LUMEN ET VIRTUS
ISSN: 2177-2789

FABRY DISEASE: CASE REPORT AND LITERATURE REVIEW

DOENÇA DE FABRY: RELATO DE CASO E REVISÃO DA LITERATURA

ENFERMEDAD DE FABRY: INFORME DE CASO Y REVISIÓN DE LA LITERATURA

https://doi.org/10.56238/levv16n53-095

Submission date: 09/23/2025 **Publication date:** 10/23/2025

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ABSTRACT

Fabry disease is a rare X-linked disorder caused by α-galactosidase A (α-GAL) deficiency, leading to accumulation of glycosphingolipids (Gb3/Lyso-Gb3) and multisystemic manifestations, particularly renal, cardiac, and neurological. We report the case of a 44-year-old man with significant proteinuria and rapid progression to end-stage chronic kidney disease requiring hemodialysis, initially attributed to nonsteroidal anti-inflammatory drug use, later diagnosed as Fabry disease. This case highlights the phenotypic heterogeneity and the risk of underdiagnosis in nephropathies of uncertain etiology. The literature review emphasizes renal involvement as a key prognostic determinant, related to podocyte injury induced by Gb3/Lyso-Gb3 and by inflammatory/fibrogenic pathways. Diagnosis should integrate clinical evaluation, enzyme activity measurement, genetic testing, and, in selected scenarios, renal biopsy. Enzyme replacement therapy remains the mainstay of treatment, while migalastat represents an alternative for amenable variants. Emerging strategies—substrate reduction therapy, pegunigalsidase-α, and gene therapy—expand the therapeutic landscape. Prognosis depends on phenotype, sex, and timing of diagnosis, with early intervention associated with better outcomes. In conclusion, Fabry disease should be considered in the differential diagnosis of nephropathies with significant proteinuria and rapid progression, and timely initiation of disease-specific therapy and nephroprotective measures is essential.

Keywords: Fabry Disease. Proteinuria. Chronic Kidney Disease. Enzyme Replacement Therapy. Migalastat.

RESUMO

A doença de Fabry é uma doença rara ligada ao cromossomo X causada pela deficiência de α-galactosidase A (α-GAL), levando ao acúmulo de glicoesfingolipídeos (Gb3/Liso-Gb3) e manifestações multissistêmicas, particularmente renais, cardíacas e neurológicas. Relatamos o caso de um homem de 44 anos com proteinúria significativa e rápida progressão para doença renal crônica terminal, necessitando de hemodiálise, inicialmente atribuída ao uso de anti-inflamatórios não esteroidais, posteriormente diagnosticada como doença de Fabry. Este caso destaca a heterogeneidade fenotípica e o risco de subdiagnóstico em nefropatias de etiologia incerta. A revisão da literatura enfatiza o

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envolvimento renal como um determinante prognóstico chave, relacionado à lesão podocitária induzida por Gb3/Liso-Gb3 e por vias inflamatórias/fibrogênicas. O diagnóstico deve integrar avaliação clínica, mensuração da atividade enzimática, testes genéticos e, em cenários selecionados, biópsia renal. A terapia de reposição enzimática continua sendo a base do tratamento, enquanto o migalastat representa uma alternativa para variantes tratáveis. Estratégias emergentes — terapia de redução de substrato, pegunigalsidase-α e terapia gênica — expandem o panorama terapêutico. O prognóstico depende do fenótipo, do sexo e do momento do diagnóstico, com intervenção precoce associada a melhores desfechos. Em conclusão, a doença de Fabry deve ser considerada no diagnóstico diferencial de nefropatias com proteinúria significativa e progressão rápida, sendo essencial o início oportuno da terapia específica para a doença e de medidas nefroprotetoras.

Palavras-chave: Doença de Fabry. Proteinúria. Doença Renal Crônica. Terapia de Reposição Enzimática. Migalastat.

