Original Article

Journal of Inborn Errors of Metabolism & Screening
2016, Volume 4: 1–9
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DOI: 10.1177/2326409816661352
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Cardiac Manifestation of Fabry Disease: From Hypertrophic Cardiomyopathy to Early Diagnosis and Treatment in Patients Without Left Ventricular Hypertrophy

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Abstract

Although Fabry disease was identified a century ago, it is still a challenging condition to diagnose and treat. Registries data suggest that at least 10% of patients may first present with a cardiac event and that cardiac disease is 1 of the 3 major causes of morbidity and mortality in affected males and females. Cardiac involvement in Fabry disease may be expressed as left ventricular hypertrophy (LVH), coronary disease, atrioventricular conduction disturbances, arrhythmias, and valvular involvement. The exact mechanism by which hypertrophy and fibrosis in the heart occur is not fully understood. Lysosomal globotriaosylceramide accumulation in the myocardium is responsible for only 3% of the mass in the hypertrophic heart, indicating that the LVH is not a direct result of substrate infiltration. One of the most important contributions that cardiologists can make is to consider the diagnosis of Fabry disease in patients with cardiac manifestations preceding the development of LVH and conduct family screening to identify patients with early cardiac involvement which will benefit more from enzyme replacement therapy (ERT). Fabry patients without cardiac manifestations of the disease should be evaluated annually by a cardiologist specialized in Fabry disease, regardless of the indication for ERT.

Keywords

Fabry disease, hypertrophic cardiomyopathy, enzyme replacement therapy, lysosomal GL-3 accumulation, cardiac involvement

Introduction

Hypertrophic cardiomyopathy (HCM) is defined by the presence of a thickening of the left ventricular wall not accounted for by abnormal loading conditions only.[1-3] It is the most common genetic disease (1 of 500 births) caused by mutations in different genes encoding proteins of the cardiac sarcomere, and a low percentage is a result of other genetic disorders including metabolic diseases, genetic syndromes, and hereditary neuromuscular diseases, and in approximately 25% to 30% of patients no mutation can be identified despite a complete genetic study.[3,4] Therefore, there are diseases in which genetic and metabolic causes interact and have similar phenotypic manifestations (phenocopies) as in the case of Fabry disease (FD).[1-6] Although FD was originally considered as an X-linked recessive disorder, we now know that heterozygous females may be severely affected, is a relatively common cause of HCM, and is associated with significant morbidity and premature death due to heart failure or sudden cardiac death (SCD).[7-10] Although the prevalence of FD in patients with HCM is estimated between 0% and 6%, recent studies including more patients showed a prevalence of 0.5% to 1%.[11-17] However, given that the development of left ventricular hypertrophy (LVH) in FD is progressive, we must find cardiac manifestation of FD even in patients who do not still have LVH.

Pathophysiology

Fabry disease is caused by reduced or absent activity of the hydrolase α-galactosidase A (αGAL) enzyme due to mutations in the gene encoding the αGAL protein (GAL).[7-10] Patients with FD are not able to catabolize the membrane neutral

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Received February 13, 2016. Accepted for publication May 25, 2016.

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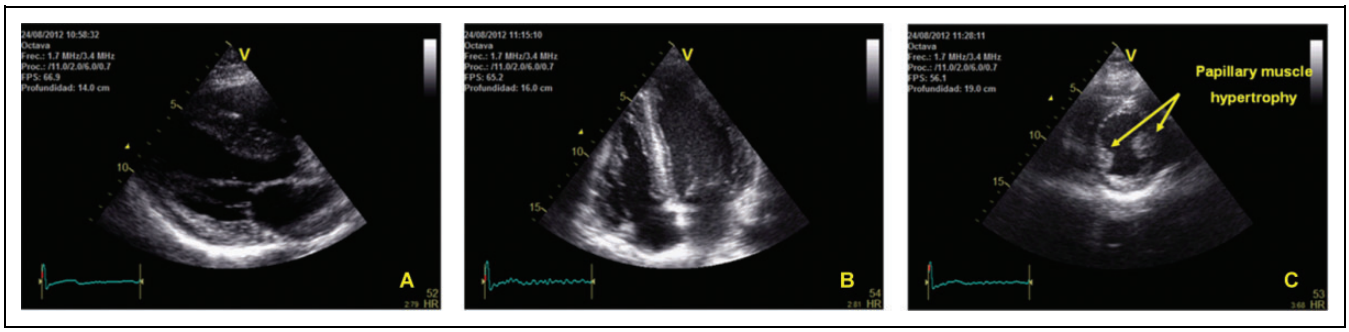

