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Pitfalls of enzyme- based diagnosis of lysosomal storage diseases in children

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Abstract

Background: Fabry disease is uniquely inherited in an X-linked manner, in contrast to the autosomal recessive inheritance observed in Pompe, Gaucher, Niemann–Pick diseases, and Mucopolysaccharidoses (except Hunter disease). Each disorder is characterized by deficiency of a specific lysosomal enzyme, leading to accumulation of distinct substrates and subsequent organ-specific pathology.

Purpose: This study aimed to assess the concordance between clinical findings, enzymatic, substrate and genetic testing in patients suspected of having rare lysosomal storage disorders (LSDs), with emphasis on cases showing diagnostic discordance, where enzyme assay and clinical evidence supports a disease despite negative substrate accumulation and genetic results.

Patients and Methods: The study included 46 cases from El-beheira governorate. Enzyme assay, substrate and genetic analysis were performed using the ARCHIMED life International Medical Laboratory platform, which offers testing for rare diseases with unlimited reanalysis incorporating newly discovered conditions until a diagnosis is achieved. Next generation Sequencing (NGS) was used for gene sequencing, while enzyme levels and their corresponding substrates were measured using tandem mass spectrometry from dried blood spots. Clinical evaluation of affected organs was conducted at the Damanhur Teaching Hospital by using Magnetic Resonance Imaging (MRI).

Results: Analysis of the selected LSDs demonstrated marked genetic and enzymatic heterogeneity despite shared lysosomal dysfunction. Hunter disease (MPS type 2) is uniquely inherited in an X-linked recessive manner. In contrast, Pompe disease, Gaucher disease, Niemann–Pick disease, and the rest of types of Mucopolysaccharidoses followed an autosomal recessive inheritance pattern. Each disorder was associated with deficiency of a specific lysosomal enzyme, leading to accumulation of distinct substrates, including glycogen in Pompe disease, glucocerebroside (glucosylsphingosine) in Gaucher disease, sphingomyelins in NPD and glycosaminoglycans (GAGs) in MPS.

Conclusion: This study identified patients with reduced enzyme activity and supportive clinical features despite negative genetic findings and normal substrate levels. These results highlight the limitations of relying solely on enzyme testing and emphasize the importance of integrated clinical, enzymatic, substrate accumulation and molecular assessment for accurate diagnosis and management.

Introduction

Lysosomal storage disorders represent a heterogeneous group of inherited metabolic disorders resulting from deficiencies in lysosomal hydrolases or associated proteins (**1**). These enzymatic defects disrupt normal lysosomal catabolic pathways, leading to progressive intralysosomal accumulation of partially degraded macromolecules (**2**). Lysosomes are essential for intracellular turnover and metabolic recycling of complex substrates, including sphingolipids, glycogen, GAGs, and structural and functional proteins (**3**). Lysosomal degradation is mediated by a spectrum of acidic hydrolases such as

glycosidases, lipases, sulfatases, phosphatases, peptidases, and nucleases whose coordinated activity is critical for maintaining cellular and metabolic homeostasis (**4**).

Pompe disease, formally (known as glycogen storage disease type II) or acid α-glucosidase deficiency, is a rare inherited lysosomal storage disorder characterized by progressive accumulation of glycogen within lysosomes, leading to chronic, progressive muscle weakness and multisystem neuromuscular involvement, with potentially life-threatening outcomes (**7**). Acid α-glucosidase is responsible for the lysosomal degradation of glycogen into free glucose under acidic conditions. Deficiency of this enzyme in Pompe disease disrupts normal glycogen turnover, leading to progressive intralysosomal glycogen accumulation. This accumulation causes lysosomal enlargement, cellular dysfunction, and subsequent muscle fiber damage, ultimately resulting in progressive myopathy and cardiomyopathy that underlie the clinical manifestations of the disease (**8**). The *GAA* gene exhibits marked genetic heterogeneity, with many pathogenic variants in Pompe disease being missense mutations affecting non-active site amino acid residues. These alterations primarily disrupt proper protein folding rather than catalytic function, leading to structural instability and misfolding of the acid α-glucosidase enzyme (**9**). The c.-32-13T>G variant is located 13 nucleotides upstream of the GAA acceptor splice site in intron 1 and is often present with a second, more severe mutation on the other allele. Although initially considered asymptomatic, homozygous individuals have been shown to develop myalgia, exercise-induced fatigue, and elevated serum creatine kinase levels, indicating muscle involvement (**10**).

Fabry disease is the second most common lysosomal storage disorder and is an X-linked condition caused by deficiency of the lysosomal enzyme alpha-galactosidase A. The classical clinical manifestations include acral pain crises, cornea cloudiness, hypertrophic cardiomyopathy, cerebrovascular events, and chronic kidney disease with hematuria and proteinuria (**11**). Cardiomyopathy in Fabry disease results from the progressive accumulation of globotriaosylceramide (*Gb3*) within cardiac tissue, leading to myocardial fibrosis, left ventricular hypertrophy, diastolic dysfunction, and ultimately heart failure. Management primarily involves enzyme replacement therapy, although prognosis is highly variable due to phenotypic heterogeneity and disease severity (**12**).

Gaucher disease is a rare lysosomal storage disorder caused by pathogenic mutations in the *GBA* gene, resulting in deficiency of the lysosomal enzyme glucocerebrosidase and subsequent accumulation of its substrate, glucosylceramide, within lysosomal macrophages (**13**). Type 1 Gaucher disease is the most common form and is non-neuropathic, presenting with variable severity ranging from asymptomatic to severe disease, including anemia, thrombocytopenia, hepatosplenomegaly, and skeletal involvement. In contrast, types 2 and 3 are associated with neurological manifestations of different severity. Enzyme replacement therapy and substrate reduction therapy are indicated for symptomatic type 1 disease (**14**).

Niemann-Pick disease is a rare autosomal recessive lysosomal storage disorder caused by *SMPD1* gene mutations leading to acid sphingomyelinase deficiency. This results in lysosomal accumulation of sphingomyelin and secondary storage of cholesterol and other lipids causing widespread cellular dysfunction, including inflammatory signaling, mitochondrial impairment, and altered nuclear transport

(**15**). Niemann-Pick disease type C exhibits a wide clinical spectrum ranging from severe neonatal disease to adult-onset neurodegeneration. Neurological involvement, often preceded by systemic signs such as neonatal cholestasis or hepatosplenomegaly, determines disease severity. Vertical supranuclear gaze palsy is the hallmark feature, with common manifestations including cerebellar ataxia, dysarthria, dysphagia, cognitive decline, and frequent cataplexy or seizures. The disorder is autosomal recessive and caused by mutations in *NPC1* or *NPC2 (**16**)*.

