Ann Med Res

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Annals of Medical Research

journal page: annalsmedres.org

Evaluating awareness of lysosomal storage diseases: A step toward early diagnosis

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MAIN POINTS

- Most physicians demonstrated limited awareness of lysosomal storage diseases (LSD).
- Only a minority of physicians recognized that LSD can manifest at any age, indicating that adult-onset cases may be overlooked.
- Despite the availability of non-invasive diagnostic methods, many physicians still include invasive procedures, such as bone marrow aspiration and liver biopsy, in the diagnostic process.
- The findings highlight the urgent need for targeted educational programs to enhance awareness and promote early diagnosis of LSD.

Cite this article as: Burgac E, Yoldas Celik M, Koseci B. Evaluating awareness of lysosomal storage diseases: A step toward early diagnosis. *Ann Med Res*. 2026;33(7):326–331. doi: 10.5455/annalsmedres.2025.11.349.

ABSTRACT

Aim: Lysosomal storage diseases (LSD) are a diverse group of rare inherited metabolic disorders that frequently go undiagnosed for extended periods because of their non-specific, overlapping clinical features. Raising awareness among healthcare professionals is crucial for facilitating early diagnosis and improving outcomes. This study aimed to evaluate physicians' awareness of and knowledge about five LSDs: Gaucher disease, Fabry disease, mucopolysaccharidoses, Pompe disease, and Niemann--Pick types A/B.

Materials and Methods: A descriptive cross-sectional survey was conducted among 106 physicians, including 56 pediatricians and 50 internal medicine specialists. A 17-item online questionnaire assessed participants' knowledge of LSD symptoms, diagnosis, and treatment.

Results: 81.9% of the physicians participating in the study reported limited knowledge of LSD. When the pediatric and internal medicine groups were compared, pediatric specialists generally exhibited higher levels of awareness than their internal medicine counterparts. This difference was statistically significant for MPS and Gaucher disease (p=0.016 and p=0.012, respectively). Among the participants, only 25.7% recognized that LSD can occur at any age. 86.7% of respondents identified genetic testing as accurate, while 38% and 58.1% indicated roles for bone marrow aspiration and liver biopsy, respectively, in diagnosis. The vast majority of physicians (99%) emphasized the need for increased training in this field.

Conclusion: Our study demonstrates that physicians working at a tertiary training hospital lack sufficient awareness of LSD. Therefore, strengthening educational programs for physicians is essential to enhance awareness and improve early diagnosis of the disease.

Keywords: Lysosomal storage diseases, Awareness, Early diagnosis

Received: Nov 13, 2025 **Accepted:** Feb 06, 2026 **Available Online:** Jul 24, 2026

INTRODUCTION

Lysosomal storage diseases (LSD) are a heterogeneous group of genetically inherited disorders; they result from deficiencies or functional impairments of lysosomal enzymes, this leads to widespread damage across organs and systems [1]. Although rare, these conditions can be life-threatening. The diagnostic and therapeutic processes are often challenging and prolonged, as symptoms are usually recognised late, and clinical manifestations may overlap with those of more common disorders. Awareness of the symptoms of LSD and recognition of the importance of early diagnosis and treatment play a crucial role in improving diagnostic timelines and patient outcomes. Furthermore, novel therapeutic approaches, such as enzyme replacement therapy (ERT), substrate reduction therapy (SRT) and gene therapy, are being developed at an increasing rate, which further emphasises the importance of early detection [2]. Accordingly, raising awareness among healthcare professionals of LSD is critical to ensuring early diagnosis and access to effective treatment.

This study aimed to evaluate the knowledge of physicians from various specialties regarding five LSDs: Gaucher disease, Fabry disease, mucopolysaccharidoses (MPS), Pompe disease, and Niemann–Pick types A/B, which are considered more prevalent in our region than in other regions.

The findings are expected to contribute to the development of strategies aimed at improving awareness and facilitating earlier recognition of these disorders.

MATERIALS AND METHODS

Study design

This was a cross-sectional descriptive survey. The questionnaire was prepared using the online platform Google Forms and distributed by email and through social media to 226 physicians working in the Departments of Pediatrics and Internal Medicine at the Adana City Training and Research Hospital. Participants were asked to respond voluntarily. No names or personal identifiers were collected from the physicians included in the study. A total of 106 physicians completed the survey, including 56 pediatricians and 50 internal medicine specialists (response rate: 46.9%). Data collection was carried out between April and May 2025. The study protocol was designed in accordance with the 1964 Helsinki Declaration and approved by the Ethics Committee of Adana City Training and Research Hospital (Decision No: 478, Date: 10.04.2025).

