Narrative review on Morbus Fabry: diagnosis and management of cardiac manifestations

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Abstract: Fabry disease (FD) is an X-linked lysosomal storage disorder due to reduced or undetectable α-galactosidase A (AGAL-A) enzyme activity caused by pathogenic variants in the AGAL-A gene (GLA). Tissue and organ changes are caused by widespread progressive accumulation of globotriaosylceramide (Gb₃) and globotriaosylsphingosine (lysoGb₃). The classical form of FD is multisystemic with cutaneous (angiokeratomas), neurological (peripheral neuropathy, premature stroke), renal (proteinuria and renal insufficiency), and cardiac involvement. Later onset variants may be limited to the heart. The objective of this review is to summarize the current knowledge on cardiac manifestations of FD and effects of targeted therapy. Cardiac involvement is characterized by progressive hypertrophy, fibrosis, arrhythmias, heart failure and sudden cardiac death (SCD). Targeted therapy is based on enzyme replacement therapy (ERT). Recently, small molecular chaperone, migalastat, became available for patients carrying amenable pathogenic GLA variants. The management of cardiac complications requires a complex approach. Several measures differ from standard clinical guidelines. Betablockers should be used with caution due to bradycardia risk, amiodarone avoided if possible, and anticoagulation used from the first appearance of atrial fibrillation. In Fabry cardiomyopathy SCD calculators are inappropriate. The awareness of FD manifestations is essential for early identification of patients and timely treatment initiation.

Keywords: Fabry disease (FD); hypertrophic cardiomyopathy (HCM); enzyme replacement therapy (ERT); molecular chaperones

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Introduction

Fabry disease (FD) (OMIM # 301500) is an X-linked lysosomal storage disorder due to reduced or undetectable α-galactosidase A (AGAL-A) enzyme activity caused by pathogenic variants in the AGAL-A gene (GLA). Tissue and organ changes are caused by widespread progressive accumulation of globotriaosylceramide (Gb₃) and its deacylated form globotriaosylsphingosine (lyso-Gb₃) (1).

The disease is usually more severe in hemizygous males as compared to heterozygous women in whom the degree of symptoms depends on the degree of X-chromosome inactivation (XCI). The classical form of FD is a multisystemic disorder. A variety of symptoms present early, usually from childhood. However, a large proportion of patients have a late-onset phenotype manifesting predominantly as cardiac variant characterized by cardiac hypertrophy and frequently misdiagnosed as hypertrophic cardiomyopathy (HCM).

For two decades FD is being widely treated by enzyme replacement therapy (ERT) (2,3). Recently, a molecular
chaperone—migalastat was introduced for patients carrying amenable mutations in whom residual enzyme activity is effectively increased by its administration (4,5).

The objective of this review is to increase the awareness of FD as the timely diagnosis is of utmost importance since targeted therapies have shown a capacity to halt or slow down the disease progression. However, their efficacy is limited in patients with irreversible organ damage.

The key questions addressed by this review is to describe typical manifestations of FD and indicate appropriate roads to timely diagnosis. In addition, we review effects of targeted therapies and indicate specific measures to be considered when treating FD-related cardiac complications. We present the following article in accordance with the NARRATIVE REVIEW reporting checklist (available at http://dx.doi.org/10.21037/cdt-20-593).

Methods
We performed a comprehensive search of recently published evidence in FD and selected most relevant papers describing larger patients’ cohorts, randomized clinical trials and registry reports related to pathophysiology, clinical manifestations, diagnostic methods, treatment issues and targeted therapies.

Discussion
Etiology, epidemiology, and pathophysiology

Etiology
FD is caused by pathogenic variants in the GLA gene located on the X chromosome (Xq22.1). So far, over 1,000 variants distributed across the GLA gene have been reported. However, the interpretation of gene sequencing should be done with caution since several GLA variants previously reported to be disease-causing may be of uncertain significance or neutral (6).

The multisystemic early-onset disease is usually caused by variants associated with absent or very low AGAL-A enzyme levels. The late-onset (cardiac) phenotype is usually due to missense variants allowing for residual AGAL-A activity.

Female patients are usually heterozygous with a variable penetrance of the disease which may be partly explained by the process of lyonization (XCI). Females with skewed XCI in favor of the wild-type allele may be oligosymptomatic while those expressing predominantly the mutated allele may have a severe disease comparable to hemizygous males (7,8).