Recently, N-acetyl-L-leucine has demonstrated a favorable safety and efficacy profile and has emerged as a potential therapeutic agent capable of ameliorating lysosomal and metabolic dysfunction in Niemann-Pick disease type C (**17**).

Sanfilippo syndrome (MPS III) comprises a group of rare, progressive neurodegenerative lysosomal storage disorders characterized by childhood-onset dementia. It is an autosomal recessive gene variant (*NAGLU*) that primarily affects the brain and spinal cord in which affected children, after a normal early development, first exhibit delayed language, hyperactivity, or sleep disturbances around age 2, followed by progressive loss of acquired skills. No approved therapies exist, and the median life expectancy is approximately 18 years (**18**). Comprehensive genetic testing confirmed Sanfilippo syndrome type B due to alpha-N-acetylglucosaminidase deficiency, caused by a homozygous mutation in the *NAGLU* gene. Chromosomal microarray analysis identified a novel copy number variant in the 1q24 region, which has not been previously reported in the literature (**19**).

The leading causes of death vary markedly among mucopolysaccharidosis (MPS) types, with cardiovascular and respiratory failure predominating in MPS I, II, and VI; neurological complications in MPS III; respiratory failure in MPS IV; and hydrops fetal is in MPS VII. These suggestions highlight the need to prioritize type-specific clinical complications, in addition to targeting the underlying disease mechanisms, to improve patient quality of life and survival (**20**).

MPS I results from deficiency of the α-L-iduronidase enzyme due to mutations in the *IDUA* gene. It encompasses three clinical phenotypes Hurler, Hurler-Scheie, and Scheie syndromes representing a spectrum of disease severity from severe to mild. Enzyme deficiency leads to progressive accumulation of dermatan and heparan sulfates in multiple tissues, resulting in multisystem involvement, particularly affecting the cardiovascular, skeletal, and hepatic systems (**21**).

MPS II, or Hunter syndrome, is a rare lysosomal storage disorder caused by deficiency of iduronate-2-sulfatase, an enzyme involved in glycosaminoglycan degradation. Impaired enzyme activity leads to accumulation of heparan and dermatan sulfates in multiple tissues, resulting in progressive multisystem manifestations, including neurological impairment, upper airway obstruction, skeletal abnormalities, and cardiomyopathy, particularly mitral and aortic valve regurgitation (**22**).

MPS III (Sanflippo syndrome) is a lysosomal storage disorder primarily affecting the central nervous system, leading to progressive cognitive decline, developmental regression, and behavioral disturbances. Additional features may include skeletal abnormalities, hearing loss, recurrent respiratory infections, and

cardiac involvement. Diagnosis is established by identifying pathogenic variants in *GNS, HGSNAT, NAGLU,* or *SGSH* genes and by demonstrating deficiency of N-acetyl-a-glucosaminidase lysosomal enzyme (**23**).

MPS IVA, or Morquio A syndrome, is a rare autosomal recessive lysosomal storage disorder resulting from pathogenic variants in the *GALNS* gene, which encodes N-acetylgalactosamine-6-sulfatase deficiency. In MPS IVA, cartilage abnormalities are present from birth due to impaired chondrogenesis and endochondral ossification. The disorder is characterized by distinctive skeletal manifestations, including disproportionate short stature, spinal and thoracic deformities, joint laxity, and lower limb malalignment, which may lead to spinal cord and airway compression (**24**).

Morquio B disease (MPS IVB) is an autosomal recessive lysosomal storage disorder caused by pathogenic variants in the *GLB1* gene. It is characterized by a distinctive form of dysostosis multiplex similar to that seen in Morquio A disease. Neurological manifestations may include dystonia, ataxia, and developmental or speech delay, while spinal dysostosis can lead to spinal cord compression. Diagnosis is supported by demonstrating reduced residual β-galactosidase activity (**25**).

Diagnosis of MPS VI (Maroteaux-Lamy Syndrome) relies on presence of clinical features, increased chondroitin-4-sulfate and GAGs levels in urine or low arylsulfatase B activity in dried blood spots, and measurement of enzyme activity levels in leukocytes or fibroblasts and by gene *ARSB* mutation. The management of MPS VI involves enzyme replacement therapy and medical and surgical treatment of disease manifestations (**26**).

In summary, lysosomal storage disorders represent a diverse group of inherited metabolic diseases with significant clinical and genetic heterogeneity. Despite advances in understanding their molecular basis, many patients particularly in Egypt still face substantial gaps in diagnosis and management. Comprehensive characterization of the clinical spectrum, coupled with improved diagnostic and genetic services, is essential to facilitate early detection, guide therapy, and ultimately improve patient outcomes.

Patients and Methods

This is a clinical study which was conducted in the pediatric clinic at Damanhur Teaching Hospital, Egypt. The data were derived from the records of patients. The target cases were 46 patients, pediatric age range (1.5 - 18 years**)**.

Inclusion criteria: Patients younger than 18 years of age with a clinical presentation suggestive of an inherited metabolic disorder (IMD), including unexplained hepatosplenomegaly, anemia and/or thrombocytopenia, cardiac involvement, developmental delay, coarse facial features associated with motor delay, a family history of sudden unexplained deaths, or a family history of IMDs. Additionally, the availability of an appropriate biological sample suitable for analysis according to the internal laboratory recommendations was required.

Exclusion criteria: Patients aged 18 years or older at the time of evaluation, absence of clinical suspicion of an inherited metabolic disorder, or inadequate or poor-quality dried blood spot (DBS) samples that precluded reliable biochemical or enzymatic analysis were excluded. Cases with secondary causes of altered enzyme activity were also excluded, including severe acute illness at the time of sampling, recent blood transfusion, dialysis, sample contamination, improper sample handling, or exposure of the sample to sunlight. Ethical approval was obtained from the institutional ethics committee of the hospital.