RESUMEN

La enfermedad de Fabry es un trastorno poco frecuente ligado al cromosoma X causado por la deficiencia de α-galactosidasa A (α-GAL), que provoca la acumulación de glucoesfingolípidos (Gb3/Lyso-Gb3) y manifestaciones multisistémicas, en particular renales, cardíacas y neurológicas. Presentamos el caso de un hombre de 44 años con proteinuria significativa y rápida progresión a enfermedad renal crónica terminal que requirió hemodiálisis, inicialmente atribuida al uso de antiinflamatorios no esteroideos, y posteriormente diagnosticada como enfermedad de Fabry. Este caso destaca la heterogeneidad fenotípica y el riesgo de infradiagnóstico en nefropatías de etiología incierta. La revisión bibliográfica enfatiza la afectación renal como un determinante pronóstico clave, relacionada con la lesión podocitaria inducida por Gb3/Lyso-Gb3 y por vías inflamatorias/fibrogénicas. El diagnóstico debe integrar la evaluación clínica, la medición de la actividad enzimática, las pruebas genéticas y, en determinados casos, la biopsia renal. La terapia de reemplazo enzimático sigue siendo la base del tratamiento, mientras que el migalastat representa una alternativa para las variantes susceptibles. Las estrategias emergentes —terapia de reducción de sustrato, pegunigalsidasa-α y terapia génica— amplían el panorama terapéutico. El pronóstico depende del fenotipo, el sexo y el momento del diagnóstico, y la intervención temprana se asocia a mejores resultados. En conclusión, la enfermedad de Fabry debe considerarse en el diagnóstico diferencial de las nefropatías con proteinuria significativa y progresión rápida, y es esencial el inicio oportuno de la terapia específica para la enfermedad y de medidas nefroprotectoras.

Palabras clave: Enfermedad de Fabry. Proteinuria. Enfermedad Renal Crónica. Terapia de Reemplazo Enzimático. Migalastat.

1 INTRODUCTION

Fabry disease (FD) is a rare, hereditary disorder linked to the X chromosome and caused by a deficiency or absence of the enzyme α-galactosidase A (α-GAL). This enzymatic defect leads to the progressive accumulation of glycosphingolipids, mainly globotriaosylceramide (Gb3) and its deacetylated form, globotriaosylsphingosine (Lyso-Gb3), in several tissues such as the vascular endothelium, kidneys, heart, and nervous system. As a consequence, multisystemic clinical manifestations develop, including neuropathic pain, cutaneous lesions, cardiomyopathy, chronic kidney disease (CKD), and cerebrovascular events (1, 2, 5).

Although it is considered a rare condition, with an estimated prevalence ranging from 1:40,000 to 1:117,000 live births, neonatal screening studies have suggested a higher apparent prevalence, especially among patients with late-onset phenotypes and variants of uncertain significance (1, 3). Due to the heterogeneous clinical presentation, the diagnosis is commonly delayed, even after symptom onset, leading to a significant impact on both quality of life and patient morbidity and mortality (1, 2, 4).

Diagnosis is based on a combination of methods, including reduced α-GAL enzyme activity (particularly useful in men), genetic analysis of the GLA gene, and, in selected situations, tissue biopsy demonstrating Gb3 accumulation. Biomarkers such as Lyso-Gb3 may assist in confirmation and monitoring of the disease (2, 5).

In recent years, the availability of specific therapies—such as enzyme replacement therapy (ERT) and pharmacological chaperones (for example, migalastat, effective for amenable GLA variants)—has significantly modified the course of the disease, making early diagnosis and treatment crucial (4–6).

In this context, case reports play a fundamental role in medical literature, especially for rare diseases, as they contribute to the recognition of unusual clinical presentations and phenotypic variations, and also aid in discussing diagnostic and therapeutic challenges.

Therefore, this study aims to report the case of a patient with Fabry disease, highlighting the main clinical, laboratory, and therapeutic aspects, and to provide a review of the current literature on the topic, discussing pathophysiology, diagnosis, and management while emphasizing the importance of early recognition for better prognosis.

2 OBJECTIVES

2.1 GENERAL OBJECTIVE

To report a case of Fabry disease in an adult patient with renal manifestations and to review the literature regarding the pathophysiology, clinical manifestations, diagnosis, and treatment, emphasizing the importance of early recognition of the disease.

2.2 SPECIFIC OBJECTIVES

I) To describe the clinical course of the patient presented.

II) To review the main epidemiological, pathophysiological, clinical, and therapeutic aspects of Fabry disease.

III) To compare the presented case with the available literature, highlighting points of similarity and divergence.

