Review Article

FABRY DISEASE AND THE HEART: A COMPREHENSIVE REVIEW.

Azevedo O, Cordeiro F, Gago MF, *et al. Int J Molecular Sciences* 2021;22:4434.

Overview

- Fabry disease (FD) is a rare lysosomal storage disorder caused by mutations in the *GLA* gene, leading to deficiency in the enzymatic activity of α-galactosidase A.[1]
- Globotriaosylceramide (GB3 or GL-3) and other glycosphingolipids consequently accumulate in body fluids and lysosomes of cells throughout the body, including the heart.[1]
- *GLA* mutations causing a virtually null enzymatic activity (< 5 % of the normal mean) are associated with severe and early onset classical phenotypes, characterised by the development of clinical manifestations in childhood or adolescence.[1]
- *GLA* mutations leading to a residual enzymatic activity are associated with attenuated and late-onset phenotypes, characterised by the development of cardiac, renal and/or cerebrovascular manifestations in adulthood.[1]
- In this X-linked disorder, heterozygote females are not merely carriers and their clinical spectrum ranges widely from asymptomatic to full-blown disease (as severe as in affected males).[1]

Cardiac involvement in Fabry disease

- Fabry disease leads to GL-3 accumulation in virtually all cardiac cells.[1]
- GL-3 deposits are found in cardiomyocytes, valve fibroblasts, endothelial and smooth muscle vascular cells, and cardiac conduction cells, representing 1-2 % of the cardiac mass.[1]
- GL-3 accumulation activates common signaling pathways leading to hypertrophy, inflammation, apoptosis, necrosis and fibrosis.[1]
- The cardiac involvement in FD is progressive; progressive cardiomyocyte hypertrophy ultimately ends in cell death of enlarged substrate-engorged cardiomyocytes, either by necrosis or apoptosis, which leads to fibrosis.[1] Accordingly, the cardiomyocyte diameter, the lysosomal glycosphingolipid area and the extent of necrosis, apoptosis and fibrosis are all positively correlated with disease severity and age.[1]
- Endomyocardial biopsies have shown an immune-mediated myocarditis in 56 % of FD patients.[1]

Cardiac manifestations of Fabry disease

- Cardiac manifestations of FD include ventricular hypertrophy and fibrosis, valve thickening or regurgitation, heart failure, angina, dysrhythmias, cardiac conduction abnormalities and sudden death.[1]

Table 1 below lists the frequency of cardiac symptoms in FD.[1]

Cardiac Manifestations	Frequencies
Cardiac signs or symptoms	• 60 % in males Mean age of onset 29.2 ± 14.4 years • 50 % in females Mean age of onset 34.5 ± 17.6 years
Cardiac symptoms as presenting symptoms	• 13 % in males • 10 % in females

Hypertrophic cardiomyopathy (HCM) is the main cardiac manifestation of FD.[1]

Left ventricular hypertrophy

- Left ventricular hypertrophy (LVH) arises earlier and progresses more rapidly in males than in females.[1]
- The prevalence of LVH has been reported to increase with age, occurring in 76.9 % of patients aged ≥ 75 years.[1]
- Left ventricular (LV) mass index also increases with age and correlates inversely with estimated glomerular filtration rate (eGFR).[1]
- Cardiac magnetic resonance imaging (MRI) can detect cardiac involvement even when the LVH severity is mild.[1]
- LVH secondary to FD is most commonly concentric and symmetric.[1]
- Prominent papillary muscles are a characteristic feature of FD.[1] Hence, the inclusion of papillary muscle mass in LV mass calculation is recommended for the earlier detection of LVH in Fabry patients.[1]

Left ventricular storage, inflammation and fibrosis

- Intramyocardial late gadolinium enhancement (LGE) on the basal inferolateral left ventricular (LV) segments is typically seen on cardiac MRI of Fabry patients and may develop before LVH.[1]
- In FD patients with basal inferolateral LGE, troponin levels and T2 values are increased, suggesting that LGE may also represent inflammation.[1]
- Increased inflammatory markers, such as interleukin-6 and tumour necrosis factor have also been associated with increased disease burden (LVH and fibrosis).[1]

Left ventricular function

- Diastolic function is abnormal in 69.4 % of those with LVH and 63 % of those with LGE.[1]
- Diastolic dysfunction occurs more commonly as an abnormal relaxation or a pseudonormal pattern, and it has been associated with the presence of LGE.[1]
- LV systolic and diastolic dysfunction can be detected before the development of LVH, not only by Tissue Doppler Imaging (TDI), but also by speckle-tracking.[1]