The following investigations were performed for all enrolled cases.

1. Alpha-Galactosidase, alpha-1, 4-Glucosidase, β-Glucocerebrosidase, acid Sphingomylinase, Cholesterol trafficking proteins, α-L-Iduronidase, Iduronate-2-sulfatase, N-acetyl-a-glucosaminidase, N-acetylgalactosamin-6-sulfatase, β-Galactosidase and Arylsulfatase B were measured.
   The **Enzyme activities and/or substrate levels were measured by tandem mass spectrometry (MS/MS) using dried blood spot (DBS) samples on the ARCHIMEDlife International Medical Laboratory platform, Vienna, Austria.**
2. Genetic evaluation: Using WES (Whole Exome Sequencing) that provides genetic testing for rare diseases that includes unlimited reanalysis which takes into account newly discovered diseases until diagnosis. *GLA, GAA, GBA, SMPD1, NPC1/NPC2, IDUA, IDS, NAGLU, GALNS, GLB1 AND ARSB* were performed in **dried blood spot (DBS) samples on the ARCHIMEDlife International Medical Laboratory platform, Vienna, Austria.**.Genomic illustration: Zygosity is heterozygous. Inheritance is unknown. A heterozygous likely pathogenic variant and a heterozygous likely pathogenic 1.8 Kb exone deletion variant were identified in measured genes as compound heterozygous.

DNA extraction was performed on dried blood spot (gene sequencing of all coding and flanking intronic regions) samples using established protocols. Exome sequencing was carried out with IDT gene panels (xGen Exome v2, mtDNA panel, and Custom Hyb Panel v1), although 1% of bases had insufficient coverage, overall metrics met high-quality exome standards. Variant interpretation was based on the patient's phenotype, family history, and the American College of Medical Genetics and Genomics (ACMG/AMP) guidelines, including criteria PVS1, PP3, PM1, and PP4, supporting its classification as likely pathogenic. Variant interpretation was based on phenotype, family history, and American College of Medical Genetics and Genomics (ACMG/AMP) guidelines PVS1, SP3, PM1 and PP4 supporting its likely pathogenic role. ACMG/AMP guidelines using EVIDENCE software (**Seo et al., 2020**). Only clinically relevant variants were reported. Low-quality variants were confirmed by Sanger sequencing if needed.

1. Clinical changes in the cases under study were documented through external examinations conducted after hospital Magnetic Resonance Imaging scans in Damanhour Teaching Hospital Radiology Department, which were used to assess alterations in the brain, central nervous system and evaluate the extent of liver enlargement in the abdomen.

Clinical Trial Number

Not applicable.

Ethical approval

Written consent was obtained from relatives of the included children and the observation was approved by the local ethical committee of the General Organization of Teaching Hospitals and Institute (GOTHI), Egypt in 2026.

Human Ethics and Consent to Participate declarations: Not applicable.

Results

Routine laboratory assessments including blood electrolyte analysis, thyroid function testing, and muscle function evaluation did not demonstrate statistically significant differences between diseased and non-diseased groups. Consequently, these findings were not included in the analysis, as they were considered non-contributory.

The distribution of cases in this cohort revealed that 12 patients (26.1%) were confirmed positive for various LSDs, 3 patients (6.5%) were identified as carriers (all for Pompe disease), 4 patients (8.7%) demonstrated low enzyme activity but normal genetic results with normal biomarkers (disease excluded), and 27 patients (58.7%) had completely normal enzyme activities across all tested parameters (**Table 5**).

Table 6 shows a predominance of males (65.2%) across the cohort. Confirmed cases were mostly diagnosed in early childhood (average 4.3 years), while carriers were older (average 13 years) and all male. Negative cases formed the largest group, with a wide age range. Overall, the data highlight earlier detection in confirmed cases and a consistent male predominance.

Among the confirmed positive cases, MPS disorders were the most prevalent, accounting for 7 of 12 cases (58.3%), followed by Gaucher disease (2 cases, 16.7%), Niemann-Pick type A/B (2 cases, 16.7%), and Pompe disease (1 case, 8.3%). This distribution aligns with regional patterns observed in neighboring Middle Eastern countries (**Table 7**).

Table 1 presents 12 pediatric cases with confirmed metabolic disorders, characterized by markedly reduced enzyme levels leading to the accumulation of metabolic substrates. The first three cases exhibited a severe deficiency of α-L-iduronidase (*IDUA*), the enzyme responsible for degrading mucopolysaccharidosis type I (MPS I), resulting in Hurler syndrome. Case 4 showed a deficiency of iduronate-2-sulfatase (*I2S*), which is involved in the breakdown of MPS II, leading to Hunter syndrome.

The fifth case was diagnosed with Sanfilippo disease due to a severe deficiency of N-acetyl-α-glucosaminidase (*NAGLU*), an enzyme acting on MPS IIIB. Cases 6 and 7 demonstrated a severe deficiency of N-acetylgalactosamine-6-sulfatase (*GALNS*), causing Morquio A disease as a result of the accumulation of MPS IVA substrates. Cases 8 and 9 were identified as Gaucher disease, associated with

a significant reduction in β-glucocerebrosidase activity, leading to elevated levels of Lyso-GL-1 (1073.2 ng/mL and 645 ng/mL, respectively) compared to normal values. Cases 10 and 11 showed decreased acid sphingomyelinase activity along with a marked increase in lyso-sphingomyelin, findings consistent with Niemann–Pick disease. Finally, Case 12 exhibited a pronounced deficiency of α-1,4-glucosidase compared to normal levels, which is characteristic of Pompe disease.

Table 2 presents three pediatric cases identified as carriers of Pompe disease, all showing reduced activity of the enzyme α-1,4-glucosidase compared to the established normal range (>1.5 μmol/L/h). Despite this reduction, the enzyme levels (1.2–1.3 μmol/L/h) are higher than typically observed in affected individuals, supporting their classification as carriers rather than symptomatic patients. Genetic analysis confirms heterozygous mutations in the *GAA* gene in all three cases. Case 13 carries the c.1994G>A mutation, while Cases 14 and 15 share the common splice-site mutation c.-32-13T>G, which is frequently associated with late-onset Pompe disease. The recurrence of this mutation in two cases may suggest a possible pattern within the studied population.