3 CASE REPORT

This case concerns a 44-year-old white male patient, a stair assembler, born in São Paulo and residing in Sorocaba. At the age of 41, he began to experience persistent low back pain and made frequent use of nonsteroidal anti-inflammatory drugs (NSAIDs) for symptomatic control. Four months after the onset of back pain, he developed anasarca associated with proteinuria.

In July 2022, he sought care at an emergency department, where laboratory tests revealed impaired renal function. He was discharged after evaluation, without hospital admission for further investigation. In the following weeks, he presented with progressive clinical deterioration characterized by nausea, vomiting, low back pain, and headache, prompting another visit to the hospital. On that occasion, he was referred to a tertiary care center for nephrological evaluation, and hemodialysis was indicated. Initially, the renal failure was attributed to chronic NSAID use.

In the review of systems, the patient reported chronic pain in the lower limbs, heat intolerance, anhidrosis, occasional palpitations, nonspecific visual changes, nonspecific hearing loss, and a history of angiokeratomas in the abdominal region, the last of which was not currently present.

After clinical stabilization, the patient was discharged from the hospital and continued outpatient follow-up on a regular hemodialysis program three times a week. In October 2024, during the investigation of the etiology of renal failure, measurement of α-GAL enzyme activity was performed, revealing reduced levels. Subsequently, the patient underwent genetic testing for Fabry disease, which identified a pathogenic variant in hemizygosis in the GLA

gene. The same sample was also used to measure Lyso-Gb3 concentration, which showed a significant accumulation, confirming the diagnosis of Fabry disease.

Subsequently, family screening was carried out, which identified the same mutation in his mother and two sisters. There was no history of consanguinity or reports of renal or cardiac disease in young relatives.

Currently, the patient remains on a regular hemodialysis program three times a week and reports maintaining a good subjective quality of life. So far, enzyme replacement therapy has not been initiated.

Table 1

Relevant laboratory tests during clinical follow-up

Date	Test	Result	Reference value
10/14/2024	α-galactosidase A (α-GAL) activity	0.08 µmol/L/h	≥ 1.68 µmol/L/h
10/29/2024	GLA gene sequencing	Pathogenic variant identified in hemizygosis in the GLA gene (NM_000169.3)	No pathogenic variant
12/06/2024	Lyso-Gb3 biomarker measurement	54.4 ng/mL	≤ 0.8 ng/mL

4 LITERATURE REVIEW

4.1 SEARCH STRATEGY

The literature review was conducted using the PubMed database with the English search terms “Fabry disease AND renal.”

4.2 SELECTION CRITERIA

Articles available in English and Portuguese were included, without an initial time restriction, in order to encompass both classical publications and recent evidence. The studies were analyzed and selected according to their relevance to understanding FD in adult patients, with emphasis on renal manifestations. Priority was given to studies addressing epidemiology, pathophysiology, renal clinical manifestations, diagnosis, treatment, and prognosis. Articles limited to pediatric contexts or exclusively addressing other organ systems without correlation to renal aspects were excluded.

4.3 DATA ANALYSIS

At the end of this process, fourteen main articles were included, encompassing narrative and systematic reviews, multicenter observational studies, case reports, and

relevant guidelines. This body of evidence allowed for the construction of a critical and updated synthesis of FD in adults with renal involvement, providing theoretical support for contextualizing the case report and discussing therapeutic and prognostic advances.

4.4 SUMMARY OF FINDINGS

Fabry disease is a lysosomal storage disorder linked to the X chromosome, caused by pathogenic variants in the GLA gene that reduce α-GAL activity and lead to systemic accumulation of glycosphingolipids, particularly Gb3 and Lyso-Gb3 (5, 7, 16). It is considered a rare condition, with an estimated incidence of 1:40,000 to 1:60,000 males for the classical forms. However, this perception has changed with screening programs (neonatal and in at-risk populations), which revealed a higher frequency of late-onset phenotypes and a wide range of clinical expressions, including in heterozygous women (5, 7, 12, 16).

The sex distribution reflects the inheritance pattern: hemizygous males usually present with earlier and more severe disease, while females may show variable phenotypes, ranging from asymptomatic cases to severe multisystemic manifestations, influenced by X-chromosome inactivation and the type of variant (7, 12, 16). Moreover, the distinction between the classical phenotype—generally more severe due to absent or minimal α-GAL activity—and the non-classical (or late-onset) phenotype—associated with residual enzyme activity—has epidemiological implications. Multicenter studies have shown a higher lifetime risk of renal, cardiac, and cerebrovascular events in classical phenotypes, particularly in men, while non-classical forms typically present with later cardiac and renal involvement (13).

