9	6	7	+	+	–	–	+	–	+	p.Asn409Ser/p.Asn409Ser
GD-9	M	12	5	12	–	+	+	–	+	–	+	p.Asn409Ser/p.Asn409Ser
GD-10	M	8	7	8	+	+	+	–	+	–	+	p.Asn409Ser/p.Asn409Ser

* GD-1 and GD-2 are sib pairs

Other identified LSDs included five cases with ASMD, two with Farber disease, two with nephropathic cystinosis, and one with Pompe disease. Patients with ASMD generally presented in the first 4 months of life with hepatosplenomegaly and neurological impairment, and they were diagnosed by detection of low acid sphingomyelinase enzyme activity. The two cases with Farber disease presented in the first 3-4 months of life with hoarse cry, painful joint swelling and nodules, and failure to thrive, and their acid ceramidase enzyme activity was low. The two cases with nephropathic cystinosis presented during the fifth year of age with Fanconi syndrome and progressive deterioration of renal functions, and the diagnosis was confirmed by the detection of increased leucocyte cystine content. Last, one case with Pompe disease presented at the age of one year with muscle weakness and hypertrophic cardiomyopathy and showed low acid α-1,4-glucosidase enzyme activity (**Table 4**).

Table (4): Characteristics of other children with lysosomal storage diseases

ID	Disorder	Gender	Age	Age at presentation	Age at Diagnosis	Consang.	Cardinal features	Diagnostic test
NP-1	ASMD	M	3.2 y	1 m	3 m	+	HSM, impaired neurodevelopment	Low acid sphingomyelinase enzyme activity
NP-2	ASMD	M	7 m	4 m	5 m	–	HSM, impaired neurodevelopment	Low acid sphingomyelinase enzyme activity
NP-3	ASMD	F	16 m	2 m	12 m	+	HSM, impaired neurodevelopment	Low acid sphingomyelinase enzyme activity
NP-4	ASMD	M	12 m	2 m	8 m	–	HSM, impaired neurodevelopment	Low acid sphingomyelinase enzyme activity
NP-5	ASMD	M	10 m	2 m	6 m	+	HSM, impaired neurodevelopment	Low acid sphingomyelinase enzyme activity
FD-1	Farber	F	7 m	3 m	4 m	+	Hoarse cry, painful joint swelling and nodules	Low acid ceramidase enzyme activity
FD-2	Farber	M	18 m	4 m	6 m	+	Painful joint swelling and nodule, failure to thrive	Low acid ceramidase enzyme activity
NC-1	Cystinosis	M	10 y	4.5 y	7 y	+	Polyuria, rickets, ocular problems, CKD	Increased leukocyte cystine content
NC-2	Cystinosis	M	10 y	4 y	5 y	+	Polyuria, rickets, fair complexion, CKD	Increased leukocyte cystine content
P-1	Pompe	F	8 y	12 m	5 y	+	Muscle weakness, hypertrophic cardiomyopathy	Low acid α-1,4-glucosidase enzyme activity

ASMD, acid sphingomyelinase deficiency; CKD, chronic kidney disease; HSM, hepatosplenomegaly NC1 and NC2 are sib pairs

DISCUSSION

The present study investigated the spectrum, relative frequency, and characteristics of LSDs in 42 Egyptian children. We identified 10 different LSDs, constituting 14% of all patients diagnosed with IEMs at our medical center. The most frequent LSDs groups were MPS (52.4%) and sphingolipidoses (40.8%), while the most commonly diagnosed individual LSDs were MPS I (26.2%), Gaucher disease (23.8), MPS III (16.7%), and ASMD (11.9%). Parental consanguinity and having another sibling with the same disease were present in 73.8% and 26.2% of patients respectively. The median age at presentation was 2 years (range 1 m – 7 y) with a median diagnostic delay of 12 months (range 1 wk – 7 y). The most common clinical manifestations were delayed development, intellectual disability, visceromegaly, coarse facial features, and skeletal abnormalities. Finally, we provided genetic data for 12 patients, (8 with Gaucher disease, and 4 with MPS). These data enhance our knowledge on LSDs in southern Egypt and are important for increasing physicians' awareness for timely diagnosis and management, which is crucial for a better outcome.

In the present study, MPS was the most frequent group of LSDs (52.4%), followed by sphingolipidosis (40.5%). Our data are consistent with a previous Egyptian selective screening study, which identified MPS and sphingolipidoses in 44.5% and 30.3% respectively, among 211 children with LSDs [6]. Similarly, in a study from Eastern China on 376 patients with LSDs, MPS was the most frequent group (50.5%), followed by sphingolipidosis (25.4%) [8]. MPS has been also the most common group of LSDs in studies from Australia [9] and India [10]. However, sphingolipidosis has been reported as the predominant group of LSDs in many other studies from India [4, 11, 12], Portugal [13], Czech Republic [14], The Netherland [15], Saudi Arabia [16], UAE [17], and Oman [18].

