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Fabry disease and the heart

Nora Seydelmann , MD, Professor [a],
Christoph Wanner, MD, Professor [a, b],
Stefan Störk, MD, Professor [a, b], Georg Ertl, MD, Professor [a, b],
Frank Weidemann, MD, Professor [a, b, *]

[a] Department of Medicine, University Hospital, Wuerzburg, Germany
[b] Comprehensive Heart Failure Center, University of Wuerzburg, Germany

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Fabry disease is induced by a mutation in the alpha-galactosidase A gene, causing a deficiency of the enzyme alpha-galactosidase A. (1) The enzyme defect leads to progressive intracellular accumulation of globotriaosylceramide in lysosomes of various tissues and organs, including heart, kidney and nerve system. Cardiac involvement is common and is presenting as concentric left ventricular hypertrophy. Myocardial replacement fibrosis is a typical feature of more advanced stages of Fabry cardiomyopathy, first limited to the mid-myocardial layers of the basal postero-lateral wall, then spreading to transmural fibrosis. Since 2001, enzyme replacement therapy is available. If therapy is started early, before myocardial fibrosis has developed, a long-term improvement of myocardial morphology, function and exercise capacity can be achieved. In end-stage cardiomyopathy enzyme replacement therapy might prevent further progression of the disease. This review provides an overview of Fabry disease, with a focus on cardiac involvement with its characteristic features, clinical presentation and possible treatment.

* Corresponding author. Medizinische Klinik und Poliklinik I, Universitätsklinik Würzburg, Oberdürrbacher Str. 6, 97080 Würzburg, Germany. Tel.: +49 931 2010; Fax: +49 931 201 39012.
E-mail address: Weidemann_F@medizin.uni-wuerzburg.de (F. Weidemann).

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Introduction

Anderson Fabry disease is a rare genetic lysosomal storage disorder with X-chromosomal inheritance [1]. Reported incidence is about 1:40,000 worldwide [2]. However, due to underdiagnosed atypical phenotypes and mutations with limited alpha-galactosidase A activity, the actual incidence is likely to be much higher. The clinical significance of these mutations, however, has not yet been satisfactorily clarified [3]. The disease is induced by a mutation in the alpha-galactosidase A gene (GLA) causing a deficiency of the hydrolase alpha-galactosidase A (alpha-GalA). Absent or reduced enzyme activity leads to the inability to catabolize globotriaosylceramide (Gb3) and related glycosphingolipids, with the result of a progressive intracellular storage of Gb3 in various tissues and organs and an elevated plasma concentration of lyso-Gb3. The most commonly affected organs are heart, vascular endothelium of the kidney, nervous system, eyes, and skin (Fig. 1) [4]. Cardiac manifestations including arrhythmias, chronic heart failure and small vessel disease occur frequently. Of note, malignant arrhythmias [5] are the predominant cause for the substantially increased morbidity and reduced life expectancy [6]. Beside the classical variant of Fabry disease, an atypical variant is also known, characterized by residual alpha-galactosidase A activity. In those cases the clinical manifestation starts later in life, often with single organ involvement, as heart or kidney [7,8].

Anderson Fabry disease is one of the rare lysosomal storage disorders for which a cause-specific therapy is available [9,10]. Enzyme replacement therapy (ERT) has been approved since 2001. Two different enzyme preparations are available: agalsidase alfa and agalsidase beta. Clinical studies have shown that enzyme replacement therapy (ERT) may slow or halt disease progression [9–12]. However, the success of therapy appears to depend heavily on the stage of the disease [12].

Pathophysiology

The malfunction of alpha-Gal A leads to a progressive accumulation of Gb3 in all body cells containing lysosomes, including vascular endothelium and smooth muscle cells [13]. Intracellular accumulation starts *in utero* and is probably the pathogenetic trigger event of the disease [14,15].