The observed prevalence varies depending on the search strategy. In high-risk populations, screening among hemodialysis patients identifies sporadic FD cases with low but clinically relevant prevalence, often associated with late-onset variants. In this context, targeted screening is important to reveal underdiagnosed cases and assist in family counseling (14). In patients with chronic pain, the DOUFAB/DOUFABIS studies evaluated nearly 900 individuals and found FD in 1:1000 subjects, suggesting that indiscriminate screening in chronic pain is not cost-effective but should be considered in the presence of family history and suggestive findings (10).

In Brazil, it is important to suspect FD in CKD of undefined etiology, disproportionate proteinuria, and unexplained left ventricular hypertrophy (LVH), even in women (15). The age at diagnosis has prognostic implications: an Argentine study demonstrated a correlation between late diagnosis and greater renal impairment (lower glomerular filtration rate and higher proteinuria), reinforcing the importance of early diagnosis (19).

After analyzing the epidemiological distribution, it is important to understand the pathophysiological mechanisms underlying the clinical manifestations, particularly renal involvement. The variability of phenotypes and the severity of outcomes described in different populations (7, 10, 13, 14, 19) directly reflect the impact of the enzymatic defect on target tissues.

The pathogenesis of the disease is related to deficiency or absence of α-GAL, a lysosomal enzyme responsible for the degradation of glycosphingolipids. Pathogenic variants in the GLA gene, located on the X chromosome, result in reduced or absent enzymatic activity and progressive accumulation of Gb3 and its deacetylated form, Lyso-Gb3, in multiple tissues (5, 7, 16).

Lyso-Gb3, beyond being a biochemical marker, actively participates in pathophysiology by stimulating inflammatory and proliferative responses. Elevated serum levels are associated with the classical phenotype and greater severity of renal involvement, reinforcing its value as a prognostic biomarker (5, 16). This relationship explains why patients with classical variants—characterized by almost absent enzymatic activity—develop earlier and more aggressive forms of the disease, whereas those with non-classical variants, who retain residual activity, exhibit later and often organ-restricted presentations, typically renal or cardiac (5, 13, 16).

In the kidney, this accumulation occurs in podocytes, tubular epithelial cells, and endothelial cells, progressively compromising the glomerular filtration barrier. Clinically, this process manifests as proteinuria and a gradual decline in the glomerular filtration rate (GFR), potentially progressing to interstitial fibrosis, glomerulosclerosis, and, in advanced stages, end-stage CKD (15).

The clinical profile varies according to the genetic variant. In classical phenotypes, onset tends to occur earlier and disease progression is faster, with significant multisystemic manifestations. In non-classical forms, residual enzymatic activity allows for later presentations, frequently restricted to the kidney or the heart (13, 16).

In clinical practice, signs and symptoms present heterogeneously due to the progressive accumulation of glycosphingolipids in target tissues. In adults, renal involvement plays a central role, usually beginning silently with albuminuria, followed by a gradual decline in GFR until the development of advanced CKD. In many cases, this progression occurs without an established diagnosis, reinforcing the need for targeted screening strategies in at-risk populations (14, 15).

Renal involvement constitutes one of the most significant manifestations of FD and is an important prognostic determinant. It is characterized as a hereditary metabolic

podocytopathy responsible for the early development of proteinuria and gradual progression to CKD in most patients (20, 21).

Podocytes, highly differentiated cells with limited regenerative capacity, are particularly vulnerable to Gb3 and Lyso-Gb3 deposition. Moreover, Lyso-Gb3 induces inflammatory and fibrogenic pathways such as activation of transforming growth factor beta 1 (TGF-β1) and expression of integrins associated with podocyte loss—phenomena that contribute to glomerulosclerosis and interstitial fibrosis (5, 21).

Renal biopsy enables identification of characteristic deposits even in early stages, when renal function is preserved and proteinuria is absent. Furthermore, it assists in evaluating genetic variants of uncertain significance. Among typical histopathological findings are podocyte vacuolization, the presence of zebra bodies (characteristic lamellar deposits), and thickening of the glomerular basement membrane (22, 23).

