Fabry Disease: Why Early Recognition in Cardiology and Nephrology Clinics Remains Elusive

Written by The Life Science Feed Editorial Team · Edited by Mara Voss

Fabry disease, a rare X-linked lysosomal storage disorder, frequently masquerades as more common cardiac and renal conditions, delaying diagnosis and appropriate management. The progressive accumulation of globotriaosylceramide (Gb3) in various cell types, including cardiomyocytes and renal podocytes, drives a complex pathology that often goes unrecognised until advanced organ damage has occurred. This diagnostic challenge highlights a critical unmet need in clinical practice, particularly for specialists who routinely encounter patients with unexplained kidney disease or hypertrophic cardiomyopathy.

KEY TAKEAWAYS

- The Pivot: Fabry disease is a treatable condition, but its protean manifestations often lead to misdiagnosis or delayed diagnosis in specialist clinics.
- The Data: While no specific trial data is provided, the clinical literature consistently highlights a significant diagnostic delay, often exceeding a decade from symptom onset to confirmed diagnosis.
- The Action: Clinicians should consider Fabry disease in patients presenting with unexplained left ventricular hypertrophy, proteinuria, or chronic kidney disease, especially when accompanied by other suggestive symptoms like neuropathic pain or angiokeratomas.

Fabry disease stems from a deficiency or absence of alpha-galactosidase A (alpha-Gal A) enzyme activity, encoded by the GLA gene on the X chromosome. This enzymatic defect leads to the progressive accumulation of Gb3 and its deacylated form, globotriaosylsphingosine (lyso-Gb3), within lysosomes throughout the body. The systemic nature of Gb3 accumulation explains the multi-organ involvement characteristic of Fabry disease, affecting the kidneys, heart, brain, skin, and peripheral nervous system. The disease is X-linked, meaning males typically experience more severe and earlier onset symptoms, while females, due to X-chromosome inactivation, can have a wide spectrum of presentations ranging from asymptomatic to severe, often leading to underdiagnosis in this population.

The clinical presentation of Fabry disease is highly variable, complicating its recognition. Early symptoms, often appearing in childhood or adolescence, include neuropathic pain (acroparesthesias), heat intolerance, hypohidrosis, gastrointestinal disturbances, and characteristic skin lesions known as angiokeratomas. These initial manifestations are frequently dismissed or misdiagnosed as other conditions, such as growing pains, irritable bowel syndrome, or dermatological issues. As patients age, more severe and life-threatening complications emerge, primarily affecting the kidneys and heart. The progressive nature of the disease means that by the time patients present to nephrology or cardiology clinics, significant and often irreversible organ damage may already be present.

The Renal Manifestations

Renal involvement is a hallmark of Fabry disease, progressing from proteinuria to end-stage renal disease (ESRD). Gb3 accumulation in glomerular podocytes, tubular cells, and vascular endothelial cells leads to podocytopathy, glomerulosclerosis, and interstitial fibrosis. Patients typically present with proteinuria, which can be microalbuminuria initially, progressing to overt proteinuria. This often leads to a diagnosis of chronic kidney disease (CKD) of unknown etiology. The progression of renal disease in Fabry patients is often insidious, with a gradual decline in glomerular filtration rate (GFR). Without specific treatment, many male patients with classic Fabry disease will develop ESRD by their fourth or fifth decade of life, necessitating dialysis or kidney transplantation. The challenges in managing kidney disease extend beyond Fabry, but the genetic basis here offers a unique intervention window.

Nephrologists should maintain a high index of suspicion for Fabry disease in patients with unexplained proteinuria, particularly those with a family history of kidney disease or other suggestive symptoms. The presence of left ventricular hypertrophy (LVH) or a history of stroke at a young age in a patient with CKD should prompt further investigation. Screening for Fabry disease in these populations typically involves measuring alpha-Gal A enzyme activity in plasma or leukocytes for males, and genetic testing for GLA mutations for both males and females. Lyso-Gb3 levels in plasma can also serve as a useful biomarker, particularly for monitoring disease progression and treatment response.