Epidemiology
The incidence of classical FD is estimated around 1:40,000. However, newborn screening programs revealed a higher incidence of later-onset variants and detected a large number of variants of unknown significance (9). Due to founder effect some later-onset cardiac variants may be highly prevalent in countries like Taiwan (IVS4+919G>A) or Portugal (p.F113L) (10,11).

High-risk populations screening programs demonstrated that about 1% of patients originally diagnosed with HCM or unexplained left ventricular hypertrophy (LVH) are suffering from FD (12,13).

Pathophysiology
The storage of Gb₃ occurs in various types of cells throughout the body. Lamellar storage “zebra” bodies could be found in all cardiac cells: cardiomyocytes, endothelial and vascular smooth muscle cells; valvular fibroblasts, and conduction tissue cells (Figure 1). Storage causes both structural and functional cellular impairment interfering with lysosomal functions, endocytosis and autophagy and compromising cellular energy handling. The complex interplay of disrupted cellular functions induces compensatory hypertrophy, inflammation, and ischemia leading to apoptosis, and fibrosis of the myocardium. All these changes lead to clinical manifestations, i.e., cardiac hypertrophy and replacement fibrosis, leading to signs of heart failure. The involvement of conduction system and myocardial fibrosis are responsible for various types of arrhythmias.

Since several years it became obvious that the tissue damage cannot be explained solely by Gb₃ storage. Multiple studies revealed that one of the disease potentiating factors could be lyso-Gb₃. It seems that lyso-Gb₃ is responsible for activation of secondary mechanisms aggravating tissue damage acting namely as trophic and proinflammatory trigger (1).

While functional impairments such as energy depletion and alterations in autophagy represent a potentially reversible stage of the disease, development of interstitial and replacement myocardial fibrosis are beyond the reach of any current therapeutic interventions. Modifying the primary mechanisms by ERT or chaperone therapy at this stage may be ineffective as the disease worsening is due to mechanisms compensating for this irreversible damage (2,3).
Clinical manifestations

Clinical features of the multisystemic FD
The multisystemic FD begins usually in early childhood by signs of painful peripheral neuropathy (acroparesthesias), reduced sweating, heat intolerance and febrile crisis. At this stage gastrointestinal symptoms are also frequent. However, these symptoms are not specific. Patients may complain about diarrhea or constipation, abdominal pain, and early satiety sensations without any clearly detectable changes on endoscopy.

Cutaneous manifestations—angiokeratomas, developing mainly in boys, represent one of the most pathognomonic signs of the disease (Figure 2). The second specific finding appearing usually in adult patients is cornea verticillata—a spoke-like pattern on cornea resembling opacities seen in chronic amiodarone or chloroquine users.

Significant impairment of vital organs including the heart begins to appear usually in the third decade or later. Neurological signs include magnetic resonance imaging (MRI)-detectable white matter lesions, development of premature and often recurrent stroke, tinnitus, and hearing impairment. Renal involvement begins with microalbuminuria progressing to overt proteinuria and renal insufficiency. Development of end-stage renal disease is particularly threatening male patients (14).

Cardiac manifestations
In general, a clinically significant heart disease becomes apparent in adulthood, usually in the third or fourth decade of life in males and about ten years later in females. Later onset variants may be limited to the heart or associated with modest signs of renal disease (microalbuminuria, slight reduction of glomerular filtration rate) and appearance of cornea verticillata. The most prevalent genetic variant leading to predominant cardiac involvement is p.N215S (15).

Symptoms related to cardiac FD involvement include shortness of breath and impaired exercise tolerance, peripheral edema, palpitations, syncope, and chest pain. The underlying causes include LVH and fibrosis causing heart failure; fibrosis and conduction system involvement
triggering arrhythmias responsible for palpitations and syncope; and LVH and vascular involvement precipitating the anginal pain (16).

The most frequent appearance of cardiac disease is LVH. Its pattern is usually concentric and diffuse without left ventricular outflow tract (LVOT) obstruction (Figure 3). However, cases presenting as obstructive or apical cardiomyopathy are not exceptional. Prominent papillary muscle hypertrophy and associated right ventricular hypertrophy is seen in advanced cases. Therefore, the most frequent misdiagnosis of FD is HCM (12,13).