Clinically, renal involvement in FD manifests as microalbuminuria or mild proteinuria from childhood or adolescence, progressing to persistent proteinuria, hypertension, and CKD in adulthood. Men with the classical phenotype have a higher risk of reaching end-stage disease around the fourth or fifth decade of life, whereas progression in women is more variable due to the pattern of X-chromosome inactivation (23).

In addition to nephropathy, other signs can precede diagnosis and should raise suspicion: neuropathic pain in extremities, hypohidrosis, characteristic angiokeratomas, cornea verticillata, as well as auditory and vestibular changes (7, 8). In the cardiovascular system, left ventricular hypertrophy (LVH), arrhythmias, and conduction abnormalities are common, particularly when arising without a clear cause, and frequently coexist with proteinuria or renal dysfunction (13, 15).

Diagnosis is based on a combination of clinical suspicion, laboratory assessment (particularly enzyme activity measurement and genetic testing), and, when necessary, histopathological findings. In men, measuring α-GAL activity represents the first step, as reduced values strongly support the diagnosis (7). In women, enzyme activity may be normal due to X-chromosome inactivation mosaicism; therefore, GLA gene sequencing is recommended for both sexes and becomes essential in heterozygotes (7, 12, 16). Interpretation of genetic variants requires caution, distinguishing pathogenic mutations from benign alterations (12, 16).

Lyso-Gb3, beyond being a biochemical marker, is also useful in screening and follow-up: elevated levels are associated with the classical phenotype and greater clinical severity, including renal involvement, although they may be less pronounced in non-classical variants and in women (5, 16). Baseline renal evaluation should include urinalysis (where hematuria

may be mild or absent), quantification of albuminuria/proteinuria, and GFR estimation, forming the longitudinal monitoring basis for renal involvement (5, 15). Renal biopsy is not mandatory when genetic or enzymatic confirmation has been established but can be useful in uncertain or atypical phenotypes, revealing zebra bodies under electron microscopy as a characteristic finding (5, 15).

In clinical practice, a pragmatic diagnostic algorithm in adults with CKD of unknown cause, disproportionate proteinuria, and/or unexplained LVH begins with α-GAL measurement (especially in men), followed by GLA gene sequencing and Lyso-Gb3 quantification to strengthen phenotypic classification and prognosis. After confirmation, family screening is essential given the X-linked inheritance pattern (5, 7, 12, 15, 16). This approach is critical because early diagnosis is associated with less severe nephropathy and enables timely therapeutic intervention (5, 19).

Given the impact of renal involvement, disease management should prioritize early diagnosis and intervention to modify the natural history of FD (20–23). The therapeutic goal is to reduce glycosphingolipid accumulation and consequently delay outcomes such as end-stage CKD and cardiovascular events (7–9, 16, 18).

ERT, with agalsidase alfa or beta, is considered the cornerstone of specific treatment and has shown to reduce Gb3 deposits and improve clinical outcomes, particularly when started early. In advanced stages with established fibrosis, the benefit is limited (9, 11, 12, 23). The pharmacological chaperone migalastat is an option for amenable variants, with efficacy and safety demonstrated in pivotal clinical trials (including ATTRACT) and other major studies (4, 6, 13). Emerging strategies include substrate reduction therapy (such as lucerastat), pegunigalsidase-α (a pegylated enzyme with extended half-life), and gene therapy, which may enhance enzymatic correction in selected scenarios (10, 12, 16, 18). Adjunctive measures, such as ACE inhibitors or ARBs, are recommended for proteinuria control and nephroprotection (23).

Prognosis depends on phenotype (classical vs. non-classical), sex, and—critically—the age at diagnosis and time to treatment initiation. Men with the classical phenotype tend to reach end-stage renal disease in their 40s or 50s, whereas women show a more heterogeneous course (7, 13, 19, 23). Active case identification is essential: screening in dialysis populations and clinical cohorts (e.g., chronic pain) has shown higher-than-expected prevalence, indicating underdiagnosis (10, 14). The spectrum of presentation includes late-onset forms with renal and cardiac involvement, underscoring the need for high clinical suspicion and appropriate diagnostic algorithms (11, 12). Renal biopsy may assist in confirming involvement and tissue staging, supporting therapeutic decisions (22).