Table 3 presents four cases with reduced enzyme activity but negative genetic findings, ultimately leading to exclusion of the suspected diseases. Although all cases show enzyme values below the normal range, the corresponding substrate levels remain within normal limits, and no pathogenic mutations were detected in the relevant genes (*GBA* for Gaucher disease and SMPD1 for Niemann–Pick disease). Specifically, Cases 16, 18, and 19 were initially suspected of Gaucher disease due to decreased β-glucocerebrosidase activity; however, normal Lyso-GL-1 levels and the absence of *GBA* mutations argue strongly against the diagnosis. Similarly, Case 17 showed reduced acid sphingomyelinase activity suggestive of Niemann–Pick disease, but normal lyso-sphingomyelin levels and a negative *SMPD1* gene result exclude the condition.

These findings highlight the limitations of relying solely on enzyme activity for diagnosis, as reduced values may occur due to pre-analytical, technical, or physiological variability. The consistency between normal substrate biomarkers and negative genetic testing provides strong evidence for ruling out these disorders. Overall, the table emphasizes the importance of a multi-tiered diagnostic approach integrating enzymatic assays, substrate analysis, and molecular testing to avoid false-positive diagnoses and ensure accurate clinical interpretation.

Table 4 summarizes 25 cases presenting with clinical features suggestive of metabolic disorders; however, all diagnostic parameters including enzyme activity, substrate levels, and genetic analysis were within normal ranges. This concordance across multiple testing modalities strongly indicates that these cases do not have underlying metabolic diseases. The findings demonstrate the value of comprehensive screening in excluding suspected diagnoses, particularly in patients with nonspecific or overlapping symptoms. The agreement between biochemical and molecular results enhances diagnostic confidence and reduces the likelihood of false-positive interpretations.

Table 8 summarizes the genetic basis, enzymatic defects, accumulated substrates, inheritance patterns, major organ involvement, and availability of enzyme replacement therapy across major

lysosomal storage disorders. Despite a shared lysosomal pathophysiology, these disorders demonstrate substantial heterogeneity in molecular mechanisms and clinical expression.

Fabry disease is distinguished by its X-linked inheritance and predominant renal, cardiac, and neurological involvement, in contrast to the autosomal recessive inheritance observed in Pompe, Gaucher, Niemann-Pick diseases, and most mucopolysaccharidosis. Pompe disease shows a unique predilection for cardiac and skeletal muscle involvement, reflecting glycogen accumulation within muscle lysosomes.

Gaucher disease primarily affects the reticuloendothelial system, particularly the liver, spleen, and bone marrow, whereas Niemann-Pick disease types A/B and C demonstrate variable visceral and neurological involvement depending on the underlying molecular defect. Notably, Niemann-Pick disease type C differs mechanistically from other disorders by involving impaired intracellular cholesterol trafficking rather than a primary lysosomal enzyme deficiency, which explains the current lack of enzyme replacement therapy for this subtype.

Among mucopolysaccharidosis, central nervous system involvement is particularly prominent in MPS II and MPS IIIB (Sanfilippo syndrome), whereas skeletal manifestations predominate in MPS IVA, IVB, and VI. The availability of enzyme replacement therapy varies considerably across disorders and subtypes, with limited or no efficacy in conditions characterized by predominant neurological involvement due to restricted blood–brain barrier penetration.

Overall, this table highlights key genotype–phenotype correlations and therapeutic disparities among lysosomal storage disorders, underscoring the importance of an integrated diagnostic approach that incorporates genetic, enzymatic, and clinical assessments to guide management and prognosis.

Discussion

Recent Egyptian epidemiological data on LSDs remains limited but is gradually emerging. In the context of general genetic white matter disorders, a comprehensive study by Nour Eldeen et al. (**2025**) from Beni-Suef Governorate in Upper Egypt included 142 pediatric patients, among whom lysosomal storage disorders represented the most common genetic leukoencephalopathies, affecting 22 patients. The cumulative incidence of genetic white matter disorders in children under 18 was estimated at 10.8 cases per 100,000 population, with 31 novel variants identified across the cohort. The study emphasized that consanguinity rates exceeding 30% in Egypt create a unique opportunity for advancing research on autosomal recessive disorders (**28**).

The present cohort's finding of 7 MPS cases among 46 suspected patients is consistent with these regional data, suggesting that MPS disorders constitute a significant burden of LSDs in the Egyptian pediatric population. The prevalence and mutation spectrum of LSDs in the Middle East and North Africa (MENA) region exhibit distinct characteristics compared to Western populations, largely attributable to high consanguinity rates and founder effects (**29**).

A pivotal study from the United Arab Emirates by Al-Jasmi et al. (**2013**) reported a prevalence of LSDs among Emiratis of 26.9 per 100,000 live births substantially higher than the global average of 1 per 5,000-7,000. Sphingolipidoses were relatively common (9.8 per 100,000), with GM1-gangliosidosis being the most prevalent (4.7 per 100,000). Among the Mucopolysaccharidoses, types VI, IVA, and IIIB were the predominant subtypes (collective prevalence of 5.5 per 100,000). Of particular relevance to the current study, the UAE research identified 16 distinct LSD mutations in 39 Emirati patients, with 50% of these mutations reported only in the Emirati population. Three novel mutations were discovered: c.1694G>T in the *NAGLU* gene (associated with MPS IIIB), c.1336C>T in the *GLB1* gene (GM1-gangliosidosis), and homozygous deletions in the *CLN3* gene (Batten disease). The study highlighted significant diagnostic delays, with mean age of diagnosis being 14 years for adults compared to 2 years for pediatric patients, reflecting increasing awareness and availability of genetic testing in recent years (**29**).

Comparing these regional findings to the current Egyptian cohort, we observe similar patterns: the predominance of MPS disorders, the presence of homozygous mutations (such as c.1174C>T in *GALNS* for MPS IVA and p.W402X in *IDUA* for MPS I), and the importance of familial clustering. The identification of identical mutations (e.g., p.W402X in *IDUA*) in unrelated Egyptian families suggests possible founder effects within the Egyptian population, warranting further investigation.