Questionnaire design

The survey comprised 17 questions designed to evaluate physicians' professional experience and their knowledge of LSD, as well as their awareness of potential clinical manifestations, diagnostic approaches, treatment methods, and educational requirements. Participants' specific knowledge of and ability to recognize symptoms related to Gaucher, Fabry, MPS, Pompe, and Niemann-Pick A/B diseases were also evaluated. Most of the questions were multiple-choice or allowed multiple responses, with open-ended responses limited to the 'Other, please specify' option. The survey was developed based on input from a pediatric metabolism specialist and was not adapted from previously published instruments; however, pilot testing was not conducted.

Statistical analysis

Statistical analysis was performed using the IBM SPSS Statistics for Windows version 23.0 (IBM Corp., Armonk, NY, USA). The distributions of numerical variables were assessed for Kolmogorov-Smirnov test. Continuous variables were presented as means ± standard deviation or medians (minimum [min]-maximum [max]) according to distribution of data and categorical variables as numbers and percentages (%). Statistical analyses were conducted using tests appropriate for the type and distribution of the variables. Categorical variables were compared using the Chi-square test. A p-value <0.05 was considered statistically significant.

RESULTS

81.9% of the participants considered their knowledge of LSD inadequate. When awareness of LSD was analyzed separately among pediatric specialists (N = 56) and internal medicine specialists (N = 50), the majority of participants in both groups reported having "no knowledge" or "limited knowledge" of these diseases (pediatric specialists: 3.4% "no knowledge", 77.6% "limited knowledge"; internal medicine specialists: 6.7% "no knowledge", 78% "limited knowledge"). A smaller proportion of participants in both groups reported a moderate level of knowledge (pediatric specialists, 19%; internal medicine specialists, 15.6%). There was no statistically significant correlation between years of experience and knowledge level among physicians (p=0.479). However, when the pediatric and internal medicine groups were compared, pediatric specialists generally exhibited higher awareness than their internal medicine counterparts (Figure 1). This difference was found to be statistically significant for MPS and Gaucher disease (p=0.016 and p=0.012, respectively). Of the participants, 66.7% indicated that LSDs manifest during infancy and childhood, while 25.7% believed that they could occur at any age. When assessing knowledge levels for five different LSD, Gaucher disease received the highest proportion of participants reporting a 'moderate level of knowledge'; (76.3%), while Niemann-Pick A/B disease received the lowest (31.1%). The highest rates of correct responses to questions about commonly observed symptoms were obtained for MPS (91.4%) and Gaucher disease (86.7%) (Table 1). In terms of diagnostic methods, enzyme analysis (98.1%) and genetic testing (86.7%) were the options most frequently indicated by the participants. Thirty-eight per cent of participants reported that bone marrow aspiration plays a role in diagnosis, while 58.1 per cent reported a role for liver biopsy. In terms of treatment, 85.7% of the participants were aware that ERT was used. When responses regarding treatment for the five lysosomal storage diseases (Gaucher, Fabry, MPS, Pompe, and Niemann-Pick A/B) were evaluated, most participants (95.2%) reported that treatment improved outcomes. Only 2.9% indicated that the treatment had no effect on improvement. The majority of participants (85.7%) acknowledged the availability of ERT as a treatment option, and 44.8% were aware of SRT. Additionally, 95.2% of participants reported that early diagnosis and treatment facilitate improvement; 99% indicated that educational programs for physicians should be improved.

DISCUSSION

Individuals with rare diseases, such as LSD, often initially present to the departments of pediatrics and internal medicine. It is crucial that these physicians are aware of these diseases to enable early diagnosis and treatment, and to improve the patients' quality of life. However, these conditions may not exhibit obvious clinical signs initially, and metabolic conditions in adults can be easily overlooked. According to the National Commission on Orphan Diseases, 30% of individuals with rare diseases wait up to five years to receive an accurate diagnosis, whereas 15% require six years or longer [3]. Taking a detailed family history, accurately documenting symptoms, and ensuring timely referral to the relevant specialist can reduce diagnostic delays and enable earlier intervention. Therefore, it is crucial for physicians to consider LSD in their clinical practice and in differential diagnoses.