Left ventricular obstruction

- Obstruction at the LV outflow tract (LVOT) may occur, but massive LVH involving the papillary muscles has also been reported to cause mid-ventricular obstruction.[1]
- Obstruction at rest is rare but may be elicited by exercise in 43 % of patients, also contributing to heart failure.[1]

Right ventricular involvement

- Right ventricular (RV) systolic function in Fabry cardiomyopathy tends to be preserved.[1] However, RV global and free wall systolic strain may be reduced despite normal function on conventional echocardiography; RV systolic dysfunction has been associated with RV wall thickness and fibrosis.[1]

Atrial involvement

- Glycolipid deposition in the atria may ultimately cause atrial dilation, which occurs more commonly in patients with LVH and fibrosis.[1]
- Atrial dilation is associated with atrial fibrillation, which also contributes to heart failure.[1]

Heart failure

- Ventricular hypertrophy and fibrosis result in diastolic and systolic dysfunction, which together with dysrhythmias and conduction disorders, valve disease and myocardial ischaemia contribute to heart failure.[1]

Table 2. Frequency of manifestations related to ventricular hypertrophy, fibrosis and dysfunction in FD[1]

Cardiac Manifestations	Frequencies
LVH	• 43 % in males Mean age of onset 39 ± 10 years • 26 % in females Mean age of onset 50 ± 11 years
	• 76.9 % in patients ≥ 75 years
	In late-onset phenotype with predominant cardiac involvement • 73.1 % of males Mean age at diagnosis of 57 ± 10 years • 19.0 % of females Mean age at diagnosis of 73 ± 8 years
LGE	• 50 % of patients
	In late-onset phenotype with predominant cardiac involvement • 21.4 % of patients
LV diastolic dysfunction	• 63 % of patients with LGE
	In late-onset phenotype with predominant cardiac involvement • 29.2 % of patients • 69.4 % of patients with LVH
LV systolic dysfunction (reduced EF)	• 6.7 % of patients
Latent LVOT obstruction	• 43 % of patients
RV hypertrophy	• 31–71 % of patients
Heart Failure (or Dyspnoea)	• 19.4 % in untreated males • 19.7 % in untreated females
	• 34.6 % in patients ≥ 75 years
	• Severe heart Failure (NYHA class ≥ III) in 10 % • Annual incidence of severe heart failure: 1.62 per 100 person-years
	In late-onset phenotype with predominant cardiac involvement • 32.9 % of males Mean survival free from heart failure: 64 ± 1 years • 14.8 % of females Mean survival free from heart failure: 76 ± 2 years

EF, ejection fraction; LGE, late gadolinium enhancement; LV, left ventricular; LVH, left ventricular hypertrophy; LVOT, left ventricular outflow tract; NYHA, New York Heart Association; RV, right ventricular.

As a consequence of dysrhythmias and cardiac conduction disorders, Fabry patients may experience symptoms, such as palpitations and syncope.[1]

- Palpitations have been reported in 15.3 % and 21.3 % of untreated male and female Fabry patients, while syncope has been reported in 5.6 % and 2.4 %, respectively.[1]

Bradycardia, chronotropic incompetence and cardiac conduction disorders

- At an earlier stage, GL-3 accumulation may lead to accelerated atrioventricular (AV) conduction, which manifests as a short PR interval.[1]
- As FD progresses, GL-3 accumulation and fibrosis lead to the development of AV and bundle-branch blocks and sinus node dysfunction, which may require a pacemaker.[1] Bradycardia at rest is common (72 %).[1]
- Chronotropic incompetence with exercise due to autonomic nervous dysfunction may occur and contribute to heart failure; exercise stress testing or cardiopulmonary exercise testing could be useful in the differential diagnosis of dyspnoea.[1]

Tachydysrhythmias

- Dysrhythmias occur especially in late stages of the disease.[1]
- GL-3 deposition in the atria and subsequent fibrosis, together with LVH and diastolic dysfunction and atrial dilation, are the proposed mechanisms of development of atrial fibrillation.[1]
- GL-3 accumulation in cardiac conduction systems has been reported in FD patients presenting with ventricular tachycardia (VT) in the absence of LVH, suggesting that GL-3 deposits may precipitate VT.[1] However, the major mechanism of sustained VT in FD appears to be re-entry related to myocardial fibrosis.[1]

Table 3 below lists the frequency of other cardiac manifestations in FD[1]

Cardiac Manifestations	Frequencies
Angina	• 22 % in males • 23 % in females
	• Mean age of onset in males: 42 ± 5 years • Mean age of onset in females: 49 ± 13 years
Myocardial infarct	• < 2 %
	• 2.7 % in males • 1.5 % in females
Aortic valve dysfunction	• 47 % of patients
Mitral valve dysfunction	• 57 % of patients
Aortic dilation	At the sinuses of Valsalva • 32.7 % in males • 5.6 % in females At the ascending aorta • 29.6 % in males • 21.1 % in females
Aortic aneurysm	• 9.6 % in males • 1.9 % in females