Figure 1. Doppler echocardiography in a patient with Fabry disease. A, Parasternal long axis (left). B, Apical 4-chamber view showing advanced cardiomyopathy with asymmetrical septal hypertrophy. C, Short-axis echo view (right) showing a prominent papillary muscle hypertrophy.

glycosphingolipids having galactose α-glycosidic terminal, especially globotriaosylceramide (GL-3; also abbreviated as Gb3) and the deacylated GL-3 (lyso-globotriaosylceramide [lyso-GL3]), which therefore accumulates mainly in the heart, skin, kidneys, blood vessels, peripheral nerves, and central nervous system. In the heart, the GL-3 deposits occur in cardiomyocytes, conduction system cells, valve fibroblasts, and endothelial cells of the different types of blood vessels. It has been shown that GL-3 deposits occur in only 3% of the myocardium, and the increased wall thickness is also due to hypertrophy of cardiomyocytes by mechanisms that are not fully determined.[18-26] For this reason, histologically FD cardiomyopathy is expressed by myocyte hypertrophy and vacuolization.[18-26]

Cardiac Involvement

The main manifestation of cardiac involvement in FD is the progressive thickening of the heart walls and therefore may be expressed as an HCM. The patients with FD may also present atrioventricular (AV) conduction disturbances, arrhythmias, valvular involvement, and coronary disease. Left ventricular hypertrophy is usually concentric but may also exhibit asymmetrical shapes (Figure 1). Patients with FD have also been recently described with other forms of phenotypic expression similar to HCM caused by mutations in genes encoding sarcomeric proteins. For example, there are reports of patients with FD expressed as apical HCM, HCM forms associated with midventricular obstruction, and even FD manifested as noncompaction cardiomyopathies.[27-29] Other relatively common finding in FD is the presence of prominent papillary muscles.[30] In the so-called cardiac FD variant, the heart may be the organ involved predominantly, and this presentation is usually more common in females.[31] The intracellular accumulation of GL-3 also occurs within the valves and vascular endothelium of the heart.[5,32,33] However, it is important to note that the earliest cardiovascular manifestations are pathophysiological changes involving the microvasculature, with arterial remodeling and intima–media thickening of the small and medium arterioles.[34-36]

