Algorithm for Investigation of Fabry Disease in Cardiomyopathies

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Sandra Marques e Silva[1], Ândrea V. F. Chaves[2], Murillo O. Antunes[3], Natalia R. Roque[4], Eduarda M. S. Montenegro[4], Isabelle Malbouisson[4], Maurício A. de Paula[4] and Edileide B. Correia[5]

Abstract

Fabry disease (FD) is a rare, x-linked lysosomal storage disease caused by mutations in the GLA gene that leads to total or partial alfa galactosidase A deficiency. Its prevalence ranges between 1:117,000 and 1:8,454. Mutations in the GLA gene result in alpha galactosidase A deficiency leading to the progressive accumulation of globotriaosylceramide (Gb3) in lysosomes of different types of cells of the heart, kidneys, skin, eyes, central nervous system, and gastrointestinal system, and may lead to different clinical scenarios. The cardiac manifestation most frequently found in FD is the presence of left ventricular hypertrophy (LVH) in a concentric pattern, although asymmetric forms are also reported. In clinical practice, it is often difficult to differentiate between FD and other diseases associated with LVH. In adults with LVH, a prevalence of FD of 3-5% has been reported. Therefore, diagnosing these patients is of fundamental importance, as specific treatment for FD has the potential to change the prognosis, especially if instituted early. The purpose of this article is to describe an algorithm developed through a thorough literature review to assist in the identification of FD in patients with cardiomyopathies.

Keywords

Hypertrophic cardiomyopathy, Fabry disease, left ventricular hypertrophy.

Introduction

Fabry disease (FD) is a rare, X-linked lysosomal storage disorder caused by mutations in the GLA gene leading to total or partial deficiency of alfa-galactosidase A and the progressive accumulation of globotriaosylceramide (Gb3) deposits in several tissues and organs [1,2]. The classical phenotype is more commonly seen in males due to complete enzyme inactivity leading to multisystemic symptoms such as neuropathic pain, cornea verticillata, angiokeratomas, sweating abnormalities, gastrointestinal impairment, stroke at young ages, and cardiac and kidney disfunction [3,4]. Manifestations of the later-onset phenotype appear later in life usually during adulthood due to higher levels of residual α-Gal A may be seening in both males and females. Although hemizygous males and heterozygous females are affected by Fabry disease, heterozygous females can present a heterogeneous range of signals and symptoms, from milder to severe clinical manifestations [5,6]. Heterozygous females can present a heterogeneous range of signals and symptoms, disease severity and organ involvement, that are related to the proportion of skewed X-chromosome inactivation of normal or mutant alleles [5,6,7]. As a result of the residual enzyme activity often found in their lysosomes, the disease may clinically manifest with single-organ involvement of the heart or kidney [8–11]. Long-term complications of the disease include progressive renal failure, stroke, and cardiomyopathy. All tissues in the heart are affected, leading to left ventricular hypertrophy (LVH), disturbances in the conduction system such as short PR interval and bradycardia [12–14], valvar regurgitation and ischemic myocardial disease [15–17].

The prevalence of FD among patients with LVH is 3 to 5% [2,18,19]. Therefore, diagnosing these patients is of crucial importance, as specific treatment for FD can potentially change

[1]Hospital de Base do Distrito Federal, Brasília, DF, Brazil.
[2]Rarus – Serviço de Referência em Doenças Raras, Recife, PE, Brazil.
[3]Universidade São Francisco, Bragança Paulista, SP, Brazil.
[4]Sanofi Specialty Care, São Paulo, SP, Brazil.
[5]Instituto Dante Pazzanese de Cardiologia, São Paulo, SP, Brazil

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Corresponding Author:
Sandra Marques e Silva, E-mail: smarquesmd@gmail.com

the prognosis, especially if instituted early [20–23]. However, clinically, it can be challenging for physicians to differentiate Fabry cardiomyopathy from other diseases associated with LVH, such as sarcomeric disease, amyloidosis, hemochromatosis, Noonan Syndrome, and neuromuscular disorders [24–26]. Currently, there are many algorithms for the investigation of FD [25–30], but little have a focus on cardiac involvement [31,32]. In this review, a group of cardiologists with expertise in Fabry cardiomyopathy propose an algorithm to enable an easy, accurate, timely and cost-effective screening of the Fabry cardiomyopathy.

