Revista ARACÊ
ISSN: 2358-2472

FROM NONSPECIFIC SYMPTOMS TO TIMELY DIAGNOSIS IN FABRY DISEASE: PRACTICAL STRATEGIES FOR EARLY DETECTION AND MANAGEMENT

https://doi.org/10.56238/arev7n8-249

Date of submission: 07/25/2025 **Date of publication:** 08/25/2025

Janaína Justino do Nascimento[1], Eduardo Diniz de Castro Menezes[2], Marcus Vinicius Jesus da Silva[3], Gabriella Alves Ramos[4], Lucia Helena Ferreira Vasconcelos[5], Danielle Furtado de Oliveira[6], Nathalia Lopez Duarte[7]

ABSTRACT

Fabry disease (FD) is an X-linked inherited disorder caused by α-galactosidase A deficiency (α-GalA), leading to accumulation of globotriaosylceramide and its metabolite globotriaosylsphingosine (Gb3/lyso-Gb3), with progressive damage primarily to the heart, kidneys, and nervous system. It presents as classic and late phenotypes, ranging from onset in childhood to adulthood, with great heterogeneity, especially in women. Multisystem manifestations include acroparesthesias, heat intolerance with hypo/anhidrosis, pain crises, and gastrointestinal complaints; characteristic signs are angiokeratomas and cornea verticillata. If untreated, progression to left ventricular hypertrophy, proteinuria/ chronic kidney disease (CKD), and cerebrovascular events is common. The diagnosis combines measurement of α-GalA activity (more informative in men), genetic testing (essential in women), lyso-Gb3 biomarkers and family screening. Specific treatment includes enzyme replacement therapy (ERT) and oral pharmacological chaperones for eligible variants, complemented by supportive, multidisciplinary care. Given the frequent diagnostic delay, early recognition of warning signs in primary and general care is critical to start therapy before irreversible damage, improving outcomes and quality of life. This brief narrative review synthesizes evidence on clinical presentation, practical diagnostic strategies, and current management, underscoring the importance of early clinical suspicion and family screening.

Keywords: Fabry Disease. Diagnosis. Clinical Suspicion. Family Screening. Quality of Life.

[1]Physician. Hospital Municipal Ronaldo Gazolla. Rio de Janeiro, Brazil. E-mail: janajnascimento@yahoo.com.br
[2] Physician. Hospital Municipal Ronaldo Gazolla. Rio de Janeiro, Brazil.
E-mail: eduardocastromenezes@gmail.com
[3]Physician. Hospital Municipal Ronaldo Gazolla. Rio de Janeiro, Brazil.
E-mail: vinicius_meduerj2015@hotmail.com
[4]Physician. Hospital Municipal Ronaldo Gazolla. Rio de Janeiro, Brazil. E-mail: gabriella_ramos@outlook.com
[5]Physician. Hospital Municipal Ronaldo Gazolla. Rio de Janeiro, Brazil.
E-mail: luciavasconcelos.riosaude@gmail.com
[6]Researcher. Hospital Municipal Ronaldo Gazolla. Rio de Janeiro, Brazil.
E-mail: daniellefurtadooliveira@gmail.com
[7] Researcher. Hospital Municipal Ronaldo Gazolla. Rio de Janeiro, Brazil.
E-mail: nathalialopezduarte@gmail.com

Revista ARACÊ
ISSN: 2358-2472

DOS SINTOMAS INESPECÍFICOS AO DIAGNÓSTICO OPORTUNO DA DOENÇA DE FABRY: ESTRATÉGIAS PRÁTICAS PARA DETECÇÃO E TRATAMENTO PRECOCE