Clinical Presentation and Confirmation of the Disease

Although imaging methods may lead to the suspicion of FD, it is very important to note that the diagnosis is predominantly clinical and is based on the search for extracardiac signs and symptoms, for this is an entity featuring systemic involvement.[3,5] Cardiologists must suspect the disease in patients with family history of heart disease, unexplained early death, premature stroke, chronic kidney disease, and absence of male-to-male transmission.[5] Many of the male patients develop a classic severe phenotype with early onset of the characteristic symptoms and signs of FD as the presence of angiokeratomas, acroparesthesias, hypohidrosis, tinnitus, and gastrointestinal symptoms. On physical examination, we must also look for the presence of cornea verticillata, proteinuria, and hearing loss.[5] As FD progresses patients also report symptoms related to the degree of cardiovascular impairment and renal failure, such as angina pectoris, dyspnea, and palpitations due to cardiac arrhythmias.[7-9] Heterozygous females may be affected and can express phenotype of FD ranging from asymptomatic to major involvement of different organs, and the worsening of the disease usually occurs later in life than in men.[7-10] However, the clinical diagnosis of FD can sometimes be difficult, as most of the signs and symptoms resemble those of other common diseases.[3] The most common detection method is the measurement of the αGAL activity in dried blood on filter paper (DBS).[37,38] However, any positive result on a DBS, must be confirmed by direct methods, such as the dosage of αGAL activity in leukocytes, serum, cultured fibroblasts, or by genotyping.[5,38] Although a decrease in activity of αGAL in DBS can confirm the diagnosis of FD in hemizygous males, this is not the most reliable diagnostic method in heterozygous females, since in this group of patients the enzyme activity levels may be within the normal range in a percentage close to 40.[38,39] For this reason, women with high clinical suspicion should undergo genotyping to confirm the diagnosis.[3,38,39] It should be underscored that currently, most laboratories worldwide performing genetic studies to investigate the cause of HCM include the gene encoding the enzyme αGAL in their panels.[3,4,40] When the mutation has been identified in the index case, targeted mutation analysis may be used to identify other affected family members.[3,4] Patients with a positive genotype but without

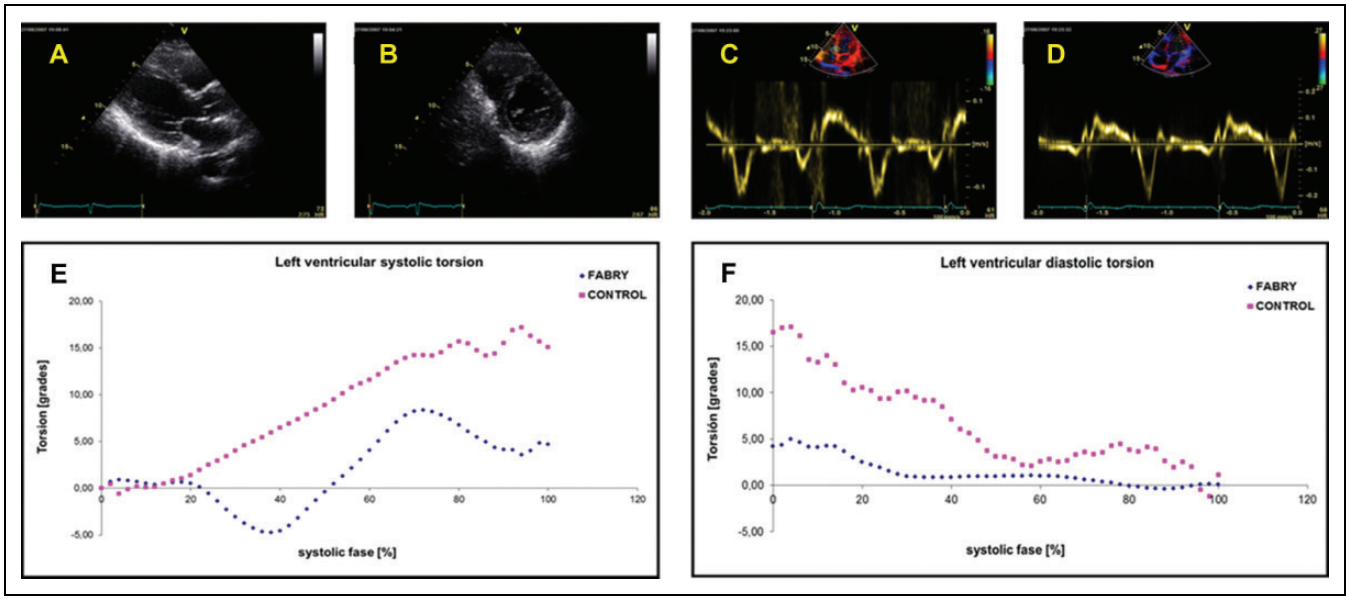

Figure 2. Doppler echocardiography in a 21-year-old asymptomatic patient with Fabry disease (FD). A and B, Parasternal long axis (left) and left parasternal short axis, respectively, with normal characteristics. C and D, Pulsed tissue Doppler of septal and lateral mitral annulus, respectively, with normal characteristics. E and F, Twisting and untwisting analysis comparing this patient with FD (blue dots), with average of 6 age-matched healthy individuals (red dots), showing twist and untwist alterations as early manifestations of FD.