In summary, management should be individualized, integrating genotype (and migalastat eligibility), disease stage, and renal injury burden. Early introduction of specific therapies, combined with nephroprotection and structured monitoring, represents the strategy with the highest potential to slow renal progression and reduce morbidity and mortality (4, 6–13, 16–19, 23).

5 DISCUSSION

The presented case describes a 44-year-old man with heavy proteinuria, rapid progression to chronic kidney disease (CKD), and the need for hemodialysis, with renal deterioration initially attributed to the use of nonsteroidal anti-inflammatory drugs (NSAIDs). This case exemplifies the diagnostic challenges of late-onset Fabry disease (FD) and the risk of underdiagnosis in situations of nephropathy with uncertain etiology (7–9, 12, 14). The clinical course, characterized by subtle and nonspecific systemic symptoms such as pain in the limbs, hypohidrosis, hearing and visual alterations, and a history of angiokeratomas, illustrates the phenotypic heterogeneity described in the literature and reinforces the need for a high index of suspicion, particularly in men presenting with significant proteinuria and renal decline without an identifiable cause (7, 8, 13).

From a pathophysiological standpoint, the renal progression observed is consistent with a metabolic podocytopathy, explaining the early onset of proteinuria and progressive decline in glomerular filtration rate (GFR) (5, 20, 21). In this case, diagnostic confirmation was achieved through reduced α-GAL enzyme activity, identification of a pathogenic hemizygous GLA variant, and elevated Lyso-Gb3 levels, which eliminated the need for renal biopsy. However, it should be noted that biopsy can provide valuable information in uncertain diagnostic scenarios, atypical phenotypes, or when clarifying variants of uncertain significance, as well as aiding in tissue staging (5, 22).

The delayed diagnostic journey has therapeutic implications, as enzyme replacement therapy (ERT) offers the greatest benefit when initiated before the establishment of renal fibrosis or sclerosis (9, 11, 12, 23). For amenable variants, migalastat represents an effective and safe alternative, with evidence from pivotal trials and the ATTRACT study showing stabilization of renal parameters in eligible subgroups (4, 6, 13). In parallel, emerging treatments such as substrate reduction therapy, pegunigalsidase-α, and gene therapy expand the therapeutic arsenal and may play a role in selected future scenarios (10, 12, 16, 18). Regardless of the specific therapy, adjunctive measures such as angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) remain essential for proteinuria control and nephroprotection (23).

In terms of prognosis, phenotype, sex, and age at diagnosis are critical factors: the later the diagnosis, the greater the severity of nephropathy and risk of progression to end-stage disease, particularly in men with the classical phenotype (7, 13, 19, 23). The findings in this case demonstrate a diagnosis made at the dialysis stage, aligning with evidence of underdiagnosis in dialysis units, where the observed prevalence exceeds estimates—supporting the importance of active case-finding strategies and systematic family screening (10, 14). In the Brazilian context, special attention should be paid to CKD of undefined etiology, disproportionate proteinuria, and unexplained left ventricular hypertrophy (LVH), including among women (15).

Among the limitations applicable to this case and discussion are the absence of renal histology data (diagnostic confirmation was based on enzymatic and genetic evidence) and the lack, so far, of follow-up under specific therapy to assess biological and clinical response. Nevertheless, the available data allow integration of clinical experience with published evidence, providing practical insights for clinical practice.

Given this context, several important implications for clinical management can be drawn: maintain clinical suspicion for FD in unexplained nephropathies with significant proteinuria; prioritize diagnostic algorithms combining enzymatic activity (in men), genotyping, and Lyso-Gb3 quantification, with renal biopsy in selected cases; initiate specific therapy early when eligible; and associate systematic nephroprotective measures while being aware of therapeutic limitations in advanced disease (4–13, 15, 16, 23).

6 CONCLUSION

The reported case reinforces that Fabry disease (FD) should be included in the differential diagnosis of chronic kidney disease (CKD) with significant proteinuria and rapid progression, particularly in adult men with no defined etiology. Podocyte injury mediated by Gb3 and Lyso-Gb3 explains the clinical course and supports the need for early intervention. Enzyme replacement therapy (ERT) remains the therapeutic cornerstone; migalastat is a valid alternative for amenable variants; and adjunctive measures are essential for nephroprotection. The timing of diagnosis and treatment is decisive: early identification, appropriate therapy initiation, and structured follow-up are strategies with the greatest potential to delay renal progression and reduce morbidity and mortality.

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