The replacement fibrosis develops predominantly within the mid-myocardial layer of the posterolateral LV segments leading to regional impairment of contractility (Figure 4) (17). Advanced stages may be associated with wall thinning and aneurysmal bulging causing secondary mitral regurgitation (Figure 5).

Functional impairment associated with LVH is constant. Patients have signs of impaired LV filling while systolic function is usually preserved until very advanced stages. FD patients accumulate findings suggested as markers of heart failure with preserved ejection fraction—LVH, diastolic dysfunction by Doppler echocardiography, dilated left atrium and elevated levels of natriuretic peptides. Should the investigation of the underlying disease stop at this stage, FD would remain unrecognized (18).

Valvular disease in FD is frequent, usually characterized by mitral and aortic valvular thickening and mild regurgitations. A subset of patients presents with mitral valve prolapse (19).

Electrocardiographic (ECG) signs include a large spectrum of abnormalities (Figure 6). Development of
ECG signs of LVH is frequent, usually associated with extensive repolarization abnormalities. At early stage, short PR interval without other signs of pre-excitation is found in some patients reflecting accelerated atrioventricular (AV) conduction. Subsequently, sinus bradycardia and chronotropic incompetence may be due to sinus node or autonomic dysfunction. With progression of conduction system disease, a proportion of patients develop bundle branch or AV blocks necessitating pacemaker implantation (20). Atrial fibrillation is the most frequent arrhythmia possibly facilitated by LV diastolic dysfunction and atrial enlargement. The occurrence of ventricular arrhythmias is frequent in patients with significant LVH and fibrosis (21).

**Clinical investigations in Fabry cardiomyopathy**

**Electrocardiography**

In patients with significant FD-related cardiac disease the ECG is always abnormal, usually showing signs of LVH and repolarization changes (*Figure 6*). Conduction abnormalities include PR shortening, bundle branch or AV blocks. A proportion of patients have sinus bradycardia, atrial fibrillation or ventricular ectopy or non-sustained ventricular arrhythmias (NSVT). Prolonged Holter monitoring or loop recorders may be particularly useful for detection of clinically silent episodes of atrial fibrillation or NSVTs (22,23).

**Echocardiography**

Echocardiography is the most accessible clinical method for LVH assessment. However, due to its limited reproducibility and relatively slow progression of the disease, it is not ideal for longitudinal assessments of disease progression or treatment-induced changes.

Echocardiography does not allow to establish FD diagnosis. However, a suspicion of FD may be expressed particularly in presence of diffuse LVH with prominent papillary muscles or right ventricular hypertrophy, or in presence of large scars of the posterolateral wall (24,25). The use of speckle tracking strain analysis may help to reveal impairment of deformation within the areas affected by replacement fibrosis (26). Another situation potentially rising a suspicion of FD is the presence of LVH and mitral valve prolapse. In contrast, the “binary sign” described in the past as one of typical features of FD-related cardiomyopathy is not specific (27).

Echocardiography allows evaluation of left ventricular (LV) filling by a combination of transmural flow pattern and tissue Doppler measurements and evaluation of left
atrial dilatation. Available data suggest that similarly to other types of LVH, FD cardiomyopathy is associated with diastolic dysfunction (18). However, compared to amyloidosis, the prevalence of restrictive physiology is rare and limited to advanced cases (28). Pulmonary hypertension in FD is usually mild and does not explain the frequently seen right ventricular hypertrophy (25).

Echocardiography also allows the assessment of other FD-related changes including left heart valvular thickenings, mitral valve prolapse or aortic bulb and ascending aorta dilatation (19).

Cardiac magnetic resonance

Cardiac magnetic resonance provides a more accurate and reproducible assessments of cardiac structures. It also allows tissue characterization. Late gadolinium enhancement (LGE) revealed first the nature of fibrotic changes in FD cardiomyopathy (29). Our understanding of the processes was further refined by the use of T1 mapping. The low native T1 is highly specific for FD cardiomyopathy possibly reflecting the increased lipid content within the myocardium (30,31). In contrast, the pseudo-normalization of T1 within posterolateral wall suggests the development of fibrosis. Recently, the use of T2 mapping pointed out the possible inflammatory process leading to fibrotic changes within this area (32).