phenotypic manifestations must be followed with annual clinical evaluation.[3-5] To date, hundreds of different FD mutations have been identified that explain the large variation in the residual enzyme activity and clinical presentation of FD.[5,41,42] Endomyocardial biopsies (EMBs) are not routinely included in the diagnosis of HCM; however, they are used in certain clinical scenarios where there is a suspicion of a deposit or infiltrative disease such as FD.[3] In these cases, identification of GL-3 deposits in the myocardium of patients undergoing EMB may be indicative of a diagnosis of FD.[5,43]

Early Diagnosis

It is essential to identify the early signs of cardiac involvement, as younger patients and patients with less renal involvement will benefit the most from enzyme replacement therapy (ERT).[44-47] Therefore, it is important that cardiologists think of FD even in the absence of LVH and also look for early signs of cardiac involvement in patients detected by family screening. In this sense, patients with FD should be evaluated with an electrocardiogram (ECG) because ventricular repolarization disorders and conduction abnormalities may occur several years before the patient develops LVH or other cardiovascular manifestations.[48-51] Moreover, changes in the tissue Doppler velocities also precede the development of LVH, and strain rate imaging and 2-dimensional speckle tracking echocardiography may evidence left ventricle, right ventricle, and left atrium dysfunction, even when conventional cardiac parameters are normal (Figure 2).[52-56] Endomyocardial biopsy and perfusion studies with dipyridamole infusion with ^{13}N-labeled ammonia by positron-emission tomography can reveal the presence of microvascular dysfunction, which is also an early sign of cardiac involvement and precedes the development of LVH.[34-36] Endomyocardial biopsy is the confirmatory tool for the diagnosis of cardiac involvement in cases in which doubts are raised, but the evaluation must be very cautious because certain drugs such as amiodarone, chloroquine, and tamoxifen have a storage pattern similar to FD.[57,58] Cardiologists now have a new method for detecting early cardiac involvement in FD, which is the magnetic resonance noncontrast myocardial T1 mapping that may show glycosphingolipid deposits before the onset of LVH, and it is also a useful method for differentiating FD from other causes of LVH.[59] The significant reduction in the values of noncontrast myocardial T1 is the most sensitive and specific parameter by resonance in patients with FD, regardless of gender, morphology, and left ventricular function.[59-62] The reduction in resonance noncontrast myocardial T1 values before the onset of LVH is associated with parameters of early diastolic and systolic dysfunction measured by echocardiography.[59-62] Regarding biomarkers, the N-terminal fragment of the pro-brain natriuretic peptide (NT-proBNP) is elevated in patients with diastolic dysfunction in the absence of LVH and increased in relation to the stage of the cardiac involvement.[26,63,64] Even when this is correct, the specificity of this finding should be taken carefully for different reasons; for example, NT-proBNP could be elevated due to chronic kidney disease in patients with FD. The lyso-GL3 is also found in increased concentrations in the plasma of patients with FD. It has been proposed that the lyso-GL3 favors GL-3 accumulation, the proliferation of smooth muscle cells in vitro, and may have deleterious effects on the intima and media of small arterioles.[18] The lyso-GL3 predicts clinically relevant FD in patients with mutations in *GLA* gene; this is especially useful for new mutations in women with normal αGAL activity.[41]

