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ORIGINAL ARTICLE

# Awareness of Fabry disease in cardiology: A gap to be filled

**Dulce Brito[a,*], Nuno Cardim[b], Luís Rocha Lopes[c], Adriana Belo[d], Jorge Mimoso[e], Lino Gonçalves[f], Hugo Madeira[g], on behalf of the Portuguese Registry of Hypertrophic Cardiomyopathy (PRo-HCM) Investigators**

[a] *Serviço de Cardiologia, Hospital de Santa Maria, CHLN, CCUL, Centro Académico de Medicina de Lisboa, Faculdade de Medicina da Universidade de Lisboa, Portugal*
[b] *Centro de miocardiopatia hipertrófica - Hospital da Luz, Faculdade de Ciências Médicas da Universidade Nova de Lisboa, Portugal*
[c] *Centro Cardiovascular, Faculdade de Medicina da Universidade de Lisboa; Institute of Cardiovascular Centre, University College London; Barts Heart Centre, Barts Health NHS Trust, Portugal*
[d] *Centro Nacional de Coleção de Dados em Cardiologia (CNCDC), Sociedade Portuguesa de Cardiologia, Portugal*
[e] *Serviço de Cardiologia do CHU Algarve, Faro, Portugal*
[f] *Serviço de Cardiologia do CHUC-HG e Faculdade de Medicina da Universidade de Coimbra, Portugal*
[g] *Centro Cardiovascular da Universidade de Lisboa (CCUL), Faculdade de Medicina da Universidade de Lisboa, Portugal*

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**KEYWORDS**
Fabry disease;
Hypertrophic cardiomyopathy;
Registry;
Left ventricular hypertrophy

**Abstract**
*Introduction:* In adults, unexplained left ventricular hypertrophy is usually due to sarcomeric hypertrophic cardiomyopathy (HCM). Fabry disease (FD) is rare but may mimic sarcomeric HCM, and has an adverse prognosis in the absence of specific treatment. We aimed to assess cardiologists' awareness of FD based on data from the Portuguese Registry of Hypertrophic Cardiomyopathy.
*Methods:* A total of 811 index patients, aged 55±16 years, 486 (59.9%) male, were included. Three groups were characterized: A – 128 patients, 74 (57.8%) male, with pathogenic or likely pathogenic mutation(s) in sarcomeric genes; B – 234 patients, 146 (62.4%) male, with negative genetic testing; and C – 449 patients, 266 (59.2%) male, no genetic testing performed. The groups were compared in terms of whether FD was excluded in the registry. Potential red flags for FD were also analyzed and compared between groups.
*Results:* Patients in group A were younger and more frequently had familial HCM (A – 53.9% vs. B – 20.1% vs. C – 18.3%; p<0.001). FD was recorded as excluded in 217 (26.8%), similar in all groups; *GLA* gene testing was performed in only 50/217 patients (A – 48.6%, B – 25.7%, p=0.019; C – 13.4%, p=0.036 for B vs. C), mostly in women (p<0.001) in groups B and C. Alpha-galactosidase A (α-Gal A) activity was assessed in 39/217 (18%) patients, with no difference between groups, but more often in men (p=0.005).

* Corresponding author.
*E-mail address:* dulcebrito@spc.pt (D. Brito).

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Among patients with potential red flags for FD, only 46.7% underwent specific tests (*GLA* gene testing and/or α-Gal A activity). When *GLA* genotyping was performed no mutations were identified.

*Conclusions:* There is a need to improve cardiologists' alertness for the identification of FD among the Portuguese HCM population.



**PALAVRAS-CHAVE**
Doença de Fabry;
Miocardiopatia hipertrófica;
Registo;
Hipertrofia ventricular esquerda

**Perceção da doença de Fabry em cardiologia: uma lacuna a preencher**

**Resumo**

*Introdução:* Em adultos, hipertrofia ventricular esquerda inexplicada é geralmente devida a miocardiopatia hipertrófica sarcomérica (MH). A doença de Fabry (DF), rara, pode mimetizar MH e tem prognóstico adverso na ausência de tratamento específico. Avaliámos a perceção dos cardiologistas para DF com base no Registo Português de Miocardiopatia Hipertrófica.