In our study, although most clinicians were aware of LSD,

https://doi.org/10.5455/annalsmedres.2025.11.349

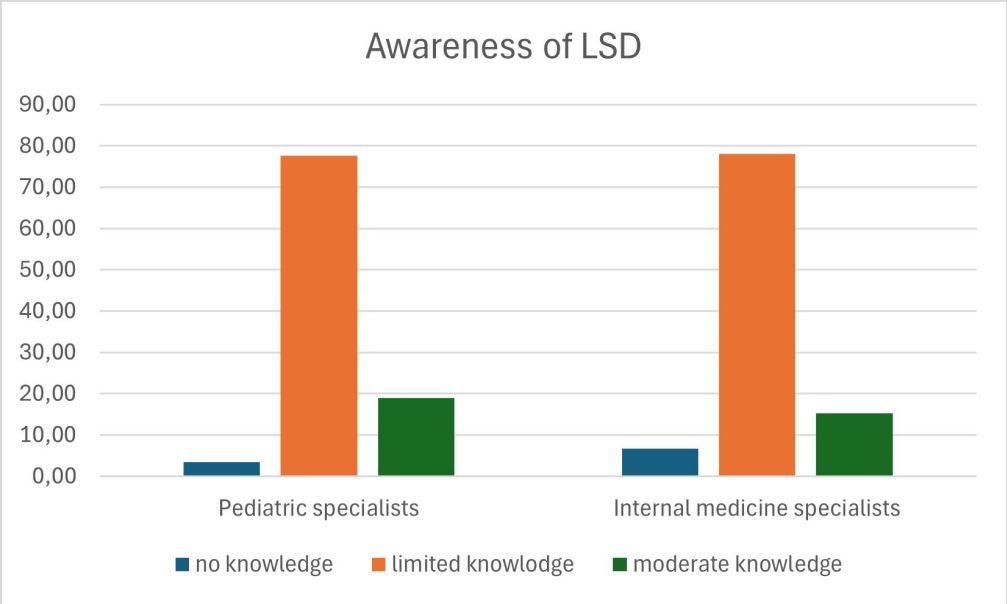

Figure 1. Awareness levels regarding lysosomal storage diseases among pediatric and internal medicine specialists.

Table 1. Distribution of clinical and laboratory findings among patients with different lysosomal storage disorders(LSDs)as reported by participating physicians.

Disease	Findings	Occurs n (%)	Does not occur n (%)
Gaucher Disease	Splenomegaly	91 (86.7)	13 (12.4)
	Hepatomegaly	95 (90.5)	9 (8.6)
	Bone pain	40 (38.1)	64 (61.0)
	Thrombocytopenia	64 (61.0)	40 (38.1)
	Neurological disorder	65 (61.9)	39 (37.1)
	Respiratory difficulty	20 (19.0)	84 (80.0)
Fabry Disease	Neuropathic pain	31 (29.5)	73 (69.5)
	Renal problem	82 (78.1)	22 (21.0)
	Angiokeratoma	48 (45.7)	55 (52.4)
	Cardiac involvement	56 (53.3)	48 (45.7)
	Visual disturbance	45 (42.9)	59 (56.2)
Mucopolysaccharidoses	Coarse facial features	96 (91.4)	8 (7.6)
	Neurological findings	91 (86.7)	13 (12.4)
	Joint restriction	69 (65.7)	35 (33.3)
	Joint laxity	28 (26.7)	76 (72.4)
	Heart valve disease	43 (41.0)	61 (58.1)
	Autism features	12 (11.4)	91 (86.7)
	Organomegaly	37 (35.2)	66 (62.9)
	Hearing loss	46 (43.8)	58 (55.2)
	Corneal clouding	25 (23.8)	79 (75.2)
Pompe Disease	Muscle weakness	78 (74.3)	26 (24.8)
	Elevated CK	71 (67.6)	33 (31.4)
	Cardiomegaly	68 (64.8)	36 (34.3)
	Respiratory failure	40 (38.1)	64 (61.0)
Niemann-Pick A/B	Hepatosplenomegaly	69 (65.7)	34 (32.4)
	Neurological findings	83 (79.0)	21 (20.0)
	Cholestasis	39 (37.1)	65 (61.9)
	Thrombocytopenia	27 (25.7)	77 (73.3)
	Respiratory problems	28 (26.7)	76 (72.4)