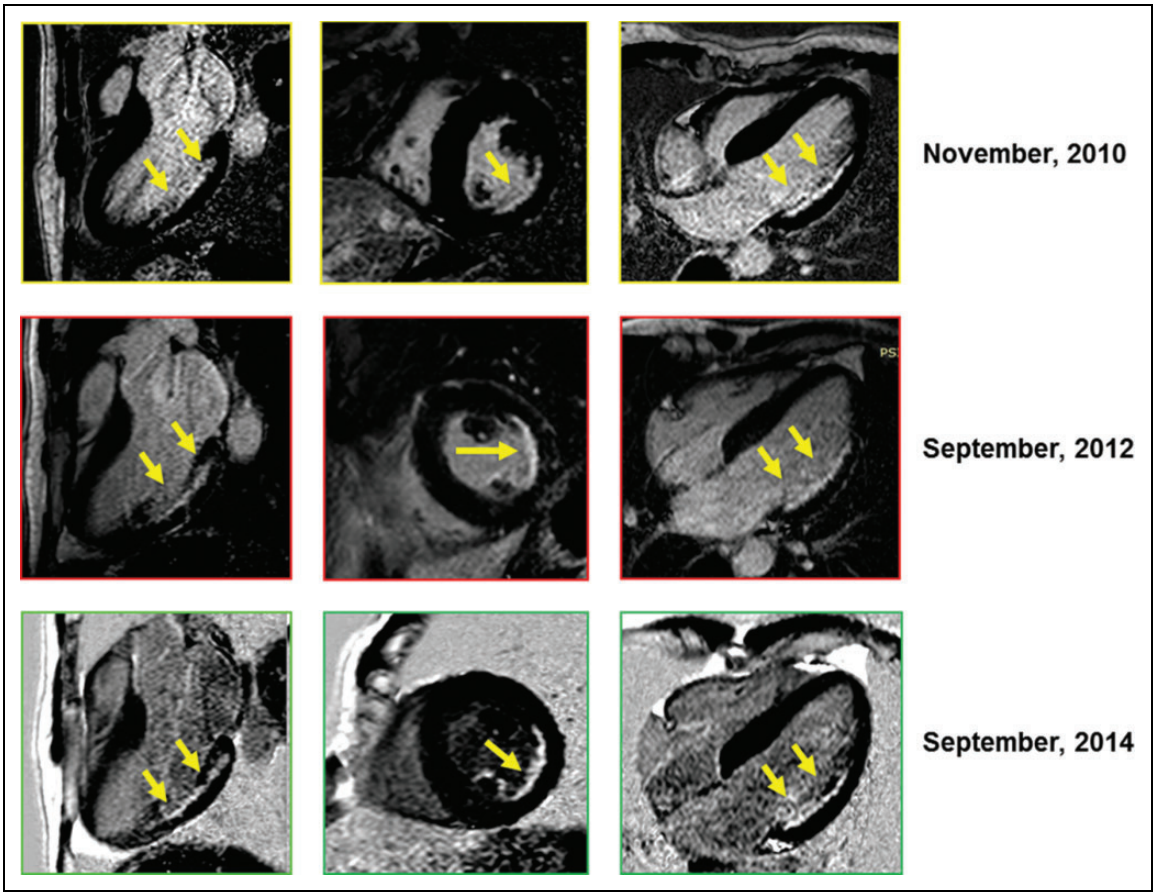

Figure 3. Cardiac magnetic resonance imaging (MRI) in patient with Fabry disease (FD) and history of inferolateral infarction—cardiac MRI is an excellent method to reveal the presence of fibrosis in FD, which is commonly located in the posterolateral basal and midlevel or subepicardial layers, but in this case, the late enhancement MRI shows subendocardial, anterolateral, and inferoposterior wall (basal and middle) enhancement in the area of circumflex coronary artery distribution (necrosis). Magnetic resonance imaging is an excellent method to guide the diagnosis, and on the other hand, it is one of the useful tools available to predict treatment response.