Methods

From March to June 2019, we searched PubMed and the Cochrane Library in the attempt to retrieve articles that defined criteria and methods for investigation of FD in patients with unexplained LVH. The key words used in the search were: "Fabry disease", "left ventricular hypertrophy", "hypertrophic cardiomyopathy", and "screening criteria". We found eight review articles and two clinical trials that were included in our review [16,24,33–40]. We read and discussed these articles with the aim of building the algorithm. By discussing the literature in a group of FD experts, we reached a consensus among authors based on a common understanding of the available evidence that lends support to the algorithm, shown below.

Rationale for the Presentation of Cardiology Algorithm in Fabry Disease

As proposed in the algorithm displayed in Figure 1, the investigation of Fabry cardiomyopathy should be initiated with the follow timelines: 1) anamnesis with the understanding of cardiac signs and symptoms and/or electrocardiographic changes related to Fabry and; 2) the next step is echocardiographic analysis of changes followed by 3) FD specific investigation.

In that way, once the clinical history reported refers to an individual presenting clinical complaints of heart failure that might start during the third decade of life associated with chest pain, palpitations resulting from supraventricular or ventricular arrhythmias, symptoms related to autonomic dysfunction such as unexplained syncope, orthostatic hypotension, recurrent dizziness, or chronotropic incompetence that are not explained by other conditions such as hypertension, diabetes mellitus or atherosclerotic coronary disease [16,18,38,41,42]. It is important to note that cardiac changes can be present at different ages even during childhood [21]. Moreover, the suspicion of FD may be enhanced by a previous history of chronic kidney disease with unknown etiology, history of stroke before 40 years of age, peripheral neuropathy at young ages, hypohidrosis or anhidrosis, the presence of angiokeratomas, or the presence of another subject with FD in the family. These criteria are not mandatory for full investigation of FD and are more likely to