Although the clinical presentation of Fabry disease is well explored, the pathomechanism linking the intracellular deposition of Gb3 to the potential cell and tissue dysfunction and finally to the clinical manifestations is still not sufficiently clarified [4]. It has been shown that the storage of Gb3 induces an excessive production of reactive oxygen species in cultured vascular endothelial cells thereby increasing oxidative stress. Gb3 also up-regulates the expression of adherence molecules in vascular endothelium [16]. Other data indicate that Gb3 may cause the release of pro-inflammatory cytokines, especially dendritic cells and monocytes [4]. Thus, it can be hypothesized that Gb3 storage triggers a cascade of pathophysiological processes leading to a structural cellular change, tissue defects, and – over time – to organ failure.

Furthermore, globotriaosylsphingosine (lyso-Gb3), a deacylated metabolite of Gb3, appears to be an additional factor in the pathogenesis of Fabry disease. Lyso-Gb3 is an inhibitor of the enzyme alpha-galactosidase A, thus promoting the storage of Gb3 as well as it stimulates the proliferation of

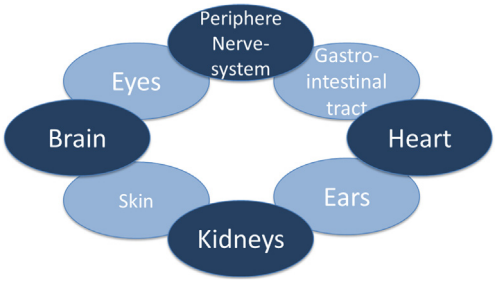

Fig. 1. Overview of the typical organs involved in Fabry disease. The dark fields represent the most important involved organs. Other organs with less effect on life expectancy are marked by a more light-colored circle.

vascular smooth muscle cells [17,18]. Another active growth-promoting factor that could be identified in the plasma of male and female Fabry patients is sphingosine-1-phosphate (S1P). It has been shown, that in-vitro S1P induces hypertrophy of the cardiomyocytes. *In vivo* the plasma level of S1P correlated strongly with the mass of left ventricular (LV) hypertrophy. Altogether it seems that S1P contributes a lot in the development of cardiovascular remodeling due to its proliferative mechanism [19].

Clinical presentation

In hemizygous males, the clinical manifestation of Fabry disease shows characteristic symptoms during childhood and adolescence, such as angiokeratoma, hypohydrosis, acroparesthesia, pain crises and gastrointestinal symptoms like diarrhea. In adulthood, progressive Gb3 accumulation in the microvasculature causes ischemic damages especially affecting the kidney, brain and heart, which may cause symptoms related to renal failure, stroke and cardiovascular diseases [18,20,21]. Heterozygous females were thought to be asymptomatic carriers. However, it is now well acknowledged that heterozygous females can also be affected and may develop the full phenotype of disease manifestation, even though the aggravation of the disease occurs later in life [5,18,22].

Cardiac involvement is frequent in Fabry patients and is one of the most important causes for reduced life expectancy and disease-related death [6]. Various cardiac manifestations, including symptoms of heart failure, angina pectoris and arrhythmias have been reported [7,8,23,24].

The above mentioned atypical “cardiac variant” of the disease presents with limited clinical manifestation. These patients are middle-aged and present with so hitherto unexplained hypertrophy of the LV. The enzyme test reveals residual alpha-galactosidase A activity, and most of the patients have less symptoms when compared to classical Fabry patients [7,8].

The Fabry cardiomyopathy

More than 50% of all Fabry patients have a cardiac involvement (ie, Fabry cardiomyopathy), most frequently concentric left ventricular hypertrophy (LVH) [6,18,23]. The intracellular accumulation of Gb3 also occurs within myocytes, valves and vascular endothelium of the heart [9,25]. Histologically, the Fabry cardiomyopathy is characterized by myocyte hypertrophy and vacuolation [26]. However, the storage of Gb3 alone is insufficient to explain the full extent of myocardial abnormalities seen in Fabry patients. In addition, the interstitial remodeling appears to be an important feature of Fabry cardiomyopathy [25]. The reason is probably a combination of intracellular lysosomal storage of Gb-3, an increase of trophic factor such as lyso-Gb3, and a neurohormonal activation in the plasma that induces hypertrophic activation and interstitial remodeling [18,25–28].