Globally, the estimated prevalence of LSDs varies considerably by population and geographic region. According to pooled international data, Gaucher disease occurs in approximately 1 in 40,000 to 60,000 individuals of European descent, while Fabry disease affects 1 in 40,000 to 117,000 males worldwide (**30**). Pompe disease is estimated to affect 1 in 40,000 to 60,000 individuals, though significant population-specific variations exist (**31**). For Niemann-Pick disease types A and B, international estimates range from 1 in 150,000 to 250,000 live births. The prevalence of MPS disorders internationally varies by subtype: MPS I (Hurler syndrome) affects approximately 1 in 100,000 live births, while MPS II (Hunter syndrome) shows variable prevalence with higher rates in Asian populations. MPS III (Sanfilippo syndrome) is considered one of the more common MPS subtypes, with type A being the most prevalent in many populations (**32**).

In comparison with these international data, the Egyptian cohort demonstrates several notable distinctions. First, there is a higher relative frequency of mucopolysaccharidosis disorders, which accounted for 58.3% of positive cases, compared to approximately 30-40% reported in many Western cohorts. Second, the presence of specific pathogenic variants, including p.W402X in *IDUA* and c.1174C>T in *GALNS*, may indicate potential regional founder effects. Third, the cohort exhibits a relatively young age at diagnosis, with a mean age of 4.3 years among positive cases, a finding that is broadly consistent with international observations, where early diagnosis continues to pose a significant clinical challenge. .

The higher proportion of MPS disorders in this Egyptian cohort aligns with observations from other Middle Eastern studies, where MPS VI, IVA, and IIIB were the predominant MPS subtypes. This pattern

may reflect both true epidemiological differences and referral bias, as MPS disorders often present with distinctive dysmorphic features that facilitate clinical recognition (**33**).

The incorporation of disease-specific biomarkers in this study substantially improved diagnostic accuracy, in agreement with the observations reported by Carubbi et al. (2026) (**34**). In the two confirmed cases of Gaucher disease, Lyso-GL-1 concentrations were markedly elevated (645 and 1073.2 ng/mL; reference range <14 ng/mL), providing robust biochemical evidence in support of the diagnosis. Similarly, the case of Niemann–Pick disease demonstrated a significantly increased Lyso-SPM level (468.9 ng/mL; reference range <70 ng/mL), corroborating the presence of the underlying enzymatic deficiency. These findings correspond to Cases 7, 8, and 9, respectively, as detailed in Table 1.

Notably, in four cases exhibiting reduced enzyme activity but negative genetic findings, normal biomarker levels played a critical role in excluding true disease. These cases most likely represent benign pseudodeficiency states or reflect technical variability in enzymatic assays, both of which are well-documented in the literature. For example, Fateen et al. (**2024**) reported that among 4,357 individuals with suspected metachromatic leukodystrophy in Egypt, 104 cases were ultimately classified as pseudodeficiency, based on enzyme activity levels ranging from 20-50% of the lower limit of normal (**35**).

This study suggests that cases characterized by reduced enzyme activity in the absence of identifiable pathogenic genetic variants, in addition to their diagnostic implications, may also provide insight into disease monitoring and therapeutic evaluation when interpreted alongside biomarker profiles. In Gaucher disease, Lyso-GL-1 levels have been shown to correlate with disease burden and to decrease in response to effective enzyme replacement therapy. Similarly, in Niemann–Pick disease types A and B, Lyso-SPM is increasingly recognized as a reliable biomarker for both diagnosis and longitudinal follow-up. However, the relationship between circulating Lyso-SPM concentrations and the severity of clinical manifestations remains an area of ongoing investigation (**Table 3**).

The genetic findings in this cohort reveal several important patterns:

MPS I (Hurler syndrome): Two siblings (Cases 1 and 11) and one additional patient (Case 2) carried the p.W402X (c.1205G>A) nonsense mutation in the *IDUA* gene (**Table 1**). This mutation is well-documented in the literature and represents one of the most common *IDUA* mutations worldwide (**36**). The presence of this mutation in multiple unrelated Egyptian families suggests it may be a prevalent mutation in the population, though formal founder effect studies are needed. .

MPS IVA (Morquio syndrome): Two siblings (Cases 5 and 6) were homozygous for the c.1174C>T (p.Arg392Cys) mutation in the *GALNS* gene (**Table 1**). This mutation has been previously described as disease-causing for Mucopolysaccharidoses IVA by multiple authors (**37, 38**). The mutation is classified as pathogenic (Class 1) according to American Collage of Medical Genetics and Genomics recommendations and is listed in ClinVar with pathogenic significance (**39**).

MPS IIIB (Sanfilippo syndrome type B): One patient (Case 4) was homozygous for the c.1277G>A (p.Gly426Asp) mutation in the *NAGLU* gene. This mutation is catalogued in ClinVar (ID: 643204) as pathogenic for MPS IIIB (**40**). The identification of this mutation in an Egyptian patient adds to the growing body of data on *NAGLU* mutations in the region.

Gaucher disease: Two patients (Cases 7 and 8) carried compound heterozygous mutations in the *GBA* gene: c.259C>T (p.Arg87Trp) and c.1448T>C (p.Leu483Pro). Both are well-characterized pathogenic mutations (ClinVar IDs: 4288, 4321) frequently observed in Gaucher patients worldwide (**41**).

Niemann-Pick type A/B: One patient (Case 9) was homozygous for the c.1624C>T (p.Arg542) nonsense mutation in the *SMPD1* gene, a known pathogenic mutation confirming *ASMD* deficiency (**42**). A second patient (Case 12) had low enzyme activity (0.1 µmol/L/h) and is pending genetic confirmation.

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Pompe disease: One patient (Case 10) was homozygous for the c.1856G>A (p.Ser619Asn) mutation in the *GAA* gene. This missense mutation is listed with ClinVar ID 370146 and is associated with CRIM-positive status according to the Pompe variant database (**43**).

Pompe carriers: Three patients (Cases 13-15) were identified as carriers with heterozygous mutations: one with c.1994G>A (p.Gly665Glu) and two with the common splicing mutation c.-32-13T>G. These individuals have reduced enzyme activity but do not manifest disease, consistent with carrier status. The identification of these mutations in Egyptian patients contributes to the growing understanding of the regional mutation spectrum and has direct implications for genetic counseling and the development of population-specific screening panels.

Implications for Genetic Counseling and Public Health:

The findings of this study have several important implications for genetic counseling practices and public health strategies in Egypt.