Prognosis and Treatment

Enzyme Replacement Therapy

Since 2001, ERT with recombinant human αGAL (rhαGAL) has been available to treat FD.[44-47,65,66] Two ERTs are currently available for FD; agalsidase-α and agalsidase-β, both administered intravenously every other week. Several studies have shown that the intravenous infusion of rhαGAL effectively reduces both plasma and urine GL-3 levels.[44-47,65,66] At cardiac level, ERT improves ventricular morphology and function and has effects on the conduction system but to optimize the benefits of ERT should be started early before irreversible organ damage occurs.[46,47,65,66] For this reason, it is fundamental to rule out FD in patients with HCM and to make an early diagnosis in affected family members.[47,65-67] Cardiac magnetic resonance imaging (MRI) is an excellent method to guide the diagnosis, and on the other hand, it is one of the useful tools available to predict treatment response (Figure 3). For example, cardiac MRI is an excellent method to reveal the presence of fibrosis in FD, which is commonly located in the posterolateral basal and midlevel or subepicardial layers.[68] Such fibrotic process begins at intramural level to then become transmural.[68,69] In patients without fibrosis or with involvement of only one segment, a reduction in LVH with ERT is observed with stabilized function and improved exercise capacity. In patients with FD having extensive fibrosis treated with ERT, LVH reduction is achieved; however, no improvement in left ventricular function is observed.[66] This cardiac replacement fibrosis is expressed by relevant electrical changes in the ECG, such as repolarization abnormalities at rest and during exercise testing, greater density of premature ventricular beat with Holter ECG. It is also one of the factors that influences exercise intolerance in these patients.[70] Women may develop fibrosis without LVH, and recently, this behavior in young male patients with FD has also been observed.[8,71] Typically, cardiologists tend to diagnose FD late, and unfortunately, cardiac involvement is the leading cause for the substantially increased morbidity and death in these patients.[32,72,73] In advanced stages of the disease, patients may develop conduction disorders, arrhythmias, progressive deterioration of ventricular function, and so on, which determine increased risk of stroke due to atrial