In most Fabry patients with a cardiomyopathy a concentric left ventricular hypertrophy with an end-diastolic wall thickness of up to 16 mm can be found. This ventricular hypertrophy increases with disease progression. The typical pattern is a concentric thickening without LV outflow tract obstruction. In these patients LV systolic function, measured by ejection fraction, is normal. This distinguishes Fabry cardiomyopathy from idiopathic hypertrophic cardiomyopathy (HCM) and can be used to screen Fabry patients among individuals with unexplained LV hypertrophy [29]. Other typical findings in Fabry cardiomyopathy are prominent papillary muscles [24,30] and a preserved global ejection fraction combined with early stages of diastolic dysfunction [6,31]. Using strain rate imaging based on tissue Doppler imaging it could be shown that regional myocardial function is impaired. Those abnormalities seem to affect mainly longitudinal contraction and start in the basal segment of the postero-lateral wall of the LV. In more advanced stages of the disease, both regional longitudinal and radial function parameters are reduced [11,12,23,31].

The end-stage Fabry cardiomyopathy is characterized by intramural replacement fibrosis also limited to the basal postero-lateral wall of the LV [24,25]. The non-invasive gold-standard to detect myocardial fibrosis is late gadolinium-enhanced magnetic resonance imaging (MRI) [25]. An indirect way to screen for regional myocardial fibrosis is functional strain rate imaging by echocardiography [32,33]. Histologically, the fibrotic changes begin in the mid-myocardial layers and sprawl with disease progression to transmural fibrosis, accompanied by thinning of these segments. Functionally, the presence of myocardial replacement fibrosis leads to wall motion abnormalities with lower regional systolic deformation values [23,33,34]. The

replacement fibrosis seems to be the main cause for cardiac arrhythmias like bradyarrhythmias or malignant ventricular arrhythmias [12], both leading to a poor prognosis for Fabry patients [23,34,35].

Another regularly reported phenomenon of the cardiomyopathy includes valve abnormalities. In general, hemodynamic significant valve abnormalities are rare findings with little clinical impact [24,36]. Only few Fabry patients exhibited mild or moderate aortic, mitral and tricuspid insufficiency, especially in end-stage cardiomyopathy [24].

Echocardiography

The most common tool to screen for Fabry cardiomyopathy is echocardiography, which is widely available and easily applicable. Especially for patients with contraindications against MRI, for example patients with implanted cardio defibrillator or pacemaker or patients with end-stage renal disease, echocardiography is the only diagnostic possibility to detect myocardial function and morphology [33]. For those patients the echocardiography is essential for diagnosis and therapy monitoring [37].

Echocardiography can be used to detect early stages of the disease mainly characterized by a concentric non-obstructive left ventricular hypertrophy and, in more advanced stages, by an asymmetrical hypertrophy presenting with a grossly thickened septum and less hypertrophy of the posterolateral wall. Other findings include the prominent papillary muscles as mentioned above (Fig. 2). Echocardiography is also the method of choice to monitor treatment effects.

There are two echocardiographic techniques to assess indirectly replacement fibrosis: strain rate imaging and speckle tracking. Ultrasonic strain-rate imaging is based on specific visual features, consisting of a “double peak sign” with two clearly identifiable peaks: i) a sharp first peak in early systole, followed by a rapid fall in strain rate close to zero; and ii) a second strain rate peak during the isovolumetric relaxation period. These indicators can be used to evaluate the quality, but not the quantity of the regional fibrosis in hypertrophic myocardium [32]. This method is highly reliable, especially in detecting sub-clinical involvement [7,32]. However, it is technically demanding, time consuming, and difficult for post processing and therefore restricted to specialized centers [32].

In contrast, 2D speckle-tracking, a relatively new imaging technique used to detect LE related functional abnormalities, is widely available, highly reproducible, and simple to implement [38]. With this technique the lower deformation values associated with the presence of myocardial replacement fibrosis can be assessed. Thus, low systolic longitudinal strain values in the basal postero and lateral LV segments indicate myocardial fibrosis [33]. The method does not allow an exact quantification of the amount of fibrosis. However, it has been shown that a systolic longitudinal strain value of more than