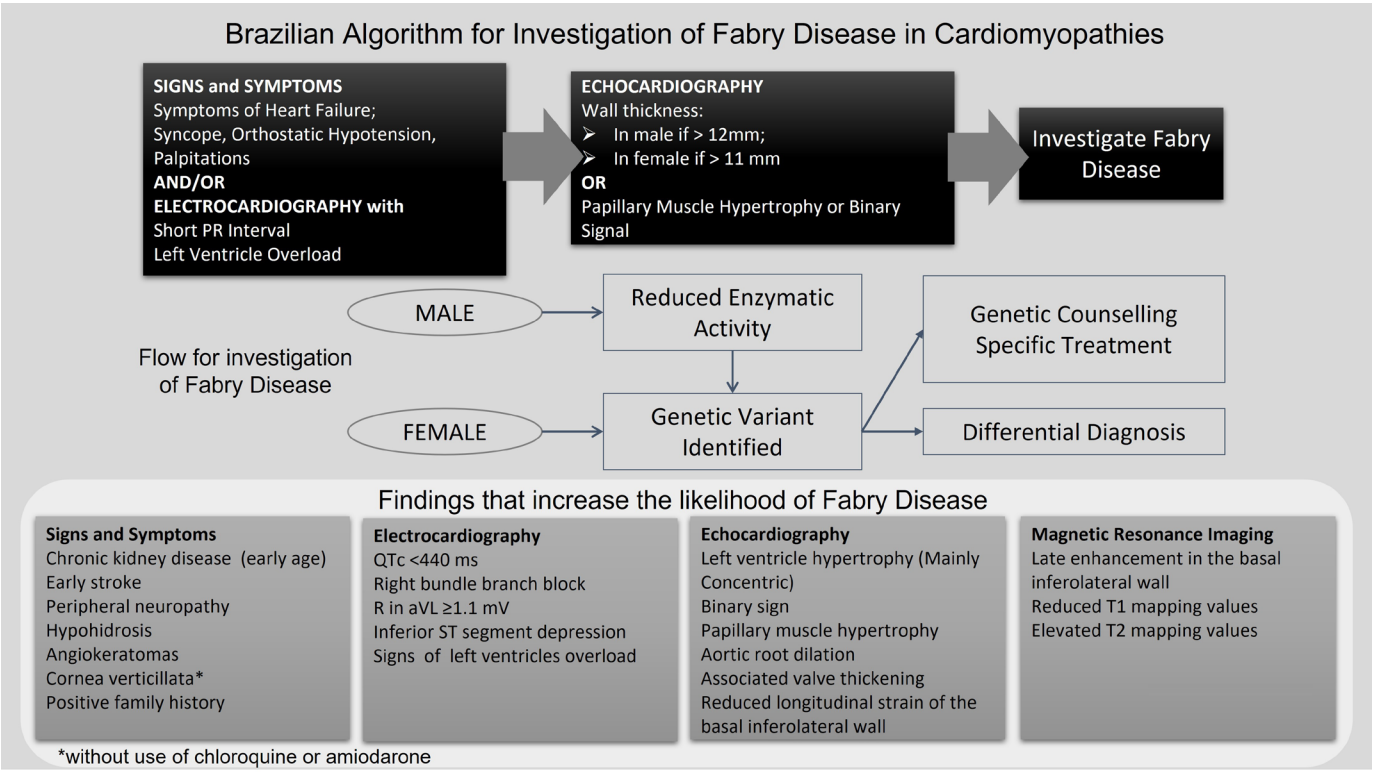

Figure 1. Proposed algorithm for screening and diagnosis of Fabry disease. The algorithm starts with the analyses of signs and symptoms and/or electrocardiography alterations follow by echocardiography investigation. As the patient reaches those criteria's, the suspicion of FD is substantial, a specific investigation is indicated. aVL: augmented vector left; QTc: corrected QT interval.

be seen in patients with classical mutation than in those with late-onset disease.

Most adult patients with FD show abnormalities in the electrocardiogram, a low-cost exam routinely performed on the first cardiological evaluation. Variable brady or tachycardic rhythms associated with a short PR interval (<120 milliseconds) and changes in the corrected QT interval are observed [43,44]. Namdar *et al.* reported a significant reduction in the P wave and PQ/PR interval in patients with FD when compared with healthy individuals, demonstrating a high sensitivity and specificity for diagnosis [43,45]. Hoigné *et al.* also described a tendency to reduce the PR interval in these patients when compared with other heart diseases presenting with LVH [24]. Another finding is the reduction of the corrected QT interval at the early stage of the disease. The corrected QT <440 ms, combined with the PQ interval minus the P-wave width in lead II <40 ms, showed 100% sensitivity and 99% specificity for FD diagnosis [44]. Arrhythmias, such as bradycardia and atrioventricular blocks, can be found in later stages [45]. Recently, Vitale *et al.* suggested the following independently predictive signs for FD diagnosis: short PR interval, prolonged QRS duration, right bundle branch block (RBBB), R in aVL ≥1.1 mV, and inferior ST depression [46]. Contrasting with other storage diseases such as amyloidosis, the deposition of Gb3 in the conduction system manifests as signs of left-ventricular overload by variable criteria (Sokolov, Cornel) [47,48].

Following patient evaluation, there is the need to perform imaging methods that allow an in-depth assessment of cardiac involvement. In this regard, the echocardiogram should be highlighted, as it is an accessible, low-cost exam capable of providing a morpho-functional substrate for the complaints previously presented, as well as providing data that influence patient prognosis [49].

Data derived from Fabry registries show that LVH is the chief manifestation [24,37,40]. Cardiac hypertrophy affects more than two-thirds of patients with FD, according to the literature [50]. Aspects related to the type of pathogenic genetic variant, age group, associated diseases and clinical management can influence the severity of LVH [24,49,51]. Concentric involvement without obstruction of the left ventricular outflow tract is most frequently seen; however, concentric remodeling, eccentric hypertrophy or even isolated apical forms have already been described, as well as hypertrophy of the papillary muscles [37,49,52]. The cut-off values for left ventricular wall thickness proposed in this algorithm are >11 mm in females and >12 mm in males. These are similar to more recent therapeutic guidelines focused on FD, such as the Canadian FD treatment guidelines [53].

Other echocardiographic findings typically seen are papillary hypertrophy, enlightenment of ventricular endocardium (Binary sign), and thickening of mitral and aortic valves leading to mild regurgitations and aortic-root dilatation. The binary sign was defined as suggested by Pieroni et al. as a hyperechogenic and bright endocardium and a hypoechogenic space between endo- and myocardium, especially visible in the interventricular septal and the apical region of the left ventricle, respectively, thus forming a binary appearance [54]. Systolic function remains preserved until the late stages of the disease unless there is the coexistence of other cardiac diseases such as uncontrolled hypertension, renal failure, diabetes mellitus, or coronary disease [41,55].