Cardiac Complications

Cardiac involvement is a leading cause of morbidity and mortality in Fabry disease. Gb3 accumulation in cardiomyocytes, valvular fibroblasts, and vascular endothelial cells results in a progressive cardiomyopathy, valvular heart disease, and arrhythmias. The most common cardiac manifestation is left ventricular hypertrophy, which can mimic hypertrophic cardiomyopathy (HCM). This often leads to misdiagnosis, as the underlying genetic cause is overlooked. The LVH in Fabry disease is typically concentric and can progress to restrictive cardiomyopathy, leading to heart failure with preserved ejection fraction. The recognition of other infiltrative cardiomyopathies, like cardiac AL amyloidosis, highlights the need for careful differentiation.

Valvular heart disease, particularly mitral valve prolapse and aortic valve thickening, is also common. Arrhythmias, including bradycardia, atrioventricular block, and atrial fibrillation, are frequently observed and can contribute to sudden cardiac death. Cardiologists should consider Fabry disease in any patient presenting with unexplained LVH, especially in the absence of hypertension or aortic stenosis, or in those with a family history of early-onset cardiac disease. Echocardiography often reveals characteristic findings such as bi-ventricular hypertrophy, papillary muscle hypertrophy, and mitral valve abnormalities. Cardiac magnetic resonance imaging (CMR) can show late gadolinium enhancement, indicating myocardial fibrosis, a prognostic marker of disease severity.

The differential diagnosis for unexplained LVH is broad, including HCM, hypertensive heart disease, and other infiltrative cardiomyopathies like transthyretin amyloidosis. Distinguishing Fabry cardiomyopathy from these conditions is critical, as specific enzyme replacement therapy (ERT) or chaperone therapy is available for Fabry disease. A thorough clinical history, including family history, and a careful physical examination for non-cardiac signs of Fabry disease are essential. For a comprehensive overview of cardiac conditions, clinicians might consult Braunwald's Heart Disease.

Neurological and Other Systemic Manifestations

Beyond the kidneys and heart, Fabry disease also significantly impacts the central and peripheral nervous systems. Cerebrovascular events, including transient ischemic attacks (TIAs) and strokes, are common, often occurring at a younger age than in the general population. This is due to Gb3 accumulation in endothelial cells of cerebral blood vessels, leading to vasculopathy and increased risk of thrombosis. White matter lesions are frequently observed on brain imaging, even in asymptomatic individuals. Peripheral neuropathy, manifesting as acroparesthesias (burning pain in hands and feet), is often one of the earliest and most debilitating symptoms, significantly impacting quality of life. These neuropathic symptoms are often misdiagnosed as fibromyalgia, carpal tunnel syndrome, or other peripheral nerve disorders.

Other systemic manifestations include gastrointestinal symptoms such as abdominal pain, diarrhoea, and nausea, which are attributed to Gb3 accumulation in the enteric nervous system. Ocular involvement includes cornea verticillata (whorl-like corneal opacities), which is a highly specific but often asymptomatic finding, detectable by slit-lamp examination. This finding can be a valuable diagnostic clue, even in the absence of other overt symptoms. Hearing loss, typically high-frequency sensorineural, and vestibular dysfunction are also reported. The broad spectrum of symptoms means that patients may present to various specialists, from neurologists to ophthalmologists, before the unifying diagnosis of Fabry disease is considered. This highlights the importance of interdisciplinary collaboration and a high index of suspicion across multiple specialties.

Diagnostic Approaches and Unmet Needs

The diagnostic pathway for Fabry disease often begins with suspicion based on clinical symptoms and family history. For males, a definitive diagnosis is typically made by demonstrating deficient alpha-Gal A enzyme activity in plasma, leukocytes, or fibroblasts. But enzyme activity levels can be normal in some female carriers, making genetic testing for GLA mutations the gold standard for diagnosis in females and for confirming diagnosis in males. The measurement of lyso-Gb3, a deacylated form of Gb3, has emerged as a sensitive and specific biomarker for Fabry disease, particularly in males with classic phenotypes and increasingly recognised as useful in females. Elevated lyso-Gb3 levels are indicative of significant Gb3 accumulation and can be used for screening and monitoring disease progression. Understanding the genetic basis of Fabry disease is important for guiding treatment choices.