Nuclear perfusion imaging

Although perfusion imaging (either by single photon emission computed tomography (SPECT) or positron emission tomography (PET)) is not representing a routine part of cardiac assessments, it improved our understanding of its pathophysiology. It was repeatedly shown that FD patients have a decreased coronary flow reserve, possibly due to microvascular involvement. Of note, the impairment of coronary perfusion was seen even in absence of LVH suggesting that ischemia may be one of the underappreciated triggers of initial myocardial damage in FD (33,34). In addition, many FD patients develop stenotic lesions of major coronary arteries (35).

Biomarkers

The use of biomarkers in FD is useful for diagnostic purposes and prognostic stratification as well. Lyso-Gb is considered the most useful biochemical parameter reflecting FD severity. The higher values are seen in genetic variants associated with the classic multisystemic disease, particularly in male patients. Cardiac variants are associated with significantly lower values. However, lyso-Gb assessment in the presence of a variant of unknown significance is particularly useful. In case of normal or minimally elevated lyso-Gb, the pathogenicity of the mutation should be doubted (36,37).

Another use of lyso-Gb is evaluation of treatment responses to ERT or migalastat. The lack of reduction or even an increase of lyso-Gb during the treatment may suggest development of antibodies in the former and limited amenability in the latter.

Cardiac markers such as natriuretic peptides and troponins may help to monitor the disease progression. Natriuretic peptides were shown to correlate with the degree of LV diastolic dysfunction and heart failure severity (38). The presence of high-sensitivity troponin increase is usually signaling a severe disease with fibrosis of the myocardium and unfavorable prognosis (39).

Endomyocardial biopsy

In most cases of FD cardiomyopathy endomyocardial biopsy is not necessary. The diagnosis can be readily made on the basis of imaging results, genetic testing and lyso-Gb analysis. It may be considered in exceptional cases with variant of unknown significance, high residual enzyme activity (typically above 10%) and low lyso-Gb. However, even benign genetic variants may be associated with minimal storage showing scarce “zebra bodies” on electron microscopy. Therefore, an evaluation by an expert pathologist is always mandated (40).

Diagnosis of FD

Strategies of FD diagnosis

The pathways to diagnosis differ according to identification of the index case. The easiest way is the cascade family screening based on gene sequencing after identifying a proband. In other situations, patients are being referred for laboratory (enzyme activity, lyso-Gb) and gene testing based on their signs and symptoms. Many patients are being diagnosed within high-risk populations screening programs (e.g., in patients with HCM, end-stage renal disease, stroke etc.). Nationwide or regional newborn screening programs are also performed (9,10).

Different strategies are used for identification of patients. In most programs, enzyme activity is being tested from leukocytes or plasma. Dry blood spot testing is often applied in large scale screening programs (41). Assessment
of enzymatic activity seems sensitive enough in male patients in whom it is always severely reduced as compared to healthy individuals (42). However, this approach fails in women in whom enzymatic activity may be overlapping with normal ranges. Therefore, some laboratories are using stratification by lyso-Gb3 measurements, others are proceeding directly to gene testing in all females (43,44).

Gene sequencing
Gene sequencing is mandatory in all suspected FD patients, particularly before initiation of any targeted therapy. It has been suggested that all adult patients with unexplained LVH should undergo a testing for FD. Subsequently, GLA was incorporated to many panels used with high throughput next generation sequencing for screening in high-risk patients including those with HCM. This has resulted in identification of many GLA variants of unknown significance. Therefore, an expert assessment of identified variants is necessary to exclude non-disease-causing variants in whom another cause of their disease should be investigated (44).

Clinical management
ERT
ERT represents a standard of FD treatment already for two decades. Two preparations—agalsidase alfa and beta—are widely used in EU. The treatment has been shown effective in slowing renal disease progression and improving several symptoms of the disease (45). However, despite many efforts a robust proof about preventability of cardiac complications and survival benefits of ERT is still vague (46). Although ERT has shown a modest reduction of cardiac mass, data about preventability of fibrosis are lacking. Moreover, only limited evidence exists about improvements of symptoms and cardiac complications (47,48). This is mainly due to the slow progression of FD. Demonstration of significant benefits would require a long-term detailed follow-up which is not achievable in any randomized controlled trial.

Beneficial effects of ERT were confirmed by analyses of large international registries (Fabry Registry, Fabry Outcome Survey) (49). In contrast, some authors were unable to show a survival benefit with ERT in their cohorts (50). However, early results were obscured by inclusion of very advanced cases with irreversible organ damage in whom the ERT has little if any impact on outcomes. Nowadays, ERT is being regarded rather as a preventative therapy to be given early in the course of the disease (51).