Regarding individual LSDs in our study, the most frequently diagnosed were MPS I (26.2%), Gaucher disease (23.8%), MPS III (16.7%), and ASMD (11.9%). The most commonly identified single LSD in **Elmonem *et al.*** [6] and **Chen *et al.*** [8] studies were MPS VI (17.1%) and MPS II (24%), respectively. However, Gaucher disease has been reported as the most common LSD in many studies from India [4, 10, 12, 19, 20], Brazil [2], Australia [9], Portugal [13], and Czech Republic [14]. Other studies revealed different findings. For instance, Krabbe disease was the most common LSD in Spanish databases between 1997 and 2015 [21] and in registries of two Swedish diagnostic laboratories [22]. Pompe disease was the most frequently detected LSD in a Mexican lysosomal NBS program (55%) [23] and a Dutch study [15]. Fabry disease was the most commonly reported LSDs in Japan [24]. Lastly, an Omani study reported late infantile NCL as the most common LSDs [18].

The variability in the prevalence, pattern, and relative frequency of LSDs among studies could be attributed to multiple reasons. True differences in birth prevalence of LSDs may occur among isolated populations on a geographical, lingual, ethnic, or religious basis. For instance, Gaucher disease type I, Tay-Sachs disease, and ASMD have a higher prevalence among Ashkenazi Jewish, aspartylglucosaminuria in the Finnish population, Pompe disease in the Netherland, Hermansky-Pudlak syndrome in northwestern Puerto Rico, and MPS VI, GM1 gangliosidosis, and fucosidosis in UAE [1, 17]. Another reason is related to different inclusion criteria among studies since certain LSDs (e.g., Fabry disease) display late-onset manifestations, therefore they will have higher relative frequencies in studies including older rather than only young patients. Moreover, the prevalence and pattern will vary among studies using newborn vs high-risk screening, since some patients identified by NBS may develop late-onset and/or mild/non-specific manifestations and remain undiagnosed. Furthermore, certain specialized diagnostic techniques are not widely available, which would preclude the diagnosis of some LSDs in resource-limited settings. Lastly, the level of physician's awareness could play important role in clinical suspicion and referral of patients to more specialized centers for comprehensive evaluation [6, 25].

In the present study, almost three-quarters of children with LSDs had consanguineous parents. This goes in line with the previously reported high rate of parental consanguinity among patients with LSD from Egypt (82%) and Oman (87.5%) [6, 18]. In contrast, Indian studies reported lower proportions of parental consanguinity among patients with LSD (24% - 32.4%) [4, 10, 11, 25]. Egypt has a high prevalence of consanguineous marriage (35.3%) due to traditional cultural values and lack of awareness about the increased incidence of autosomal recessive diseases [5]. Studies have identified a high frequency of homozygosity among Egyptian children with LSDs even for those with unrelated parents, which could be explained by the custom of marriage within the small community [6, 7]. This calls for comprehensive preventive programs, including public health education, prenatal screening, carrier detection, and genetic counseling. Additionally, our study found that a quarter of patients have at least one sibling with the same illness. Some previous studies revealed higher percentages, such as 35% in Oman [18] and 36 - 44.1% in India [4, 10]. This emphasizes the importance of confirming the diagnosis, familial screening of other family members, and proper genetic counseling.

The male preponderance among children with LSDs in the current study (male to female ratio of 1.6:1) is consistent with previous studies, such as a male to female ratio of 1.3:1 in Egypt [6], 1.4:1 in Oman [18], 1.8:1 in China [8], and 3.2–5.4:1 in India [4, 19, 25]. This could be largely explained by the prevailing gender bias among Arab and Asian populations, particularly in rural areas, who seek medical care for their diseased boys but

neglect girls [4, 7]. Moreover, the X-linked inheritance of certain LSDs contributes to the observed male predominance since Fabry disease and MPS II constitute a considerable part of reported LSDs worldwide [1]. It is important to note that most studies have a small sample size and, consequently, may not reflect the real gender ratio.

Therapeutic options have been developed for certain LSDs, but there is a great need for timely diagnosis so that treatment can be started before the onset of irreversible organ damage. However, patients with LSDs commonly experience a long diagnostic odyssey, which is associated with severe deterioration and worse outcome [2]. Patients in our study experienced a median diagnostic delay of 12 months, which is close to 14 months in **Agarwal *et al.*** [20] **.** In contrast, other studies reported a longer median diagnostic delay of 2 – 3 y [6, 8]. The diagnostic delay is attributed to multiple reasons. First is the low physician's awareness of the widely variable phenotypic presentation of these rare diseases. Non-specific system manifestations of LSDs are usually confused with more common diseases, such as MPS III and behavioral problems, MPS IV and rickets, and Gaucher disease and hemoglobinopathies.