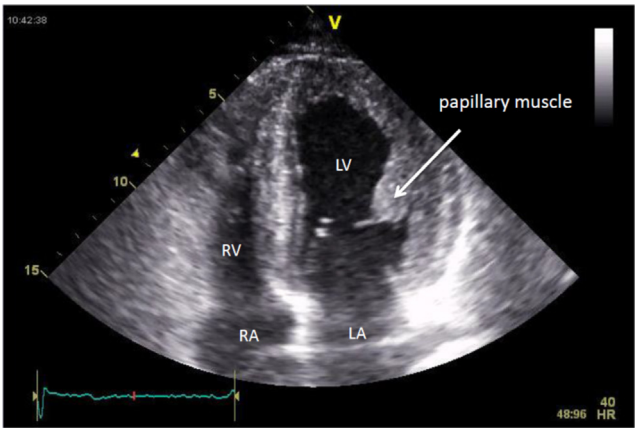

Fig. 2. Typical echocardiography image. Typical echocardiographic image of a patient with Fabry cardiomyopathy. This apical four-chamber view is showing a prominent papillary muscle as well as a thickened interventricular septum and lateral wall of left ventricle.

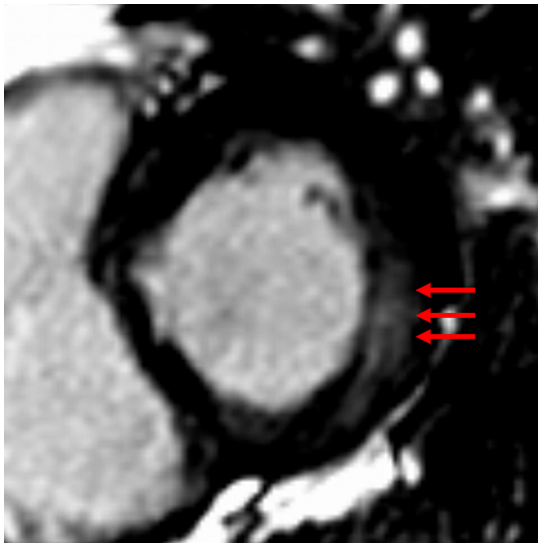

Fig. 3. Typical magnetic resonance tomography image. Magnet resonance imaging of the left ventricle from a patient with severe fibrosis. This short axis view is illustrating an area in the posterolateral wall with a significant amount of late enhancement (=fibrosis) indicated by the red arrows.

16.5% in the typical postero-lateral region makes replacement fibrosis extreme unlikely, whereas a value lower than 12.5% is related strong indicator of replacement fibrosis [33].

Magnetic resonance tomography

Besides the useful technique of echocardiography, cardiac MRI is especially important to screen for myocardial replacement fibrosis by gadolinium late enhancement imaging (Fig. 3). In areas with myocardial fibrosis, the intercellular space is increased. Chelated gadolinium then diffuses into this space and is unable to cross the cell membrane. The distribution kinetic is therefore slower, and a higher relative concentration of gadolinium is found in myocardial areas with fibrosis compared to unaffected myocardium [7,25].

The assessment of myocardial fibrosis is essential to stage the cardiomyopathy and is necessary for monitoring therapy effects [23,36]. Consequently, every adult Fabry patient should receive a cardiac MRI scan once a year if possible. This is particularly important for female patients, who often develop myocardial fibrosis in the postero-lateral wall despite otherwise non-hypertrophic myocardium. Thus, in female Fabry patients MRI with late enhancement imaging is the only possibility to detect a potential cardiomyopathy [39].

Electrocardiography

The end-stage cardiomyopathy is characterized by the co-existence of LVH, regional myocardial thinning and the presence of wall motion abnormalities in the fibrotic segment [23,34,40]. In this case characteristic changes seen on resting ECG are a positive Sokolow-Lyon index and a negative T-wave in the precordial leads (Fig. 4).