RESUMO

A Doença de Fabry (DF) é uma afecção hereditária ligada ao X, causada por deficiência da alfa-galactosidase A (α-GalA), com acúmulo de globotriaosilceramida e metabólico globotriaosilesfingosina (Gb3/lyso-Gb3) e dano progressivo sobretudo cardíaco, renal e neurológico. Apresenta como fenótipos clássico e tardio, variando do início na infância à vida adulta, com grande heterogeneidade, especialmente em mulheres. As manifestações são multissistêmicas: acroparestesias, intolerância ao calor com hipo/anidrose, crises dolorosas e queixas gastrointestinais; sinais característicos incluem angioceratomas e córnea verticilata. Sem tratamento, pode evoluir com hipertrofia ventricular esquerda, proteinúria/doença renal crônica (DRC) e eventos cerebrovasculares. O diagnóstico combina dosagem da atividade de α-GalA, (mais informativa em homens), teste genético (essencial em mulheres), biomarcadores lyso-Gb3 e rastreamento familiar. O tratamento específico inclui terapia de reposição enzimática (TRE) e chaperona oral para mutações elegíveis, além de medidas de suporte e acompanhamento multiprofissional. Dado o atraso diagnóstico frequente, o reconhecimento precoce de sinais de alerta na atenção primária e em serviços de clínica é crucial para iniciar terapia antes de dano irreversível, com potencial de melhorar desfechos e qualidade de vida. Esta revisão narrativa sintetiza evidências sobre apresentação clínica, estratégias diagnósticas factíveis e manejo atual, enfatizando a importância da suspeição clínica precoce e do rastreamento familiar.

Palavras-chave: Doença de Fabry. Diagnóstico. Suspeição Clínica. Rastreamento Familiar. Qualidade de Vida.

DE LOS SÍNTOMAS INESPECÍFICOS AL DIAGNÓSTICO TEMPRANO DE LA ENFERMEDAD DE FABRY: ESTRATEGIAS PRÁCTICAS PARA LA DETECCIÓN Y EL TRATAMIENTO TEMPRANO

RESUMEN

La enfermedad de Fabry (EF) es un trastorno hereditario ligado al cromosoma X causado por deficiencia de alfa-galactosidasa A (α-GalA), que conduce a la acumulación de globotriaosilceramida y de su metabolito globotriaosilesfingosina (Gb3/lyso-Gb3) y a daño progresivo, principalmente en corazón, riñones y sistema nervioso. Se presenta con fenotipos clásico y tardío, con inicio en la infancia hasta la edad adulta, con marcada heterogeneidad, especialmente en mujeres. Las manifestaciones multisistémicas incluyen acroparestesias, intolerancia al calor con hipohidrosis/anhidrosis, crisis dolorosas y síntomas gastrointestinales; los signos característicos son los angiocerátomas y la córnea verticilata. Sin tratamiento, es frecuente la progresión a hipertrofia ventricular izquierda, proteinuria/enfermedad renal crónica (ERC) y eventos cerebrovasculares. El diagnóstico combina la medición de la actividad de α-GalA (más informativa en hombres), pruebas genéticas (esenciales en mujeres), biomarcadores de liso-Gb3 y detección familiar. La terapia específica incluye la terapia de reemplazo enzimático (TER) y las chaperonas farmacológicas orales para variantes elegibles, complementadas con medidas de soporte y atención multidisciplinaria. Dado el retraso diagnóstico frecuente, el reconocimiento temprano de signos de alarma en la atención primaria y clínica general es crucial para iniciar el tratamiento antes de daño irreversible, mejorando los resultados y la calidad de vida. Esta breve revisión narrativa sintetiza la evidencia sobre la presentación

Revista ARACÊ
ISSN: 2358-2472

clínica, estrategias diagnósticas prácticas y el manejo actual, subrayando la importancia de la sospecha clínica precoz y del tamizaje familiar.

Palabras clave: Enfermedad de Fabry. Diagnóstico. Sospecha Clínica. Tamizaje Familiar. Calidad de Vida.

Revista ARACÊ
ISSN: 2358-2472

1 INTRODUCTION

Fabry disease (FD) is an X-linked lysosomal disorder caused by pathogenic variants in the GLA gene on Xq22 that reduce α-galactosidase A (α-GalA) activity, leading to lysosomal accumulation of globotriaosylceramide (Gb3) and globotriaosylsphingosine (lyso-Gb3) with downstream endothelial dysfunction, inflammation, and ischemic injury[1,2]. Affected tissues include vascular endothelium, central nervous system, skin, and most notably, the heart and kidneys, driving multisystem morbidity and mortality[1].