Novel echocardiographic techniques, such as the analysis of myocardial deformity or cardiac strain using the speckle-tracking technique, detects early cardiac changes in FD. These include subclinical forms of systolic dysfunction in contractile function that are sometimes imperceptible using conventional methods and result in ejection fraction disturbances. In early stages of ventricular involvement, substrate deposits and the underlying inflammatory process determine a slight reduction in the left-ventricular global longitudinal strain (LV GLS) at the basal portion of the infero-lateral wall even before the development of left ventricular hypertrophy. The development of hypertrophy generates more marked reductions in the LV GLS as well as in the radial strain (RS) of the inferolateral wall. There is also a post-systolic contraction described as a double-peak sign in the graphical representation of the deformity. In advanced stages of the disease, and with the development of fibrosis, there is substantial worsening of the values of LV GLS and RS [56,57]. Similar phenomena are observed in the free-wall strain of the right ventricle and the left atrium, even before the appearance of clinical symptoms [58]. Moreover, several studies have demonstrated the value of this novel echocardiographic method for the differential diagnosis of cardiomyopathies.

Laboratory findings of low cost and easy access may help FD cardiomyopathy staging before going to disease-specific diagnosis. Hypertrophic cardiomyopathy biomarkers such as highly sensitive troponin and N-terminal pro-B-type natriuretic peptide (NT-pro-BNP) are associated with inflammatory myocardial injury and left-ventricle volume and pressure overload as extensively discussed in the cardiomyopathies guidelines [59]. The augment of those markers may anticipate the onset of heart-failure symptoms and assist the management of disease progression [60–62].

The combined analysis of clinical information, electrocardiographic and echocardiographic changes and biomarkers seems to increase the likelihood of FD cardiomyophaty [63–65]. Moreover, this information is crucial for initial diagnosis of Fabry Disease, for disease-specific therapy indication and monitoring, as well as to manage cardiovascular symptoms and prevent undesired cardiovascular events in order to maximize therapeutic benefits [26,66].

Fabry Disease-Specific Diagnosis

Genetic confirmatory testing is mandatory in both suspected males and females, as GLA gene mutations may range from benign polymorphisms to very severe classical phenotypes [21]. However, in case of males clinical suspicion to have FD, α-Gal A activity should be measured before genotyping, as

the absence of low α-Gal activity can exclude FD and reduce diagnostic costs. Is important to note that, patients with higher enzyme activity tend to have more attenuated disease [67,68]. In females, because of genetic mosaicism, the α-Gal A activity is variable and can range from low to within normal levels [69]. In this reason, the genetic testing is indicated in suspected females without the need of enzymatic testing [21]. In that way, the timeline for Fabry disease specific diagnostic in males and females is described in Figure 1.

The assessment of specific biomarkers of FD contributes not only to diagnosis but it is also used as a tool to assess therapeutic efficacy [70,71]. In this sense, the serum levels of Lyso-Gb3 were shown to be superior to the assessment of Gb3, especially for female patients [72].

Other Useful Elements for FD Diagnosis

Magnetic resonance imaging

Cardiac magnetic resonance imaging (MRI) is considered the gold standard for the diagnosis and deeper characterization of cardiac involvement in hypertrophic diseases. Notwithstanding many favorable features, cardiac MRI is not yet widely accessible, especially in less economically developed regions. The equipment is usually installed in large urban centers, and tests are often considered expensive. Thus, in places with scarce resources, the methods presented above in the algorithm are sufficient for the initial diagnosis. Furthermore, more detailed assessments of cardiac involvement, such as the presence of fibrosis, should not delay the diagnosis or the initiation of specific treatment. In addition, some peculiarities associated with the technique, such as the need for a regular heart rhythm and the cooperation on the part of the patient when asked to perform respiratory maneuvers, may be challenging in the attempt to obtain reasonable results.

Cardiac MRI provides not only diagnostic and staging information in FD but also allows differential diagnosis with other disorders and provides prognostic information. Information regarding cardiac mass, wall thickness, cavity volumes and systolic function are accurately measured even in the presence of a difficult echocardiographic window [73,74]. The use of the MRI delayed enhancement technique with gadolinium makes it possible to locate and quantify the degree of myocardial fibrosis, typically located in the mesocardial portion of the lower basal region. The fibrosis is a marker of chronic heart disease and may lead to systolic disfunction and heart failure. Prognosis in these cases is worse due to the low response to enzyme replacement therapy [75] and increased occurrence of malignant arrhythmias, heart failure, and sudden cardiac death [76–78]. It is important to highlight that this technique is not recommended in individuals with glomerular filtration rate <30 mL/min due to the risk of nephrogenic systemic fibrosis and death [79].