Affected hearts are vulnerable to develop cardiac arrhythmias, including sinus bradycardia, bradyarrhythmias and malignant ventricular arrhythmias [35]. Therefore, patients should be regularly screened for cardiac arrhythmias by 24-h Holter-ECG. In patients with typical symptoms like dizziness or syncope with inconspicuous 24-h Holter-ECG, the implantation of a cardiac event recorder should be

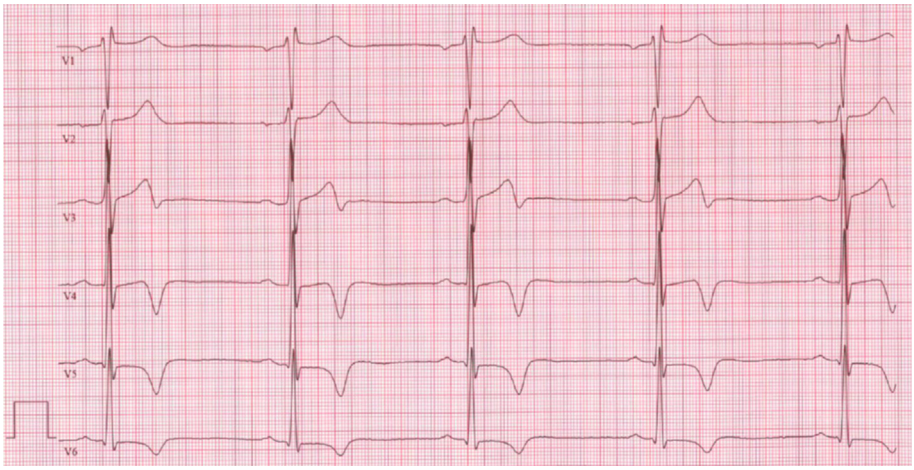

Fig. 4. Typical electrocardiographic image. Electrocardiography from a male Fabry patient with advanced Fabry cardiomyopathy. Note the positive Sokolow-Lyon index as a marker for left ventricular hypertrophy as well as the T-wave inversion in V4–V6.

discussed. This device allows continuous recording of the heart rhythm over a long time period, thus elegantly identifying potentially life-threatening arrhythmias.

Biomarkers

Two biomarkers, Gb3 and lyso-Gb3, may be used as diagnostic tools or as screening parameter for high-risk patients [40–42]. The concentration of Gb3 can best be measured in the sediment of urine. It is elevated in all hemizygous patients with the classic or the renal variant of the disease and is therefore a reliable, non-invasive, simple tool to screen for Fabry disease. However it is not an ideal biomarker to monitor therapy effects and also does not detect patients with the cardiac variant [43,44].

The most important biomarker is lyso-Gb3, a degradation product of the accumulated Gb3. It has been shown that plasma lyso-Gb3 concentration is severely elevated in all classical Fabry patients. In addition, it is slightly elevated in atypical late onset mutations. Overall, the level of lyso-Gb3 is considered to predict the potential severity of unknown mutations. This is particularly helpful to detect atypical late onset forms and women with alpha-GalA activity around the normal threshold [3,45]. Additionally, lyso-Gb3 is viewed as an independent risk indicator for white matter lesions in the brain in male patients and for left ventricular hypertrophy in female patients [17].

Therapy of the Fabry cardiomyopathy

Enzyme replacement therapy

Enzyme replacement therapy allows a causal treatment of Fabry disease. Intravenous infusion with recombinant alpha-galactosidase A replaces the missing enzyme and catabolizes the lipid deposits [9,10]. The ERT infusion has to be given intravenously every two weeks throughout life. Therefore, it is essential to carefully establish the diagnosis and define the indication for ERT. ERT aims at maintaining organ function and/or improving organ dysfunctions. So far, this therapy is the only way to stabilize the progression of the disease [22]. There are two different kinds of enzyme-products available: agalsidase alfa and agalsidase beta. In respect to cardiac function and

long term clinical outcome no significant difference between those two products has been shown so far [46].

Initial biopsy studies demonstrated that ERT effectively clears microvascular endothelial deposits of Gb-3 from the kidney, the skin and the heart of most Fabry patients [9,10,47,48]. This may then induce a decrease of LV mass, enhance regional myocardial function [11,12,49], and improve exercise capacity [12] as well as health-related quality of life [50].