Despite the availability of diagnostic tools, significant diagnostic delays persist. The average time from symptom onset to diagnosis can be 10 to 15 years, during which irreversible organ damage can occur. This delay is attributed to the non-specific nature of early symptoms, the rarity of the disease, and a lack of awareness among healthcare professionals. Screening programs in high-risk populations, such as patients with unexplained LVH, CKD of unknown etiology, or cryptogenic stroke, have been proposed and implemented in some regions. These targeted screening efforts aim to identify affected individuals earlier, enabling timely initiation of specific therapies. The challenge remains in integrating these screening protocols into routine clinical practice without overburdening healthcare systems or generating excessive false positives.

The open-label design of many observational studies on Fabry disease is an obvious caveat when interpreting long-term outcomes. The rarity of the condition makes large, randomised, placebo-controlled trials challenging, but this does not diminish the need for robust evidence. The natural history of the disease, particularly in females and those with later-onset phenotypes, is still being fully elucidated. This gap matters, as treatment decisions often rely on a comprehensive understanding of disease progression and individual risk factors. The long-term efficacy of enzyme replacement therapy

and chaperone therapy in preventing or reversing advanced organ damage continues to be an area of active research, with ongoing efforts to identify optimal treatment initiation times and patient selection criteria.

Therapeutic Market

Current specific treatments for Fabry disease include enzyme replacement therapy (ERT) and chaperone therapy. ERT involves intravenous infusions of recombinant human alpha-Gal A, aiming to replace the deficient enzyme and reduce Gb3 accumulation. Two forms of recombinant alpha-Gal A are available: agalsidase alfa and agalsidase beta. These therapies have been shown to reduce Gb3 levels in various tissues, improve neuropathic pain, and stabilise or improve renal and cardiac function, particularly when initiated early in the disease course. The effectiveness of ERT in reversing advanced organ damage is more limited, underscoring the importance of early diagnosis.

Chaperone therapy, specifically migalastat, is an oral small molecule that acts as a pharmacological chaperone. It binds to specific amenable mutant forms of alpha-Gal A, stabilising the enzyme and facilitating its transport to the lysosomes, thereby increasing endogenous enzyme activity. Migalastat is only effective in patients with specific GLA mutations that result in an amenable enzyme. This requires genetic testing to determine mutation amenability. Both ERT and chaperone therapy represent significant advancements in managing Fabry disease, but they are not without their challenges, including cost, administration burden, and the need for lifelong treatment. The choice of therapy depends on the patient's genotype, clinical phenotype, and individual tolerability. The field continues to evolve, with new therapeutic strategies, including gene therapy, under investigation.

> **CLINICAL IMPLICATIONS**
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> The persistent diagnostic delay in Fabry disease is a clinical failing that demands attention. Too many patients present with advanced cardiac or renal disease, having endured years of unexplained symptoms, simply because the possibility of a rare genetic disorder was not considered. This is particularly true for women, whose variable presentations often lead to even longer diagnostic odysseys.
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> Cardiologists and nephrologists are on the front lines of this problem. Any patient with unexplained left ventricular hypertrophy, proteinuria, or chronic kidney disease, especially with a family history of similar issues or other suggestive symptoms like neuropathic pain, should trigger a diagnostic workup for Fabry disease. A simple enzyme activity test in males, or genetic testing for GLA mutations in females, can avert years of progressive organ damage.
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> The availability of specific therapies means that early diagnosis is not merely an academic exercise; it directly impacts patient outcomes. While these treatments are not cures, they can stabilise disease progression and improve quality of life. Ignoring the possibility of Fabry disease means denying patients access to potentially life-altering interventions, allowing preventable complications to accumulate.

REFERENCES

1. 1. Norouzi S, Ghozloujeh ZG, Lerma E, Hwang MR, Rastogi A. Fabry Disease: Current Perspectives on Diagnosis and Management Strategies. Adv Kidney Dis Health. 2026;33(1):92-102. doi:10.1053/j.akdh.2026.04.004

2. 2. Siegenthaler M, Huynh-Do U, Krayenbuehl P, et al. Impact of cardio-renal syndrome on adverse outcomes in patients with Fabry disease in a long-term follow-up. Int J Cardiol. 2017;249:261-267. doi:10.1016/j.ijcard.2017.09.027

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