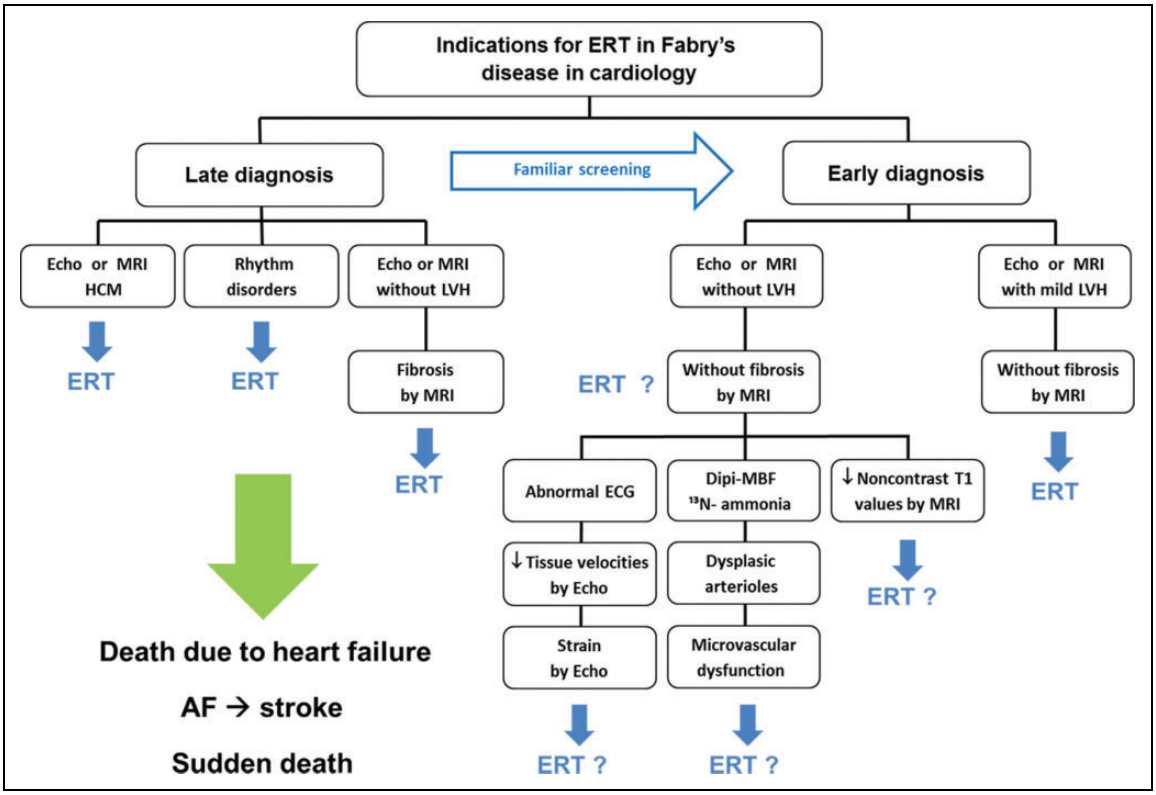

Figure 4. Indications for ERT in Fabry disease in cardiology. AF indicates atrial fibrillation; Dip-MBF, myocardial blood flow following dipyridamole infusion with ^{13}N-labeled ammonia by positron-emission tomography; ECG, electrocardiogram; Echo, echocardiogram; ERT, enzyme replacement therapy; HCM, hypertrophic cardiomyopathy; LVH, left ventricular hypertrophy; MRI, magnetic resonance imaging.

fibrillation (AF), death from heart failure, and SCD.[42,74] Patients who develop systolic dysfunction have an extensive replacement by fibrosis caused by severe microvascular dysfunction and metabolites identified as profibrotic whose levels may decrease with ERT.[34,75] Left ventricular geometry is altered in relation to the stage of the cardiomyopathy and predicts disease progression.[76-80]

Concomitant Treatment

In patients with heart failure and coronary or valve disease, it is important to add adjuvant drug therapy to ERT to improve the quality of life and survival. The first hemodynamic manifestation of cardiac involvement is usually diastolic dysfunction, which may take months or even years to cause symptoms. The conditions predisposing diastolic dysfunction, such as high blood pressure, should be treated appropriately. Blood pressure should be adequately controlled with angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARB) if ACE inhibitors are not tolerated, since a minimal increase in systolic blood pressure levels is associated with acceleration of fibrosis and adverse course of the disease.[63,81] In addition, we must take into account the nephroprotective effects of such treatment. Beta-blockers should be considered in asymptomatic patients with FD even in the absence of LVH but should be used with caution in patients who do not have pacemakers, since they can trigger conduction abnormalities. Patients with FD that evolved with systolic dysfunction should also be treated with ACE inhibitors (or ARB if ACE inhibitors are not tolerated) and diuretics since they contribute to improve symptoms, ventricular function, and therefore the prognosis of these patients.[76-80] Patients with coronary artery disease must receive aspirin and statins (see the next chapter in this issue of the *Journal* in relation to coronary disease in patients with FD). Patients with symptomatic sinus bradycardia and those with asymptomatic intermittent AV block, progressive conduction system abnormalities, or significant bradycardia should be treated with a pacemaker.[82] Septal reduction therapy with septal myectomy or septal alcohol ablation to improve symptoms may be considered in patients with a resting or provoked maximum left ventricular tract obstruction gradient of $\geq$50 mm Hg, who are severely symptomatic, despite maximum tolerated medical therapy.[1-3,12] Sequential AV pacing, with optimal AV interval to reduce the left ventricular outflow tract gradient may be considered in patients with contraindications for septal myectomy or septal alcohol ablation.[1-3] Patients who had an SCD episode should receive an implantable cardiac defibrillator (ICD) for secondary prevention.[2,3] Moreover, one of the biggest challenges cardiologists face is to identify the small percentage of patients with FD that may benefit from the implantation of an ICD for primary prevention of SCD.[82] This indication is currently based on expert opinion related to