Before starting ERT, a precise staging of disease status or progression is necessary. The therapeutic success of ERT on Fabry cardiomyopathy depends highly on the extent of myocardial fibrosis at baseline. Of note, patients with proven myocardial fibrosis may have only limited or no benefit from ERT. By contrast, the greatest effect of therapy may be achievable before myocardial fibrosis has developed [12,51,52]. In these cases, a decrease of myocardial mass, improvement of regional myocardial function or an increase in exercise capacity can be accomplished [12]. Thus, a regularly monitoring of heart morphology and function in all Fabry patients is necessary and an early start of ERT is desirable [12,51].

It has to be considered that almost all patients develop anti-agalsidase antibodies with neutralizing activity during long-term ERT. This affects predominantly male patients without any alpha-Gal A-activity. Nevertheless, female patients may also develop antibodies despite substantial levels of residual enzyme activity [53]. However, the impact of these antibodies on the effectiveness of treatment is still unknown (see chapter 5).

Additional therapy for the heart

Fabry patients, especially in more advanced stages of the disease, benefit markedly from a comprehensive clinical management including ERT but also concomitant medical treatment. First choice is the use of angiotensin-converting enzyme inhibitor (ACEi) or angiotensin receptor blockers. From other forms of myocardial hypertrophy, it is known that ACEi have positive effects on the regression of the hypertrophy [54,55]. Furthermore, ACEi reduce proteinuria and stabilize kidney function [56]. However, it is to be noted that hypotension may become a therapy-limiting side effect. Therefore, regular blood pressure monitoring after initiation of ACEi therapy is advised.

In addition, the use of β-adrenergic blocking can be necessary in order to treat tachycardic arrhythmias and to prevent ventricular arrhythmias [57]. Since many Fabry patients develop bradycardias [35], a 24-h Holter ECG should be conducted before and during therapy, especially if symptoms like dizziness or syncope are reported. If relevant bradycardia is confirmed, a pacemaker implantation should be considered [35].

Fabry patients with end-stage cardiomyopathy developing malignant ventricular arrhythmias should be evaluated for the implantation of a cardio-defibrillator (ICD) [23,57,58]. A combination of ERT with antiarrhythmic therapy as amiodarone should be avoided, because an interaction between amiodarone and ERT has been described [59].

In case of atrial fibrillation, a restoration to sinus rhythm should be discussed to avoid the risk of bradycardia, which leads to reduced exercise capacity. If a restoration to sinus rhythm is not possible, oral anticoagulation is indicated.

Conclusions

Fabry cardiomyopathy is a clinically important organ manifestation of Fabry disease. Its detection is frequently difficult, requiring a comprehensive cardiac diagnostic approach. As a consequence, all patients should need to be re-examined annually by a Fabry specialist, regardless whether ERT is indicated. Cardiac diagnostics need to focus on myocardial fibrosis, because its well-recognized impact on prognosis. A cardiologist together with the other involved disciplines should define the indication for ERT. Before and during ERT it is important to initiate additional therapy in almost every Fabry patient.

During the past 10 years, many new aspects of the Fabry cardiomyopathy have been investigated. In particular, knowledge on the clinical presentation of patients with Fabry cardiomyopathy has

expanded. However, basic research remains essential for a better understanding of the pathophysiology and thus, improved therapy. For clinical research, Fabry centers should closely cooperate in network structures that facilitate the conduct of appropriately powered clinical trials.

Conflict of interest

The following authors have received speaker's honoraria from Genzyme and Shire: Frank Weidemann, Christoph Wanner.

All authors had access to the data and a role in writing the manuscript.

Practice points

- Echocardiography is essential for diagnosis and therapy monitoring
- Especially for female patients MRI with late enhancement imaging is sometimes the only possibility to detect potential myocardial fibrosis and thus the cardiomyopathy
- If therapy is started early, before myocardial fibrosis has developed, a long-term improvement of myocardial morphology, function and exercise capacity can be achieved
- Patients in more advanced stages benefit highly of a comprehensive management including ERT and concomitant medical treatment

Research agenda

- Basic and clinical research for better understanding of the pathophysiology of Fabry Cardiomyopathy is necessary
- Investigations about new diagnostic tools like biomarkers to detect early stages of Fabry Cardiomyopathy should be done
- Trials to define the initiation and indication for ERT and the effect of ERT on the heart are needed
- The influence of anti-agalsidase antibodies on the effectiveness of treatment should be investigated

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