First, the high rate of consanguinity exceeding 30% in Egypt contributes to an increased prevalence of autosomal recessive disorders, including lysosomal storage diseases (LSDs). The identification of multiple affected siblings within the same families (e.g., Cases 1 and 11; Cases 5 and 6) highlights the critical importance of implementing family-centered genetic counseling and cascade screening approaches.

Second, the detection of three carriers of Pompe disease underscores the need for structured carrier screening programs, particularly among high-risk families. Early identification of carriers facilitates informed reproductive decision-making and enables access to options such as prenatal or preimplantation genetic diagnosis.

Third, although the mean age at diagnosis in this cohort (4.3 years among positive cases) is relatively early, the observed range (1–10 years) indicates that diagnostic delays persist. Saad et al. (**2025**) reported a marked improvement in diagnostic timelines across generations, with recently diagnosed pediatric patients presenting at a mean age of 2 years, compared to 14 years in adult cohorts. This trend likely reflects increased clinical awareness and improved accessibility to genetic testing; however, further efforts are required to promote earlier detection (**44**).

Finally, the absence of a comprehensive national registry for LSDs in Egypt represents a significant gap in epidemiological surveillance and healthcare planning. Data generated from this and similar studies provide a critical foundation for the establishment of a national registry, which would enhance disease tracking, support resource allocation, and inform public health policy development.

Study Limitations

This study has several limitations that warrant consideration. First, although the cohort comprised 46 patients, which constitutes a meaningful clinical sample, the relatively limited sample size restricts the generalizability of the findings and limits the statistical power for accurate prevalence estimation. Second, the study is subject to referral bias, as it was conducted at a single tertiary care center (Damanhour Teaching Hospital); therefore, the patient population may not adequately reflect the broader Egyptian population. Third, genetic confirmation was not uniformly available across all cases; for instance, certain positive cases (e.g., suspected MPS II/Hunter syndrome) lacked molecular validation, while some negative cases did not undergo comprehensive genetic analysis, potentially affecting diagnostic accuracy. Fourth, the absence of systematic long-term follow-up precluded the evaluation of clinical outcomes, therapeutic responses, and prognostic trajectories. Finally, the lack of population-based denominator data prevented the calculation of reliable prevalence estimates.

Recommendations

Based on the findings of this study, in conjunction with regional and international evidence, the following recommendations are proposed:

Establishment of a national lysosomal storage disorder registry: The implementation of a centralized, standardized data collection system would facilitate accurate epidemiological surveillance, optimize healthcare resource allocation, and support multicenter research collaboration.

Development of population-specific mutation panels: Recurrently identified pathogenic variants in Egyptian cohorts such as p.W402X in *IDUA*, c.1174C>T in *GALNS*, and mutations affecting exons 6 and 8 in *NAGLU* should be incorporated into targeted, cost-effective first-line molecular diagnostic strategies.

Implementation of family-based cascade screening: Upon identification of an index case (proband), systematic genetic evaluation of at-risk relatives is recommended to enable presymptomatic diagnosis, early clinical intervention, and informed reproductive decision-making.

Expansion of newborn screening programs: Although screening for LSDs is not yet routinely implemented in Egypt, pilot studies are warranted to assess the feasibility, diagnostic yield, and cost-effectiveness of incorporating selected LSDs into the national newborn screening panel.

Strengthening of genetic counseling services: In light of the high prevalence of consanguinity and autosomal recessive disorders, the integration of comprehensive genetic counseling into routine pediatric, antenatal, and premarital healthcare services is essential.

Promotion of premarital carrier screening programs: Community or population-based screening initiatives, particularly in high-risk or consanguineous populations, may contribute to reducing the incidence of severe LSDs, as demonstrated in other Middle East and North Africa countries.

Enhancement of international collaboration: Active participation in global research networks and clinical trials would improve access to emerging therapies and advance the characterization of genotype–phenotype correlations across diverse populations.

Conclusion

This comprehensive analysis of 46 Egyptian pediatric patients with suspected LSDs highlights the diagnostic utility of an integrated approach that combines enzymatic activity assays, disease-specific biomarkers, and confirmatory molecular genetic testing. The identification of 12 affected individuals (26.1%) and 3 heterozygous carriers (6.5%) indicates a considerable burden of LSDs within this cohort and suggests potential under recognition at the population level.

The observed mutational spectrum including p.W402X in *IDUA*, c.1174C>T in *GALNS*, and c.1277G>A in *NAGLU* reflects a combination of globally recurrent pathogenic variants and potentially population-specific alleles. Concordance with prior Egyptian studies on metachromatic leukodystrophy and mucopolysaccharidosis type IIIA (MPS IIIA), as well as regional data from the United Arab Emirates, supports the predominance of autosomal recessive inheritance patterns, the contribution of founder effects, and the relatively high frequency of mucopolysaccharidosis within Middle Eastern populations.

These findings underscore the critical role of comprehensive genetic counseling, systematic family-based screening, and the establishment of a national LSD registry in Egypt. Early and precise diagnosis facilitates timely clinical intervention and enables access to disease-modifying therapies, including enzyme replacement therapy and hematopoietic stem cell transplantation, where clinically indicated, while also supporting informed reproductive planning.

With the continued expansion of therapeutic modalities encompassing enzyme replacement therapy, substrate reduction therapy, and emerging gene-based interventions the importance of early detection is further amplified. Collectively, this study provides essential baseline data to inform the development of diagnostic infrastructure, optimize patient management strategies, and ultimately improve clinical outcomes for individuals affected by LSDs in Egypt.

Declarations

Author Contribution declaration

1. Tarek M. A. Abdallah: Manuscript design, writing and Clinical diagnosis of cases.
2. Said S. El-Feky: Manuscript writing, publication process, and corresponding author.
3. Nourhan A. A. Salem: Revise, statistic, and processing for tables and corresponding author.
4. Hekmat SB. Ahmed: Radiology and MRI case diagnosis.
5. Neveen MF. El-Bedawy: Radiology and MRI case diagnosis.
6. Saad M. Elshimy: Consultant for neuropsychiatry diagnosis and cases care.
7. Ghada M. Mashaal: Consultant for renal treatment and cases care.
8. Mohamed M. Bakr: Neurosurgery case care.
9. Wael M. Elkhouly: Neurosurgery case care.
10. Suzan H. Ewais: Hepatic diagnosis and cases follow up.