Clinically, FD comprises two main phenotypes: the classic form, more frequent in males, with markedly reduced or absent enzyme activity and early, diffuse complications. And the non-classic (later-onset) form, typically milder, with slower progression and predominant cardiorenal involvement[3,4]. Early manifestations are often nonspecific (e.g., acroparesthesias, heat intolerance with hypo/anhidrosis, gastrointestinal complaints, fatigue and pain crises), which contributes to prolonged diagnostic delays.

Early diagnosis integrates α-GalA activity (most informative in males), GLA genetic testing, crucial in females given variable X-inactivation, biomarkers such as lyso-Gb3, clinical and family history, and targeted assessment of organ involvement[2]. Therapeutic management centers on symptom control and disease modification with enzyme replacement therapy (ERT) and oral pharmacological chaperones for amenable variants, alongside multidisciplinary care; investigational strategies include substrate reduction, messenger RNA (mRNA) based approaches and gene therapy [2,5]. Prognostic scores combining clinical, imaging, and laboratory data support risk stratification and longitudinal monitoring[3].

This brief narrative review synthesizes evidence on pathophysiology, clinical presentation, diagnostic strategies, and current therapies, emphasizing early clinical suspicion and family screening to enable timely treatment and mitigate cardiorenal and neurological outcomes.

2 OBJECTIVE

To conduct a brief narrative review on early clinical suspicion of FD, summarizing nonspecific warning manifestations, practical diagnostic strategies (including family screening), and therapeutic options with potential impact on quality of life and organ outcomes.

Revista ARACÊ
ISSN: 2358-2472

3 MATERIALS AND METHODS

Narrative literature review of publications from 2013 – 2025 in PubMed, SciELO, LILACS, Medline, and the Virtual Health Library, using the descriptors “Fabry disease”, “differential diagnosis/clinical suspicion”, “nonspecific symptoms”, “warning signs” and “quality of life”. Inclusion emphasized studies addressing clinical presentation, diagnosis (including biomarkers and genetics), and treatment relevant to early detection and multidisciplinary management.

4 RESULTS AND DISCUSSION

4.1 EPIDEMIOLOGY

FD is a lysosomal storage disorder historically described in 1898 (initially as *“angiokeratoma corporis diffusum universal”*)[6,7]. Estimated incidence ranges from 1:40,000–1:117,000 in the general population and increases to 1:3,100 in newborn screening cohorts, reflecting detection of late-onset variants [8]. Classic mutations in males are estimated at 1:22,000–1:40,000, while atypical presentations may approximate 1:1,000–1:3,000 in males and 1:6,000–1:40,000 in females[9]. FD is more frequently detected among patients with chronic kidney disease (CKD)[1].

Neonatal screening offers earlier diagnosis but raises concerns about variants of uncertain significance (VUS) and benign variants, psychological impact, and follow-up thresholds; current evidence remains mixed[3]. In Brazil, general-population screening is not recommended; screening is advised for relatives of index cases and for individuals with compatible renal, cardiac, or neurological phenotypes without defined etiology [2].

4.2 PATHOPHYSIOLOGY

Pathogenic GLA variants reduce α-GalA activity, causing accumulation of Gb3 and lyso- Gb3, with endothelial dysfunction, oxidative stress, and chronic inflammation affecting multiple tissues, predominantly heart, kidneys, and central nervous system[3]. Lysosomal substrate accumulation disrupts cellular homeostasis and promotes fibrosis, underpinning heart failure, CKD, and stroke in advanced disease[5,7,10].