Cardiac events (defined as myocardial infarction, arrhythmia, angina pectoris, congestive heart failure, or significant cardiac procedures, such as pacemaker placement, coronary bypass, stent placement and valve replacement) have been reported in 69.9 % of males and 81.6 % of females.[1]

- Cardiac events were the first clinical events in 21.4 % of males and 16.9 % of females.[1]
- Ultimately, heart disease is the main cause of death in Fabry patients (40 % in males and 41.7 % in females).[1]

Table 4 below summarises the main recommendations for the diagnosis and monitoring of cardiac manifestations in FD[1]

Recommendations for the Diagnosis and Monitoring of Cardiac Manifestations in FD
ECG
A standard 12-lead ECG is recommended in all adult patients at first clinical evaluation, every 6–12 months and when there is development of new symptoms.
Echocardiogram
Echocardiogram is recommended in all patients at baseline, every 12–24 months and with the development of new symptoms.
Exercise echocardiography
Exercise echocardiography should be performed in all symptomatic patients to exclude latent obstruction and exercise-induced mitral regurgitation.
Cardiac MRI
Cardiac MRI should be considered in all adult patients at baseline to assess cardiac morphology and function and myocardial fibrosis; and may be considered, every 2–5 years in patients without cardiac abnormalities and every 2–3 years in patients with progressive disease, in order to assess progression of fibrosis and cardiac function. T1 mapping may also be considered to detect early cardiac involvement or to help in the differential diagnosis of LVH.
Holter monitoring
A 24 h-Holter monitoring should be considered in all adult patients at first clinical evaluation, every 6–12 months and when there is development of new symptoms.
ILR
A prolonged Holter monitoring or preferably an ILR should be considered in patients with recurrent episodes of unexplained syncope. An ILR may also be considered in patients with palpitations or recent stroke and negative Holter monitoring.
Cardiopulmonary exercise testing
Cardiopulmonary exercise testing should be considered in patients with exercise intolerance.
Coronary angiography
Coronary angiography (or CT coronary angiography) is recommended in all patients with angina CCS class ≥ II. Invasive coronary angiography is recommended in adult survivors of cardiac arrest, in patients with sustained VT and in patients with severe stable angina (CCS class III) or unstable angina.
BNP/NT-proBNP
Measurement of plasma BNP/NT-proBNP is recommended in symptomatic patients with suspected heart failure.
High-sensitivity troponin
High-sensitivity troponin may be considered to assess disease severity.
Renal function
Regular assessment of renal function and albuminuria/proteinuria is recommended in all patients.
Endomyocardial biopsy
When a genetic variant of uncertain significance is found in the *GLA* gene, an endomyocardial biopsy with electron microscopy should be considered, particularly in females or in patients with high residual enzyme activity (> 10 %) and low lyso-GB3 levels, in order to exclude FD as the cause of LVH.

BNP, brain natriuretic peptide; CCS, Canadian Cardiovascular Society; CT, computed tomography; ECG, electrocardiogram; FD, Fabry disease; ILR, implantable loop recorder; LVH, left ventricular hypertrophy; MRI, magnetic resonance imaging; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; VT, ventricular tachycardia.

Cardiac treatment in FD

Enzyme replacement therapy (ERT)

- ERT with recombinant α-galactosidase A should be initiated in classic males at the age of 16 years regardless of symptomatic status, although it should be considered earlier, on an individual basis from the age of 8-10 years.[1]
- In late-onset males and in classic/late-onset females, LVH, cardiac fibrosis or cardiac rhythm or conduction abnormalities constitute indications to start ERT.[1]

Migalastat

- Migalastat is a pharmacological chaperone therapy for FD, which has been used for the treatment of FD patients ≥ 16 years with eGFR ≥ 30 mL/min/1.73 m^2 and amenable *GLA* mutations.[1]
- No data have been published on the efficacy of migalastat specifically for the late-onset phenotypes.[1]

Supportive treatment

Table 5 below summarises the recommendations for the supportive treatment of cardiac manifestations in FD.[1]