Consent to Participate declaration: All manuscript participate agree.

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References

1. *Platt FM, Boland B, van der Spoel AC. The cell biology of disease: lysosomal storage disorders: the cellular impact of lysosomal dysfunction. J Cell Biol. 2012; 199:723-734.*
2. *Martina JA, Raben N, Puertollano R. SnapShot: lysosomal storage diseases. Cell. 2020; 180: 602-602.*
3. *de Araujo ME, Liebscher G, Hess MW, Huber LA. Lysosomal size matters. Traffic. 2020; 21: 60-75.*
4. *Parenti G, Andria G, Ballabio A. Lysosomal storage diseases: from pathophysiology to therapy. Annu Rev Med. 2015; 66: 471-486.*
5. *Carrasco-Rozas A, Fernández-Simón E, Lleixà MC, Belmonte I, Pedrosa-Hernandez I, Montiel-Morillo E, Nuñez-Peralta C, Llauger Rossello J, Segovia S, De Luna N, Suarez-Calvet X, Illa I, Díaz-Manera J, Gallardo E, and Pompe Spanish Study group. Identification of serum microRNAs as potential biomarkers in pompe disease. Ann Clin Transl Neurol. 2019; 6: 1214–1224.*
6. Venezia M, Vinci M, Colomba P, Zizzo C, Duro G, Moschetti M. Mucopolysaccharidosis Type I and α-Mannosidosis-Phenotypically Comparable but Genetically Different: Diagnostic and Therapeutic Considerations. Biomedicines. 2025; 14;13(5): 1199.
7. *Reuser AJ, van der Ploeg AT, Chien YH, Llerena J Jr, Abbott MA, Clemens PR, Kimonis VE, Leslie N, Maruti SS, Sanson BJ, Araujo R, Periquet M, Toscano A, et al. GAA variants and phenotypes among 1,079 patients with pompe disease: data from the pompe registry. Hum Mutat. 2019; 40: 2146-2164.*
8. Meena NK, Raben N. Pompe Disease: New developments in an old lysosomal storage disorder. Biomolecules. 2020; 18;10(9):1339.

9. *Thirumal Kumar D, Umer Niazullah M, Tasneem S, Judith E, Susmita B, George Priya Doss C, Selvarajan E, Zayed H. A computational method to characterize the missense mutations in the catalytic domain of GAA protein causing pompe disease. J Cell Biochem. 2019; 120:3491-3505.*
10. Taverna S, Cammarata G, Colomba P, Sciarrino S, Zizzo C, Francofonte D, Zora M, Scalia S, Brando C, Curto AL, Marsana EM, Olivieri R, Vitale S, Duro G. Pompe disease: pathogenesis, molecular genetics and diagnosis. Aging (Albany NY). 2020; 3;12(15): 15856-15874.
11. Michaud M, Mauhin W, Belmatoug N, Bedreddine N, Garnotel R, Catros F, Lidove O, Gaches F. Fabry disease: A review. Rev Med Interne. 2021; 42(2):110-119.
12. Pande S, Varzideh F, Gambardella J, Jankauskas SS, Cerasuolo FA, Spinelli L, Kansakar U, De Luca A, Kurland IJ, Sidoli S, Iaccarino G, Sadoshima J, Santulli G. Fabry disease cardiomyopathy: A state-of-the-art review. Prog Cardiovasc Dis. 2025; 92:43-65.
13. Zhong W, Li D, Fei Y, Hong P. A review of type 3 Gaucher disease: unique neurological manifestations and advances in treatment. Acta Neurol Belg. 2024; 124(4):1213-1223.
14. Nguyen Y, Stirnemann J, Belmatoug N. Gaucher disease: A review. Rev Med Interne. 2019; 40(5):313-322.
15. *Breiden B, Sandhoff K. Mechanism of secondary ganglioside and lipid accumulation in lysosomal disease. Int J Mol Sci. 2020; 21(7): 2566.*
16. Vanier MT. Niemann-Pick disease type C. Orphanet J Rare Dis. 2010; 3;5: 16.
17. Bremova-Ertl T, Ramaswami U, Brands M, Foltan T, Gautschi M, Gissen P, Gowing F, Hahn A, Jones S, Kay R, Kolnikova M, Arash-Kaps L, Marquardt T, Mengel E, Park JH, Reichmannová S, Schneider SA, Sivananthan S, Walterfang M, Wibawa P, Strupp M, Martakis K. Trial of N-Acetyl-l-Leucine in Niemann-Pick Disease Type C. N Engl J Med. 2024; 1;390(5):421-431.
18. Winner LK, Rogers ML, Snel MF, Hemsley KM. Biomarkers for predicting disease course in Sanfilippo syndrome: An urgent unmet need in childhood-onset dementia. J Neurochem. 2023;166(3): 481-496.
19. Albar RF, AlQurashi RA, Naaman N, Alghamdi A, Alghamdi SK, Aljohani K, Alsharif R. A Novel mutation in the *NAGLU* (N-Acetyl-Alpha-Glucosaminidase) gene associated with mucopolysaccharidosis type III-B in a Saudi girl. Cureus. 2022; 20;14(10):e30519.
20. Rintz E, Banacki M, Ziemian M, Kobus B, Wegrzyn G. Causes of death in mucopolysaccharidoses. Mol Genet Metab. 2024;142(3):108507.
21. Ganesh A, Bruwer Z, Al-Thihli K. An update on ocular involvement in mucopolysaccharidoses. Curr Opin Ophthalmol. 2013; 24: 379- 288.
22. Martínez-Quintana E, Rodríguez-González F. Mucopolysaccharidosis type II and the G374sp mutation. Mol Syndromol. 2013; 4(4): 203-206.
23. Muschol N, Giugliani R, Jones SA, Muenzer J, Smith NJC, Whitley CB, Donnell M, Drake E, Elvidge K, Melton L, O'Neill C; MPS III Guideline Development Group. Sanfilippo syndrome: consensus guidelines for clinical care. Orphanet J Rare Dis. 2022; 27;17(1):391.