*Métodos:* Incluímos 811 doentes-índice, 55 ± 16 anos, 486 (59,9%) homens (H). Caracterizámos três grupos: A-128 doentes, 74 (57,8%) H, com mutação patogénica/provavelmente patogénica em genes sarcoméricos; B-234 doentes, 146 (62,4%) H, com teste genético negativo; C-449 doentes, 266 (59,2%) H, sem teste genético efetuado. Os grupos foram comparados em relação à exclusão de DF, segundo a informação do registo. Sinais potenciais de alerta para DF foram também avaliados e comparados entre os três grupos.

*Resultados:* Os doentes do grupo A eram mais novos e tinham mais frequentemente MH familiar (A-53,9% *versus* B-20,1% *versus* C-18,3%; p<0,001). DF foi dada como excluída em 217 (26,8%) doentes, sem diferença entre grupos; sequenciação do gene GLA foi efetuada apenas em 50/217 doentes [A-48,6%, B-25,7%, p = 0,019; C-13,4%, p (B *versus* C) = 0,036], predominantemente em mulheres (p < 0,001) nos grupos B e C; atividade enzimática da α-Gal A foi avaliada em 39/217 (18%) doentes, sem diferença entre grupos, mas predominantemente em H (p = 0,005). Dos doentes com sinais potenciais de alerta para DF, apenas 46,7% foram submetidos a testes específicos (GLA e/ou α-Gal A). Quando o gene GLA foi estudado, o resultado foi negativo.

*Conclusões:* É necessário melhorar a perceção dos cardiologistas para a identificação da DF na população portuguesa com MH.



## Introduction

Left ventricular hypertrophy (LVH) detected by imaging techniques in the absence of common physiological or pathological causes is due in about 40-60% of cases to sarcomeric hypertrophic cardiomyopathy (HCM),[1] an autosomal dominant trait caused by mutations in cardiac sarcomeric protein genes. The disease has an estimated worldwide prevalence of 1 in 500 individuals on the basis of the echocardiographic phenotype.[1] It only affects the heart and is often benign throughout life, although it may also be associated with adverse outcomes, including sudden cardiac death (SCD).[1,2] However, in about 5-10% of cases, unexplained LVH can be caused by other non-genetic or rarer genetic disorders that may mimic sarcomeric HCM, for some of which specific treatment is available. This is the case with Fabry disease (FD),[3–5] a multisystem lysosomal storage disease caused by a deficiency of the enzyme alpha-galactosidase A (α-Gal A), encoded by the *GLA* gene on the X chromosome. The disease leads to accumulation of globotriaosylceramide (Gb3) and other glycosphingolipids in lysosomes, resulting in progressive multiorgan damage, with severe complications due to cardiac, renal or cerebrovascular lesions, and ultimately in decreased life expectancy.[6–8] Although the classic form of FD affects multiple organs and occurs early in men (hemizygotes), some forms are found particularly (though not exclusively) in women (heterozygotes), manifesting as milder disease, with a late-onset phenotype that is often confined to a single organ such as the heart, kidney, or brain.[9–11] The frequent observation of exclusively cardiac involvement in FD suggests that the heart is the most susceptible organ to α-Gal A deficiency.[12–14] Cardiac involvement is one of the main determinants of prognosis,[6,9,15,16] and includes LVH (the most common manifestation),[17] arrhythmias, small-vessel coronary disease and heart failure. Electrocardiographic (ECG) abnormalities are frequent, and brady- or tachyarrhythmias are a significant cause of morbidity and mortality, including SCD.[18,19]

The diagnosis of FD is difficult and requires a high level of clinical suspicion. Many of the typical extracardiac features

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