isolated case reports or small series, since the recommendations of major international HCM guidelines have not been validated in patients with FD.[2,3] Thus, for example, there have been reported cases of sustained ventricular tachycardia in patients with FD having apical aneurysms secondary to midventricular obstruction; also it has been reported that fibrosis progression increased the risk of fatal ventricular arrhythmias.[83,84] In these patients, we must consider an ICD for primary prevention, and also we must evaluate this indication in patients with FD having left ventricular dysfunction or significant LVH who have an unexplained syncope, in those who have nonsustained ventricular tachycardia on Holter monitoring, and in those patients with a family history of SCD.[74,83,84] Regarding patients with FD having AF, the use of Score for Determining Stroke Risk for Those with Atrial Fibrillation (CHA2DS2-VASc) is not recommended in this population.[3] Given the high incidence of stroke, patients with FD and AF should receive oral anticoagulation for life, even when they recover sinus rhythm.[3] Implantable loop recorder or 48-hour ambulatory ECG monitoring every 6 to 12 months to detect AF should be considered in patients who are in sinus rhythm and have a left atrial diameter higher than or equal to 45 mm.[3] Orthotopic cardiac transplantation may be considered in selected patients who have systolic dysfunction and New York Heart Association functional Class III to IV symptoms despite optimal medical therapy.[1-3,76-80,85]

When to Start ERT in Cardiology?

Fabry disease is a multisystemic disease, and for that reason, it should be managed by a multidisciplinary team, and the decision to initiate ERT is based on the evaluation of symptoms, signs, and organ involvement. The decision to start ERT should be made jointly by a cardiologist and physician specialized in the other areas involved. Current information on genotype–phenotype correlations in FD is very limited, and it is not enough by itself to decide the initiation of ERT in the absence of other manifestations of the disease.[5] There is general agreement on the indication to start therapy in patients with FD having evidence of HCM, heart rhythm disorders (arrhythmias and/or conduction abnormalities), and in patients with evidence of fibrosis as shown by MRI even in the absence of LVH. It is also indicated in patients with mild to moderate LVH without evidence of fibrosis in the MRI, which was previously discussed, that is, they are those who will benefit more from the ERT. We should define more precisely which patients will benefit from ERT in the presence of cardiac involvement, with no development of LVH or have not expressed fibrosis by MRI[34,36,49] (Figure 4).

Conclusion

The heart is one of the organs that may be affected by FD, and FD is one of the causes of HCM. However, we should bear in mind that when a patient with FD develops HCM, it is because we have made a late diagnosis of the disease. Therefore, at this stage, patients have a higher rate of fatal and nonfatal events (stroke, death by heart failure, SCD) that may be avoided with an early diagnosis and the early initiation of ERT. However, in patients with irreversible organ damage, ERT contributes to the stabilization of the disease, delayed progression to severe heart complications, and improved survival. One of the most important contributions that cardiologists can make is to think about a diagnosis of FD in patients with cardiac manifestations preceding the development of LVH and conduct family screening to identify patients with early cardiac involvement which will benefit more from ERT. Patients with FD without cardiac manifestations of the disease should be evaluated annually by a cardiologist specialized in FD disease, regardless of the indication for ERT.

Acknowledgments

The authors would like to thank Ms Claudia Tarazona (medical translator and interpreter) for the revision of this document and also Eduardo Guevara and Horacio Di Nunzio, Favaloro Foundation University Hospital, for providing us with echocardiography and resonance images, respectively.

Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: A.F. has received speaker's fees from Genzyme and J.P. from Genzyme, Shire, and Amicus.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

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