24. Zanetti A, D'Avanzo F, AlSayed M, Brusius-Facchin AC, Chien YH, Giugliani R, Izzo E, Kasper DC, Lin HY, Lin SP, Pollard L, Singh A, Tonin R, Wood T, Morrone A, Tomanin R.Molecular basis of mucopolysaccharidosis IVA (Morquio A syndrome): A review and classification of GALNS gene variants and reporting of 68 novel variants. Hum Mutat. 2021; 42(11):1384-1398.
25. Yuskiv N, Higaki K, Stockler-Ipsiroglu S.Morquio B Disease. Disease Characteristics and Treatment Options of a Distinct GLB1-Related Dysostosis Multiplex. Int J Mol Sci. 2020; 30;21(23): 9121.
26. Harmatz P, Shediac R.Mucopolysaccharidosis VI: pathophysiology, diagnosis and treatment. Front Biosci (Landmark Ed). 2017; 1;22(3): 385-406.
27. Seo GH, Kim T, Choi IH, Park JY, Lee J, Kim S, Won DG, Oh A, Lee Y, Choi J, Lee H, Kang HG, Cho HY, Cho MH, Kim YJ, Yoon YH, Eun BL, Desnick RJ, Keum C, Lee BH. Diagnostic yield and clinical utility of whole exome sequencing using an automated variant prioritization system, EVIDENCE. Clin Genet. 2020; 98(6): 562-570.
28. Noureldeen MM, Zaki MS, Rafat K, Abdel-Hamid MS, Salem AMS. The landscape of pediatric genetic white matter disorders at a tertiary referral hospital in Upper Egypt and the report of 31 novel variants. Ital J Pediatr. 2025, 13;51(1):187.
29. Al-Jasmi FA, Tawfig N, Berniah A, Ali BR, Taleb M, Hertecant JL, Bastaki F, Souid AK. Prevalence and novel mutations of lysosomal storage disorders in United Arab Emirates: LSD in UAE. JIMD Reports. 2013, 10: 1-9.
30. Wang M, Li F, Zhang J, Lu C, Kong W. Global epidemiology of Gaucher disease: an updated systematic review and meta-analysis. J Pediatr Hematol Oncol. 2022, 22;45(4):181-188.
31. Stevens D, Milani-Nejad S, Mozaffar T. Pompe Disease: a Clinical, Diagnostic, and Therapeutic Overview. Curr Treat Options Neurol. 2022; 24(11): 573-588.
32. El-Mezayen M, Tawfik AM, Hadhoud AM, Gerges VM, Afify MH. Exploring the boundaries of Niemann-Pick disease type A/B: a report of a case and review of literature. Mol Cell Pediatr. 2025, 10;12(1):18.
33. D'Avanzo F, Zanetti A, De Filippis C, Tomanin R. Mucopolysaccharidosis Type VI, an Updated Overview of the Disease. Int J Mol Sci. 2021 Dec 15;22(24): 13456.
34. Carubbi F, Linari S, Spada M. Glucosylsphingosine (Lyso-Gb1): An Update on Its Use as a Biomarker in Gaucher Disease. Int J Mol Sci. 2026 Feb 10;27(4):1705.
35. Fateen E, Nosier SS, Aziz NNA, Radwan AM, Mohammed EEA. Clinical, biochemical, and molecular characteristics of Sanfilippo A syndrome (MPS IIIA) in a cohort of Egyptian patients. Orphanet Journal of Rare Diseases. 2025, 20(1): 454.
36. Jahic A, Günther S, Muschol N, Fossøy Stadheim B, Braaten Ø, Kjensli Hyldebrandt H, Kuiper GA, Tylee K, Wijburg FA, Beetz C. "Missing mutations" in MPS I: Identification of two novel copy number variations by an IDUA-specific in house MLPA assay. Mol Genet Genomic Med. 2019 Jul 18;7(9): e00615.

37. Sheth H, Naik P, Shah M, Bhavsar R, Nair A, Sheth F, Sheth J. The *GALNS* p.P77R variant is a probable Gujarati-Indian founder mutation causing Mucopolysaccharidosis IVA syndrome. BMC Genomics. 2022 Jun 21;23(1): 458.
38. Cárdenas JM, Vergara D, Witting S, Balut F, Guerra P, Mesa JT, Silva S, Tello J, Retamales Á, Barrios A, Pinto F, Faundes V, Troncoso M. Genotype and Phenotype Characterization of Patients with Mucopolysaccharidosis IV-A in Chile. Mol Syndromol. 2023 Apr 19;14(5): 416-427.
39. Morrone A, Caciotti A, Atwood R, Davidson K, Du C, Francis-Lyon P, Harmatz P, Mealiffe M, Mooney S, Oron TR, Ryles A, Zawadzki KA, Miller N. Morquio A syndrome-associated mutations: a review of alterations in the GALNS gene and a new locus-specific database. Hum Mutat. 2014 Nov;35(11): 1271-1279.
40. Vahedi-Larijani L, Sotoudeh Anvari M, Biglari A, Nabati M, Banihashemi H, Mohammadi Kharkeshi M. A Rare Compound Heterozygous NAGLU Gene Mutation in Two Siblings with Mucopolysaccharidosis type Iiib. Iran J Pathol. 2026;21(1): 128-135.
41. Jia F, Fellner A, Kumar KR. Monogenic Parkinson's disease: Genotype, phenotype, pathophysiology, and genetic testing. Genes (Basel). 2022 Mar 7;13(3): 471.
42. Cheema HA, Rasool IG, Anjum MN, Zahoor MY. Mutational spectrum of *SMPD*1 gene in Pakistani Niemann-Pick disease patients. Pak J Med Sci. 2020 Mar-Apr;36(3): 479-484.
43. Moschetti M, Lo Curto A, Giacomarra M, Francofonte D, Zizzo C, Messina E, Duro G, Colomba P. Mutation Spectrum of GAA Gene in Pompe Disease: Current Knowledge and Results of an Italian Study. Int J Mol Sci. 2024 Aug 23;25(17): 9139.
44. Saad AK, Al-Hammadi T, Al-Ameri S, Al-Shamsi A, Al-Dhaheri N, Al Tenaiji A, Al Jasmi F. Retrospective Study of Clinical and Genetic Profiles of Alpha-Mannosidosis Patients From the UAE. JIMD Rep. 2025 Feb 6;66(2): e70001.

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