81.9% felt inadequately informed about these conditions. Furthermore, the lack of a significant relationship between years of professional experience and awareness levels suggests that clinical experience alone is insufficient for acquiring adequate knowledge of these rare diseases, highlighting the need for targeted educational programs. Most inherited metabolic diseases are thought to present with clinical findings shortly after birth. Consequently, metabolic disorders that present

https://doi.org/10.5455/annalsmedres.2025.11.349

with symptoms in late childhood or adulthood are often not initially suspected [4]. In our study, the low proportion of participants who selected the option indicating that LSD can present with symptoms at any age suggests that these conditions could be overlooked in adult patients. Furthermore, pediatric specialists were found to have a higher awareness of LSD than internal medicine specialists. These findings suggest that cases diagnosed in adulthood may be overlooked and emphasise the importance of raising awareness among adult physicians.

Participants most frequently reported a moderate level of knowledge about Gaucher disease, possibly because it is more commonly encountered than other LSDs. A survey study conducted in Japan found that hematologists had a greater awareness of Gaucher disease than gastroenterologists [5]. This difference was attributed to hematologists' tendency to work in larger hospitals, which provides them with greater opportunities for clinical experience and professional interaction related to the disease. By contrast, gastroenterologists, who often practise in smaller clinics, were reported to have more limited awareness of, and knowledge about, treatment. The lowest rate of "moderate level of knowledge" responses was observed for Niemann-Pick A/B disease, which presents with similar clinical features. This finding suggests that Gaucher disease is more frequently considered in the differential diagnosis of splenomegaly and thrombocytopenia, whereas Niemann-Pick A/B disease is often overlooked.

The higher correct response rates for common symptoms in MPS and Gaucher disease may reflect their more distinctive clinical features and more frequent clinical exposure. MPS cases often involve multiple systemic manifestations such as cardiac findings, corneal clouding, recurrent ear infections, hearing loss, hernias, and spinal deformities; therefore, patients are frequently referred to various medical specialties [6]. Therefore, it is crucial that not only pediatricians but also clinicians from other specialties recognize the characteristic manifestations of this disease. This highlights the need for broader studies assessing awareness across various medical disciplines. Coarse facial features are among the most frequent and diagnostic clinical signs of MPS. In our study, the majority of participants correctly identified this clinical feature associated with MPS. However, the literature indicates that diagnostic delays are common, particularly in patients with mild disease phenotypes. A survey by Bruni et al. emphasized that MPS type I is not widely recognised, and that training in differential diagnosis is needed to promote an earlier diagnosis [7]. Although a majority of participants correctly identified the most common clinical feature of MPS, 80% reported having 'no knowledge' or 'limited knowledge' of the disease. This suggests that physicians tend to focus primarily on the most obvious and typical symptoms of MPS, potentially overlooking milder or atypical symptoms.

It has been reported that there is usually a diagnostic delay of at least three years in Fabry disease, and the diagnosis is most often established after the age of 20 [8]. Bulbul et al. evaluated the awareness of physicians working in the province of Kırıkkale regarding Fabry disease and reported that only 22% of them considered Fabry disease as a differential diagnosis in patients presenting with compatible clinical findings [9]. In our study, 75.7% of the participants reported having no or limited knowledge about Fabry disease; this indicates insufficient awareness among physicians. It has been reported that peripheral neuropathic pain is the most common presenting complaint among patients with Fabry disease and is included as the first step in most diagnostic algorithms [10]. However, when Fabry-related symptoms were evaluated in our study, only 29.5% of participants reported peripheral neuropathic pain. This suggests that peripheral neuropathic pain is not widely recognized by physicians. Conversely, the results suggest that physicians are more familiar with the association between Fabry disease and renal complications in patients with diabetes. These findings suggest that awareness of the early clinical manifestations of Fabry disease is limited, with peripheral neuropathic pain , a characteristic symptom potentially, being overlooked.