In addition, infants and toddlers have somewhat variable development. Therefore, pediatricians often follow up late-infantile patients with LSDs for multiple months until developmental milestones become clearly outside the normal range before referring the patient to a pediatric neurologist, who may also take multiple months of investigations till reaching a final diagnosis. Furthermore, there are limited availability and high cost of specialized diagnostic facilities and lack of NBS programs in most resource-limited populations, including Egypt [1, 6]. Developing NBS programs for LSDs will enhance timely diagnosis, but this seems unlikely in Egypt in the near future given the current economic constraints of the Egyptian healthcare system. More applicable strategies to optimize the diagnosis of LSDs in Egypt include increasing awareness in the medical community about LSD and encouraging the use of diagnostic guidelines, establishing more specialized diagnostic facilities serving different geographical areas, and increasing the use of next-generation sequencing. Of note, the variable diagnostic delay among studies may reflect the uneven diagnostic capabilities across different settings. Otherwise, it could be related to different patterns and presentations of LSDs included in each study [8, 24].

More than half of patients in the current study have MPS, and the most commonly identified subtypes were MPS I (50%) and III (31.8%). Similarly, MPS I has been reported as the most frequent subtype in some studies from India [10], Australia [9], Northern Ireland [26], and Scandinavian countries (Sweden, Denmark, and Norway) [27]. However, the relative frequency of MPS subtypes varies among other studies. MPS II was the most commonly reported in India [4, 25], Brazil [2], China [8], and Taiwan [28]; MPS III in Egypt [29], Australia [9], The Netherlands [15], Portugal [13], and Czech Republic [14]; and MPS VI in Egypt [6] and UAE [17].

Among patients with sphingolipidosis in this study, Gaucher disease was the most common single disease. This comes in agreement with previous studies [2, 4, 12-14, 19-20]. All patients were classified as type I on the basis of typical manifestations and lack of neurological involvement. This agrees with a previous study from southern Egypt, which reported type I in 77% of children with GD [30]. On the contrary, another Egyptian study on 882 patients with Gaucher disease revealed type III as the most common [7].

Eight out of ten patients in this study underwent GBA analysis, five of which were homozygous for c.1226A>G (p.Asn409Ser) and three were homozygous for c.1448T>C (p.Leu483Pro). These two mutations have been the most commonly reported in previous studies from Egypt [6, 30-31] and India [4, 11, 25, 32]. P.Leu483Pro is a pan-ethnic mutation and the most commonly reported mutation in patients with Gaucher disease type I worldwide [25, 32]. It has been thought that p.Leu483Pro mutation is associated with neuronopathic GD (types II and III) [33, 34]. Indeed, in **Elmonem *et al.*** [6] study, most patients with Gaucher disease were homozygous for p.Leu483Pro and had neuronopathic types. However, p.Leu483Pro has been detected in the three types of Gaucher diseases and is even more frequently associated with type I [11, 25]. **El-Morsy *et al.*** [31] reported p.Leu483Pro homozygosity in 23.1% of patients with Gaucher disease type I but none in patients with neuronopathic types. The phenotypic variability of p.Leu483Pro mutant allele has been attributed to the effect of modifier genes [25, 35]. Of note, we can't exclude the possibility that some patients with Gaucher disease diagnosed as type I in this study may develop later-onset neurological features and, accordingly, would be reclassified as neuronopathic type.

The present study has some limitations. First, this is a single-center study with a small number of included patients, which may limit the generalizability of our findings. Second, children in the current study were investigated for LSDs based on their clinical presentation and high index of suspicion at our medical center. Therefore, it is highly likely that many other undiagnosed patients with late-onset and mild forms of LSDs were not included. In addition, it is possible that some investigated children with LSDs didn't show characteristic metabolites or low enzymatic activities, and, hence, remained undiagnosed. Large-scale future studies would better elucidate the distribution and characteristics of Egyptian children with LSDs. last, genetic data were available for less than one-third of cases, which could be explained by the limited availability and high cost of genetic testing. Molecular studies are important not only to confirm the diagnosis in the index patient but also for accurate detection of carriers in other family members, who may not be reliably identified by enzyme assay, prenatal diagnosis, and possible phenotypic prediction.

CONCLUSION

Over 4 years, we identified 42 children with 10 different LSDs, representing 14% of all cases with IEMs at our medical center. The most frequently diagnosed groups of LSDs were MPS and sphingolipidosis, and the most common single diseases were MPS I and Gaucher disease. Patients had high proportions of parental consanguinity and having another sibling with LSDs and experienced a median diagnostic delay of 12 months. The most common clinical manifestations were delayed development, intellectual disability, visceromegaly, coarse facial features, and skeletal abnormalities. Finally, we provided genetic data for 12 patients, (8 with Gaucher disease and 4 with MPS). These data enhance our knowledge on LSDs in southern Egypt and are important for increasing physicians' awareness for timely diagnosis and management, which is crucial for better outcome.

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