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General review

Fabry disease: A fundamental genetic modifier of cardiac function

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ABSTRACT

Fabry disease (FD) is an inherited X-linked metabolic storage disorder triggered by abnormalities in the *GLA* gene at Xq22, which leads to a deficiency in α-galactosidase A and massive accumulation of intralysosomal glycosphingolipids. Cardiac complications are very common in FD and are the main cause of late morbidity, as well as early mortality in both hemizygous men and heterozygous women. There is a need for a multidisciplinary approach to evaluation and management of FD patients as there is a wide range of presentation of FD, which varies with mutation and other organ involvement/dysfunction. An overview of common cardiac involvement and clinical characteristics in FD including: left ventricular hypertrophy (LVH), conduction abnormalities and arrhythmias, coronary artery disease and valvular infiltrative myopathy are provided in this review. Current therapeutic approaches such as enzyme replacement therapy as well as the emergence of novel therapeutic options such as gene therapy to optimize disease outcomes in FD patients will be highlighted in this paper.

1. Introduction

Fabry disease (FD) is a rare X-linked recessive hereditary systemic disorder caused by missense mutations in the lysosomal glycoprotein α-galactosidase A gene (α-Gal A). The resultant deficiency in α-Gal A enzymatic activity, responsible for hydrolysis of the terminal alpha-galactosyl moieties from glycolipids and glycoproteins, results in cellular accumulation of globotriaosylceramide (Gb3), and other neutral glycosphingolipids in various organ systems [1]. The progressive glycosphingolipid accumulation within cardiac myocytes, valvular fibroblasts, neuronal, vascular smooth muscle and vascular endothelial cells leads to cellular dysfunction and result in life-threatening cardiovascular disease (CVD) [2,3]. The cardiac variant of FD affects 1/50,000 individuals, including hemizygous males, as well as homozygous, and in many cases heterozygous females and could reduce the affected individuals life span by approximately 20 years [4].

2. Left ventricular hypertrophy

A cardiac variant of FD is associated with LVH without other organ involvement and correlates with glycosphingolipid deposition in myocytes and conduction tissue [5]. In hemizygous males and heterozygous females with genetically-diagnosed FD, echocardiographic analysis revealed a strong correlation between age and the severity of LVH, and cardiac structural remodeling with increased left ventricular (LV) mass was associated with significant impairment in systolic and diastolic LV function [6,7]. In a cross-sectional study designed to describe the prevalence and extent of LVH in a population of untreated FD patients, 51.5% of males and 38% of females were classified as having LVH by echocardiographic examination, with the prevalence increasing with age in both genders [8]. Cardiac magnetic resonance was able to detect that FD subjects had a 34% greater LV index compared with controls and had a significantly greater papillary muscle contribution to total LV mass even in the absence of LVH [9]. Myocyte vacuolation and intralysosomal inclusions were observed by electron microscopy in FD [10]. Deposition of Gb3 within cardiac cells contributes to the progressive weakening of ventricular contractility and diastolic function in untreated patients [11]. Several studies have reported α-Gal A gene mutations in patients with LVH and suggested that FD should be considered in all cases of unexplained hypertrophy in both males and females (Table 1). Most of these initial FD prevalence screened cohorts excluded patients with hypertension, asymmetric hypertrophy and aortic valve disease, nevertheless the recent demonstration that FD is present in 0.90% of unselected patients with LVH indicate that FD has to be incorporated in the differential diagnosis of all patients with LVH (Fig. 1).

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Table 1
Prevalence of FD in patients with LVH or hypertrophic cardiomyopathy (HCM).

Population	FD prevalence	Reported mutation	Reference
230 male patients with LVH	3%	Met296Ile, Ala20Pro	[12]
79 male patients with HCM diagnosed at $\geq$ 40 years of age	6.3%	Asn215Ser, Ile317Thr, Asp 313Tyr	[13]
74 male patients with HCM diagnosed at $<$ 40 years of age	1.4%		
62 males and 34 females with unexplained HCM	3.3% in males 12% in females	–	[14]
45 males and 30 females with HCM	Gene defects causing FD were not found	–	[15]
328 males and 180 females with HCM	0.9% in males 1.1% in females	Leu89Pro, Ala143Thr, Glu358del, Ser238Asn	[16]
56 males and 34 females with HCM	3%	Asn139Ser, Ala156Thr, Gly271Ser	[17]
885 males and 501 females with unexplained LVH	0.5%	Thr410Ala	[18]
362 males and 178 females with LVH	0.90%	Ala5Glu, Ala143Thr, c.639+6A>C	[19]
100 males with unexplained LVH	4%	Asn215Ser, splice mutation in intron 5–c.801+48 T>G, Tyr152His	[20]
23 males and 24 females with LVH	2.10%	Trp262Leu	[21]
273 patients with HCM	4.6%	–	[22]