The development of T1 and T2 mapping techniques expanded the diagnostic horizon for MRI by enabling the early detection of edema, inflammation and fibrosis even in individuals with end-stage renal disease [80]. The cardiomyopathy in FD is characterized by a decrease in T1 values on the parametric map, associated with an increase in extracellular volume. Besides Fabry cardiomyopathy, only hemosiderosis cardiomyopathy has low T1 mapping values and the finding of iron deposits in other tissues helps to differentiate between the two diseases. Other disorders that present with hypertrophy are characterized by a T1 map of higher intensity, helping in their differentiation from FD [80,81].

Differential Diagnosis

The heart involvement in FD may be confirmed by Gb3 deposits in the heart and can be evaluate by biopsy [31]. Moreover, it is important to highlight that biopsy brings more information concerning patients with low Lyso-Gb3 levels and variants of unknown significance [31].

In addition, the finding of low-voltage QRS complexes on the ECG may suggest other diagnoses, such as amyloidosis while high voltages QRS makes differential diagnosis with sarcomeric hypertrophyc cardiomiophaty [59]. Echocardiographic findings of severe hypertrophy, systolic dysfunction or valve disorders in the first years of life may be indicative of other diagnoses, such as Danon or Pompe disease [26,82]. Therefore, a confirmed diagnosis of another disorder with cardiac involvement may rule out the diagnosis of FD. Such disorders include amyloidosis, mitochondrial cardiomyopathies, Friedreich ataxia or other muscular dystrophies, valve diseases, other deposit diseases (Pompe, mucopolysaccharidosis), and genetic syndromes (Noonan, LEOPARD, and Costello) [26,82].

Discussion

In FD, early diagnosis is essential for the relief of cardiac symptoms that are highly disabling and therefore cause of intense psychological suffering. The systematization of a therapeutic strategy helps the attending physician to establish a highly effective and cost-effective investigative strategy by requesting specific diagnostic tests not only through conventional techniques but also new technologies. In this sense, it is known that the journey of a patient with a diagnosis of a rare disease is challenging. In general, patients are evaluated by physicians from different specialties with no control of symptoms or the interruption of disease progression as there is a lack of effective action on the primary cause of the disease, which is in this case the glycosphingolipid deposits. In addition, the multisystemic manifestations of FD make it necessary to perform multiple tests, some of which are highly complex and not always available in the vicinity of the patient's home. As a result, literature data indicate that there may be a delay of 14 years for male patients

and of 19 years for female patients between the onset of symptoms and the establishment of the diagnosis of FD [83].

Is a matter of fact, that in locations where the resources for diagnosis are scarce, the proposed algorithm together with the low-complexity exams may be useful to indicate the possibility of heart disease related to FD. Based on this, the patient can receive adjuvant drug treatment for symptom relief while waiting for care in reference centers where exams of higher complexity are available.

Conclusion

The proposed algorithm aims at optimizing the clinical management of FD to prevent patients from developing cardiac fibrosis or high-grade blocks in the conduction system that require high-cost procedures such as the implantation of pacemaker/cardiac defibrillators or even heart transplantation. At this stage of disease progression, it is known that specific therapies for FD have low effectiveness and may not prevent the occurrence of unfavorable outcomes such as malignant arrhythmias or sudden death [84].

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Declaration of Conflicting Interests

SMS has received speaker honoraria from Sanofi, Takeda, Pint Pharma, Amicus Therapeutics, Pfizer; AVFC has received speaker honoraria from Sanofi and Pint Pharma; MOA has received speaker honoraria from Sanofi Genzyme, Pfizer and Takeda, and grant/ research support from Novartis and Pfizer. NRR, EMSM, IM and MAP are Sanofi employees; EBC has received speaker honoraria from Pfizer, Alnylam, Jansen, Takeda and Sanofi. Genzyme, and has participated in Advisory Boards and Meetings sponsored by Pfizer, Sanofi Genzyme, Alnylam and Bristol Myers Squibb.

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