4.3 CLINICAL PRESENTATION

FD presents as a classic, early-onset phenotype (childhood/adolescence, multi-organ involvement) and a later-onset phenotype with a predominance of cardiorenal and

Revista ARACÊ
ISSN: 2358-2472

neurological disease [11]. Males typically show more severe disease, while females display variable expressivity due to random X-inactivation[4]. Common early manifestations, often misattributed to other causes, include acroparesthesias (neuropathic pain in the limbs), heat intolerance with hypo/anhidrosis, pain crises triggered by stress and temperature changes, fatigue, and gastrointestinal complaints; characteristic findings are violaceous, keratinized angioectatic skin lesions in the genital, gluteal, inner thigh, and periumbilical regions (angiokeratomas) and corneal verticillata (corneal mosaic keratopathy) [7,12]. In children, abdominal pain/diarrhea and limb pain, which may impair growth, are frequent; FD should be considered in the differential diagnosis of young patients presenting with stroke or unexplained renal failure[6]. Evidence suggests substrate accumulation begins in utero, with placental and fetal renal/cardiac involvement [13]. Heart disease includes palpitations, dyspnea, arrhythmias, angina/ischemia and left ventricular hypertrophy, pay attention to the history of tachyarrhythmias, especially if associated with a short PR interval on the electrocardiogram[14]; renal disease evolves from hyperfiltration and albuminuria/proteinuria to decline in glomerular filtration rate (GFR) and CKD; neurologic involvement includes headaches, transient ischemic attack (TIA), and stroke, with higher stroke incidence versus the general population[2].

4.4 DIAGNOSIS

Diagnosis integrates clinical evaluation with α-GalA activity and GLA sequencing. In hemizygous males, enzyme activity is typically reduced or absent; in heterozygous females, activity may be normal or slightly reduced, making genetic testing essential [3,2]. Diagnostic criteria combine low/absent enzyme activity and a pathogenic GLA variant with specific signs (neuropathic pain, cornea verticillata, angiokeratomas), elevated lyso- Gb3, and/or positive family history [15].

Enzyme assays can be performed in plasma, leukocytes, or dried blood spots (markedly low in classic disease; variable in later-onset). Lyso-Gb3 is a recommended biomarker for diagnosis and follow-up [2,16]. Imaging and laboratory assessment of organ involvement (e.g., echocardiography/cardiac MRI, renal function) aid staging and therapeutic planning. Family screening of index cases with genetic counseling is crucial to identify additional affected relatives[6]. Practical diagnostic pathways have been proposed to standardize workup and monitoring in clinical practice[8].

Revista ARACÊ
ISSN: 2358-2472

4.5 TREATMENT

Disease-specific therapy consists of ERT and oral pharmacological chaperone for amenable variants, plus symptomatic and organ-protective measures within a multidisciplinary approach[2,5]. Agalsidase alfa and agalsidase beta are administered intravenously every two weeks; migalast is an oral option for eligible mutations[9,16]. Limitations include lack of blood–brain barrier penetration and infusion reactions or anti- drug antibodies with ERT; chaperone efficacy depends on mutation amenability[3,17]. General contraindications to ERT include advanced CKD (stages 4–5), NYHA class IV heart failure, severe cognitive decline, advanced disease/comorbidities with limited life expectancy, and severe prior infusion reactions with IgE[18]. In Brazil, agalsidase alfa was incorporated into the Unified Health System (SUS) in 2023 for classical FD from 7 years of age, according to the national clinical protocol [19]. Investigational strategies substrate reduction therapy, mRNA therapy, and gene therapy, may broaden individualized options[2,10].

4.6 EARLY DIAGNOSIS AND QUALITY OF LIFE

Symptoms often begin in childhood or adolescence and are nonspecific, leading to diagnostic delays that can exceed a decade; family screening is pivotal once an index case is identified [1]. Earlier initiation of ERT has been associated with better quality of life, preservation of organ function, and lower rates of cardiorenal complications compared with treatment started after irreversible damage [20].

5 FINAL CONSIDERATIONS

FD remains underdiagnosed because early manifestations are nonspecific and phenotypic expressivity is variable, particularly in women. Timely recognition of warning features and systematic family screening after an index case can shorten diagnostic delays that commonly exceed a decade and enable treatment before irreversible organ damage. When started early, disease-specific therapy is associated with better quality of life, preservation of organ function, and fewer cardiorenal events. In practice, clinicians, especially in primary and general care, should maintain high suspicion in patients with neuropathic pain, heat intolerance with hypo/anhidrosis, persistent gastrointestinal complaints, angiokeratomas, cornea verticillata, or unexplained CKD/stroke, and apply a genetics-first strategy in women. Standardized pathways for

Revista ARACÊ
ISSN: 2358-2472

diagnosis, organ staging, and longitudinal monitoring, as recommended in national consensus documents, can further improve outcomes.