3. Conduction abnormalities and arrhythmias

Lone atrial fibrillation (AF), cryptogenic ventricular arrhythmias and sudden death have been documented in FD in the absence of clinical symptoms, electrocardiographic and cardiac magnetic resonance irregularities [23,24]. Electrophysiological abnormalities are one of the hallmarks of FD with shorter P-wave duration, PQ-interval and QRS width and/or prolonged QTc interval and pronounced repolarisation dispersion in FD patients [25]. Pacing for atrioventricular and sinus node dysfunction principally in FD patients with QRS $\geq$ 110 ms necessitate a close monitoring and pharmacological treatment as development of fibrosis and apoptosis of cardiac conduction tissue is frequent [26]. In the Fabry outcomes survey (FOS), untreated women had a similar frequency of palpitations or documented arrhythmia as untreated men and were of comparable age at onset of symptoms [27]. A longitudinal study revealed the prevalence of tachyarrhythmia in FD patients with 3.9% having persistent AF, 13.3% paroxysmal AF and 8.3% nonsustained ventricular tachycardia [28]. However, these numbers have to be treated with caution as some of the participants showed an increased left atrial diameter, diastolic dysfunction and increased LV wall thickness, all factors contributing to AF. Atrial arrhythmias alone may be initiated by substrate deposition within the atrial cells and dilation of the atria due to elevated atrial and LV filling pressures. FD patients with LVH are highly predisposed to arrhythmic episodes and ventricular arrhythmias commonly observed in elderly patients with cardiac hypertrophy are triggered by infiltration of cardiac conduction tissue with glycosphingolipids due to lower availability of alpha-gal A [24]. Clinical arrhythmia can lead to syncope and may be one of the fundamental mechanisms underlying cerebrovascular events and transient ischemic attacks in FD.

4. Coronary artery disease

Premature coronary microvascular dysfunction is a key characteristic of FD with reasonably high frequency of angina encountered both in men and women. Recurrent chest pain and dyspnea on mild effort and at rest are common clinical symptom in FD cohorts, and are reported without significant LVH in 60% of hemizygous males and heterozygous females [29]. The incidence of acute myocardial infarction was reported to be 1.4% in males and 4.3% in females, despite the high occurrence of angina [27]. Resting and hyperaemic myocardial blood flow and coronary flow reserve are reduced in FD patients independently of HDL and LDL concentrations [30]. The significant reduction in myocardial perfusion in FD patients is regularly associated with ST-segment and T wave abnormalities on ECG. Impaired cardiac perfusion reserve and increased myocardial oxygen requirements is seen on positron emission tomography [31]. Persistent cardiac troponin I elevation supportive of myocardial injury is often observed in FD patients with cardiac involvement, however non-obstructive coronary angiography in these patients support the notion that small vessel ischemic disease may be the pathogenic mechanism behind this observation (Fig. 1) [32,33]. Invasive and noninvasive studies provided evidence that perfusion dysfunction, slow coronary flow and severe blockade of intramural arteries trigger myocardial ischemia with evidence of replacement fibrosis and affects 34% of cardiac involved FD patients [34]. At the cellular level, FD cardiomyocytes isolated from myocardial tissue showed remarkably greater protein nitration, iNOS/nitrotyrosine expression with oxidative and apoptotic DNA damage [35]. Microvascular angina was also proposed to be the leading initiator of FD cardiomyopathy prior to the development of LVH attributable to endothelial dysfunction with reduced nitric oxide production in cardiac smooth muscle cells [36].

5. Valvular infiltrative myopathy

Valvular anomalies represent a major cause of early morbidity and mortality in adult patients with FD [37]. Mild to moderate LV valvular insufficiencies and aortic valve regurgitation have been reported repeatedly in advanced stages of FD [7]. Clinical evaluations in hemizygous men (mean age 39 $\pm$ 10 years) and heterozygous women (mean age 35 $\pm$ 19 years) have identified mitral (57%) and aortic (47%) valve anomalies that were often accompanied by regurgitation [6]. Echocardiographic examinations of heterozygous female patients reported aortic and mitral valve thickening (25.5%), and mitral valve prolapse (10.9%) [7]. Concomitant dilations at the sinus of Valsalva (32.7%) and ascending aorta (29.6%) that could trigger aortic regurgitation, dissection, and/or rupture were documented in young FD normotensive men [38,39]. Marked increase of aortic root dilatation correlated with the advanced stage of LVH. Transcatheter aortic valve implantation and heart transplantation are effective therapeutic alternative for FD patients with end-stage valvular heart disease [40,41]. These structural valvular alterations are sought to be primarily initiated by Gb3 deposition within valvular fibroblast; however, the underlying molecular mechanisms of Gb3 uptake are so far unknown presumably due to differences in the glycoplipid metabolism between FD mice and humans and lack of disease-relevant cell types [42–44].

6. Management of FD with enzyme replacement therapy

Enzyme replacement therapy is the primary treatment of FD as it helps to clear elevated GL-3 both from plasma and heart tissues

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