A proportion of patients develops antibodies against the infused enzyme (52). Despite an emerging evidence of clinical impacts of this adverse reaction, an appropriate management does not exist (53). It seems that at least in some cases the antibodies may be saturated by administering an excess of the enzyme (54).

Migalastat
A small molecular chaperone migalastat was approved for the treatment of FD in EU since 2016 and in USA since 2018. The chaperone is effective only in cases with residual enzyme activity which is increased by its administration. This is related to the underlying gene variant described as “amenable” mutations (4). The main argument for migalastat introduction on the market was the achievement of significant LV mass reduction in two independent trials (55). Their results were confirmed by a recently published analysis of a multicenter trial “FAMOUS” from Germany. However, its authors put in question amenability of several mutations listed originally as amenable by the drug producer. The trial also raises a concern about migalastat impacts on glomerular filtration rate decrease rate (56).

Therapies in development
Further development is aiming to improve the already approved strategy of ERT by ameliorated enzymes. Pegunigalsidase alfa is a chemically modified pegylated covalently cross-linked enzyme produced by a plant-based system. The enzyme has a substantially prolonged plasma half-life and low immunogenicity. Pegunigalsidase alfa is already in advanced stages of clinical development and testing (57). In contrast, another enzyme derived from moss is at the beginning of clinical investigations (58).

Another approach is based on substrate reduction by inhibition of glucosylceramide synthase. Two oral preparations—lucerastat and venglustat—are being tested in clinical settings after demonstrating promising effects in preclinical trials (59).

In addition, several gene therapies are being extensively tested using either in-vivo or ex-vivo gene transfer with different viral vectors (60).

Management of cardiac complications
The management of cardiac complications in FD patients usually follow the internationally validated guidelines. However, some differences should be emphasized. Several
drugs should be used with caution, such as verapamil, betablockers and ivabradine which may aggravate the chronotropic incompetence or impair AV conduction. Amiodarone should be avoided as much as possible since it has a potential to interfere with lysosomal functions (61).

Anticoagulation in atrial fibrillation related to FD should not be guided by currently proposed scoring systems. Instead, FD patients should be considered at high risk for systemic embolism and anticoagulated properly whenever atrial fibrillation develops. Although firm data are lacking, the use of direct anticoagulants may be of advantage as FD also increases risks of cerebral bleeding. Moreover, as compared to warfarin direct anticoagulants have potentially less pronounced effects on renal disease progression (62).

Sudden cardiac death estimates proposed in HCM are not applicable in FD. From the published literature it seems that patients with advanced disease with LVH, fibrosis, history of syncope or NSVTs are at higher risk and should be considered for implantable cardioverter defibrillator (ICD) implantation (63).

**Limitations of available evidence**

The understanding of pathophysiology of FD is constantly evolving, namely due to appearance of novel biomarkers such as lyso-Gb₃ or imaging techniques such as magnetic resonance T1 mapping. Since FD is a rare disease, most data available are limited by a selection bias of small cohorts described in the literature. Larger datasets are generated by international registries primarily designed to monitor ERT results. However, these data are subject to selection bias as well. Moreover, longitudinal follow-up within registries is usually limited by incomplete data reporting. This results in vague evidence of survival benefits and limited availability of data demonstrating improvements in cardiac complications achieved by current targeted therapies. Further research should focus on bridging the gaps in ERT efficacy evidence, analysis of antibody response to ERT, and on development of novel therapeutic strategies.

**Summary**

FD, particularly its later-onset phenotype, is a relatively frequent finding among patients originally diagnosed with HCM. Targeted therapies have a potential to change the course of the disease provided they are started before irreversible damage develops. This increases the importance of timely diagnosis of the probands and their family members. Since systemic signs of FD may be absent in late-onset cardiac variants, all adult patients with unexplained LVH should be tested for FD.

Even in advanced cases the appropriate management of cardiac complications may alleviate the symptoms and prolong the life of our patients. The essential measures include heart failure treatments, arrhythmia management including anticoagulation in atrial fibrillation and ICD implantation in high-risk patients.

Development of novel therapies is usually based on evaluation of surrogate endpoints such as cardiac mass, glomerular filtration rate, gastrointestinal symptoms, or pain. Once approved for clinical use they would require an international collaboration to gather large clinical datasets able to confirm their effects on survival and clinical complications.

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