REFERENCES

SODRÉ LSS, et al. Screening of relatives of patients with chronic kidney disease and Fabry disease mutation: a very important and underestimated task. Braz J Nephrol. 2020;43:28-33.

SILVA CAB, et al. Brazilian consensus on Fabry disease: recommendations for diagnosis, screening, and treatment. Committee on Rare Diseases (Comdora)- SBN/2021. Braz J Nephrol. 2022;44:249-67.

LERARIO S, et al. Fabry disease: a rare disorder calling for personalized medicine. Int Urol Nephrol. 2024;56(10):3161-72.

ANTUNES MO, et al. Fabry disease and its different phenotypes. Braz Arch Cardiol. 2025;122:e20240535.

CORDEIRO RA, et al. What should rheumatologists know about Gaucher disease and Fabry disease? Connecting the dots for an overview. Adv Rheumatol. 2024;64(1):22.

TAKIZAWA C, et al. Fabry disease: a literature review. São Paulo: Anima University Repository; 2021.

DE SÁ SOARES PHQ, et al. Fabry disease: about a case. J Fac Med Teresópolis. 2019;3(2).

SILVA SM, et al. My approach to diagnose Fabry disease. Arq Bras Cardiol: Imagem Cardiovasc. 2025;38(2).

MIGUEL CB, et al. Efficacy and safety of agalsidase alfa and agalsidase beta for intervention in Fabry disease: rapid review. Sci J State Sch Public Health Goiás "Candido Santiago". 2023;1-21.

MIGNANI R, et al. Effects of current therapies on disease progression in Fabry disease: a narrative review for better patient management in clinical practice. Adv Ther. 2025;42(2):597-635.

TOLDO CM, et al. Anderson Fabry disease. A cardiologist's perspective: you can't diagnose what you don't think about, and you don't think about what you don't know. Heart Fail. 2017;12(2):51-61.

COSTA ALFA, et al. Cornea verticillata due to Fabry disease. Einstein (São Paulo). 2014;12(4):527-8.

DARGENIO VN, et al. Unraveling the hidden burden of gastrointestinal and nutritional challenges in children with Fabry disease: a systematic review with meta- analysis. Nutrients. 2025;17(7):1194.

Revista ARACÊ
ISSN: 2358-2472

VILELA GFS, et al. Classical Fabry disease: a challenging diagnosis. Rev Cardiol Estado São Paulo. 2020;30:206.

MOISEEV S, et al. The benefits of family screening in rare diseases: genetic testing reveals 165 new cases of Fabry disease among at-risk family members of 83 index patients. Genes. 2022;13(9):1619.

VAISBICH MH, et al. Recommendations for the diagnosis and management of Fabry disease in pediatric patients: a document from the Rare Diseases Committee of the Brazilian Society of Nephrology (Comdora-SBN). Braz J Nephrol. 2022;44:268-80.

DEZUANE ARD, et al. Adherence of patients with Fabry disease to treatment. Rev Bras Desenvolv. 2021;7(4):40662-73.

MASSUDA A, et al. Clinical protocol and therapeutic guidelines for Fabry disease. Brasília: Ministry of Health; 2025. 15 p. (Joint Ordinance SAES/SECTICS No. 2, January 15, 2025).

ITRIA A, et al. Report on the recommendation of alfagalsidase for the treatment of classic Fabry disease from seven years of age. Brasília: Ministry of Health; 2023. 48 p. (SECTICS/MS Ordinance No. 26, May 18, 2023).

JOVANOVIC A, et al. A systematic literature review on the health-related quality of life and economic burden of Fabry disease. Orphanet J Rare Dis. 2024;19(1):181.