Recommendations for the Supportive Treatment of Cardiac Manifestations in FD
Angiotensin Converting Enzyme Inhibitors or Angiotensin II Receptor Blockers[1,2]
Angiotensin converting enzyme inhibitors (or angiotensin II receptor blockers, if not tolerated) should be used in patients with LV systolic dysfunction and heart failure.
Beta-blockers[3]
Beta-blockers should be considered in patients with heart failure and LV systolic dysfunction; or in patients with angina. Beta-blockers are recommended to relieve LVOT obstruction symptoms and to control the rate of atrial fibrillation/ flutter.
Mineralocorticoid receptor antagonists[1]
Mineralocorticoid receptor antagonists should be considered in patients with heart failure and LV systolic dysfunction.
Loop diuretics
Loop diuretics should be considered to treat symptoms of congestion in patients with heart failure.
Calcium channel blockers
Dihydropyridines should be considered for the treatment of angina. Verapamil is recommended in patients with LVOT obstruction symptoms and should be considered in patients with angina. Diltiazem should be considered in patients with LVOT obstruction symptoms or angina.
Ivabradine[3]
Ivabradine should be considered for the treatment of heart failure or angina, according to ESC guidelines.
Antiplatelet therapy
Antiplatelet therapy should be started in patients who suffered a stroke or myocardial infarction.
Anticoagulation
Anticoagulation should be immediately started once atrial fibrillation or flutter is detected. Direct oral anticoagulants (DOACs) should be considered as the first-line choice in patients without contra-indications.
Anti-arrhythmic drugs
Amiodarone should be avoided in FD. Dronedarone is contra-indicated in patients with heart failure (NYHA class III–IV) and renal failure (eGFR < 30mL/min). Sotalol, flecainide and propafenone are contra-indicated in patients with heart failure.
Management of cardiovascular risk factors
Control of cardiovascular risk factors, including arterial hypertension, diabetes and dyslipidaemia, is indicated.

Recommendations for the Supportive Treatment of Cardiac Manifestations in FD
Pacemaker
Pacemaker may be required to treat symptomatic bradycardia or symptomatic/advanced cardiac blocks, according to ESC guidelines. Dual chamber pacemakers should be implanted unless patients are in permanent atrial fibrillation.
ICD
ICD implantation is recommended in patients who suffered sudden cardiac arrest due to VT/fibrillation or sustained VT causing syncope/haemodynamic compromise and have a life expectancy > 1 year. ICD implantation should be considered in patients with advanced hypertrophy and fibrosis, who require pacemaker implantation and have a life expectancy > 1 year. ICD implantation may be considered in patients with severe LVH and advanced fibrosis or non-sustained VT, who have a life expectancy > 1 year. ICD implantation is recommended in patients with heart failure (NYHA class II-III) and LV ejection fraction ≤ 35%, despite ≥ 3 months of optimal treatment, who have a life expectancy > 1 year.
CRT
CRT should be considered in patients with LV ejection fraction 35 %, according to ESC guidelines. CRT-P should be considered in symptomatic patients with a pacing indication, LV ejection fraction < 50 % and QRS duration > 120 ms.
Septal reduction therapy (myectomy/alcohol ablation therapy)
Septal reduction therapy is recommended in patients with a resting or provoked LVOT gradient ≥ 50 mm Hg, who are in NYHA class III–IV, despite maximum tolerated medical therapy. Septal reduction therapy should be considered in patients with a resting or provoked LVOT gradient ≥ 50mm Hg, who suffer recurrent exertional syncope, despite maximum tolerated medical therapy.
Heart transplantation
Heart transplantation should be considered in patients with advanced heart failure with severe LV dysfunction and NYHA class III–IV despite optimal medical therapy, or intractable ventricular arrhythmia, depending on the extension of the extracardiac involvement by the disease.

CRT, Cardiac resynchronization therapy; eGFR, estimated glomerular filtration rate; ESC, European Society of Cardiology; FD, Fabry disease; ICD, Implantable cardioverter-defibrillator; LV, left ventricular; LVH, left ventricular hypertrophy; LVOT, left ventricular outflow tract; NYHA, New York Heart Association; VT, ventricular tachycardia. [1]Caution should be taken in Fabry patients with nephropathy due to the risk of hyperkalaemia or worsening of renal function; [2]Should be avoided, if possible, in patients with resting/latent LVOT obstruction; [3]Caution should be taken due to the increased risk of bradycardia in Fabry patients.

Conclusions

- Cardiac involvement remains the leading cause of death in Fabry patients.[1]
- GL-3 deposits are found in virtually all cardiac cells.[1]
- Fabry hearts exhibit myocardial hypertrophy, inflammation, apoptosis, necrosis and fibrosis, valve thickening and narrowing of intramural coronary arteries.[1]
- Cardiac manifestations include LVH, heart failure, angina, valve disease, dysrhythmias, cardiac conduction blocks and sudden cardiac death.[1]
- The severity of cardiac involvement is the same in classic and late-onset phenotypes.[1]

Reference: 1. Azevedo O, Cordeiro F, Gago MF, *et al.* Fabry disease and the heart: A comprehensive review. *Int J Molecular Sciences* 2021;22:4434.

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