The clinical presentation of Pompe disease is highly heterogeneous in terms of age at symptom onset, rate of disease progression, extent of organ involvement and overall clinical severity [11,12]. Clinical manifestations may range from the rapidly progressive classic infantile form, presenting with cardiomyopathy before the age of one, to the more slowly progressive late-onset forms. A registry study conducted by Kishnani et al. in 2013 demonstrated, as in previous reports, a significant diagnostic delay among patients with Pompe disease [13-15]. Although ERT has been available since 2006, and diagnostic methods such as enzyme activity measurement and genetic analysis are used, many patients still experience a prolonged interval between the onset of symptoms and diagnosis [12,16,17]. In our study, the overall level of knowledge about Pompe disease among participants was low. This suggests that awareness of Pompe disease is limited, which, consistent with the literature, may contribute to diagnostic delays.

A notable finding of our study is that despite the widespread use of enzyme and genetic analyses in current diagnostic processes, a significant proportion of physicians still believe that invasive methods (e.g., bone marrow aspiration and liver biopsy) play a role in diagnosis. This suggests that traditional approaches still influence the diagnosis of LSD and highlights the need to raise awareness of non-invasive, molecular-based methods. Regarding knowledge of treatment approaches, the majority of participants indicated that they believed treatment improves outcomes. While most physicians correctly identified ERT as a treatment option, fewer recognized substrate reduction therapies. This suggests that physicians are more familiar with ERT as the primary treatment for lysosomal storage diseases, while awareness of alternative approaches is relatively low. This finding is consistent with the results of A study was conducted among hematologists and

https://doi.org/10.5455/annalsmedres.2025.11.349

gastroenterologists in Japan [5]. The aforementioned study found that a significant proportion of hematologists were familiar with ERT. However, awareness of SRT was lower. This suggests that knowledge regarding the diagnosis and treatment of rare metabolic diseases remains limited.

In our study, participants generally indicated that early diagnosis and treatment positively influence disease progression in lysosomal storage diseases. Furthermore, a clear emphasis was placed on the need for enhanced educational initiatives for physicians, which may facilitate earlier recognition in clinical practice.

Limitations

This study had several limitations. Firstly, the sample size was relatively small, comprising only pediatric and internal medicine specialists from a single centre, which limits the generalizability of the findings. The voluntary nature of participation may have resulted in a higher proportion of interested physicians enrolling, thereby introducing selection bias. Moreover, the survey was not pre-tested, which may have resulted in participants interpreting certain questions differently. Nevertheless, the findings highlight the need for educational initiatives to raise awareness of lysosomal storage diseases.

CONCLUSION

The data obtained in our study, therefore, highlight the importance of expanding educational programmes for physicians about LSD and of strengthening initiatives aimed at improving awareness of early diagnostic processes. Thus, early diagnosis may increase the treatability of these diseases and improve the patients' quality of life. Further support for these findings through larger, multicentre studies would help clarify existing uncertainties surrounding the early diagnosis and management of LSD.

Acknowledgments: The authors sincerely thank all physicians who participated in this study for their valuable time and contributions.

Ethics Committee Approval: This study was approved by the Adana City Training and Research Hospital Ethics Committee (Decision No: 478, Date: 10.04.2025).

Informed Consent: Written informed consent was obtained from all participants included in the study.

Peer-review: Externally peer-reviewed.

Conflict of Interest: The authors declare that they have no conflict of interest.

Author Contributions: EB: Conception, Design, Supervision, Writing; MYÇ: Data Collection and/or Processing, Analysis and/or Interpretation; BK: Data Collection and/or Processing, Analysis and/or Interpretation. All the authors have read, edited, and approved the final version of the manuscript.

Financial Disclosure: This research did not receive any specific grant from funding agencies in the public, commercial, or non-profit sectors.

Artificial Intelligence Disclosure: AI-assisted tools (specifically ChatGPT, OpenAI, GPT-4-based model) were used in a limited capacity to support language editing and improve the clarity and readability of certain sections of the manuscript. The use of AI was restricted to linguistic refinement, minor rephrasing, and structuring of sentences in the Introduction and Discussion sections. No AI tools were used for data analysis, data interpretation, or generation of scientific content. All scientific content, including study design, data collection, statistical analysis, and interpretation of results, was entirely conducted by the authors. The manuscript reflects our original work and clinical experience. We fully acknowledge and adhere to the journal's ethical guidelines regarding the use of AI tools.

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