REVIEW

Cardiac Involvements of Fabry Disease

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ABSTRACT

Fabry disease is a rare, inherited metabolic disorder caused by deficient activity of α-galactosidase A, which leads to cellular and multiorgan dysfunction due to progressive intracellular globotriaosylceramide accumulation, extensive interstitial fibrosis and smooth muscle cell proliferation, mostly due to accelerated cellular apoptosis and/or necrosis. Cardiac involvements are frequent in Fabry disease. The patients may develop hypertrophic cardiomyopathy, arrhythmias, conduction abnormalities, valvular abnormalities and coronary heart disease. The diagnosis of Fabry disease is challenging due to the protean manifestations, which often lead to delayed diagnosis. Enzyme replacement therapy with the administration of agalsidases α and β may lead to the clearance of globotriaosylceramides from the cardiac capillaries and therefore result in left ventricular structural and functional improvements. Anticoagulant treatment is necessary for patients with Fabry disease to prevent ischaemic events. Symptomatic bradycardia and heart block frequently warrant pacemaker implantation and malignant arrhythmias may require an implantable cardioverter-defibrillator. Surgical interventions including valvular operation, myectomy and coronary artery bypass or coronary angioplasty have been attempted in a limited number of patients with Fabry disease alongside enzyme replacement therapy. The early and mid-term follow-up results have been satisfactory. This article presents a review of the pathogenesis, clinical features, diagnostic approaches and treatment strategies of the heart involvements of Fabry disease.

Keywords: Enzyme replacement therapy, left ventricular hypertrophy, lysosomal storage diseases

INTRODUCTION

Fabry disease is a rare inherited metabolic disorder caused by the deficient activity of α-galactosidase (Gal) A, which degrades the globotriaosylceramides (Gb3) and other glycosphingolipids into lower molecular weight products (1). Deficient α-Gal A activity leads to cellular and multiorgan dysfunction due to progressive intracellular Gb3 accumulation in the organs (2). Globotriaosyloceramides deposits cause extensive interstitial infiltration (3), thereby leading to smooth muscle cell proliferation and increased intima-media thickness of the arteries, including common carotid, brachial and radial arteries, *etc* (4). Globotriaosyloceramides often deposits within the cells and interstitial fibrosis frequently develops due to accelerated cellular apoptosis and/or necrosis (5). Both Gb3 deposits and elevated plasma endothelin-1 levels contribute to myocardial architectural remodelling (6).

Globotriaosylsphingosine (lyso-Gb3) is a degradation product of Gb3, and it increases dramatically in classical Fabry patients (7). Lyso-Gb3 has high diagnostic sensitivity and correlates with the left ventricular (LV) mass in late-onset Fabry disease patients (8). A comparative study revealed that the plasma sphingosine-1 phosphate levels were significantly higher in the Fabry disease patients than in those of healthy controls. In addition, a positive correlation between plasma sphingosine-1 phosphate levels and both common carotid artery intima-media thickness and LV mass index was found (9). Inhomogeneous properties of cells with

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normal X-chromosome and those with X-chromosome with α-Gal A mutations are associated with random X-chromosome inactivation (10). Various cell types can be affected by metabolite storage, and renal epithelial, myocardial and neuronal cells are the most often affected (11). As a result, 70% of patients with Fabry disease had electrocardiographic abnormalities, 60% had proteinuria and 40% had a reduced glomerular filtration rate (2).

The incidence of Fabry disease is not well defined; and neonatal screenings showed a higher incidence than cited in the literature due to detection of late-onset variants (12). Fabry disease is found in approximately 1:117 000 people or 1:40 000 males (13). It was reported that 98% of the patients had a positive family history (2). The diagnosis in female patients is often delayed, due to mild symptoms, slow progression and isolated organ involvement (2). Cardiac involvement is frequent in Fabry disease (3), accounting for 46% of the cases (2). The patients may develop hypertrophic cardiomyopathy, arrhythmias, conduction abnormalities, valvular disorders and coronary heart disease. It has been noted that Fabry cardiomyopathy with valvular disorders correlates with the severity of the disease (14). The diagnosis of Fabry disease is challenging and a delayed diagnosis is usually the case due to the protean manifestations. In order to have a better theoretical knowledge and to improve the diagnosis and treatment of the disease, the cardiovascular aspects of Fabry disease are highlighted in this article.

Cardiac manifestations

Left ventricular hypertrophy

Left ventricular dilatation and aneurysms are not typical, but they can be seen in terminal patients. The cardiomyopathy in Fabry disease is a progressive infiltrative hypertrophic cardiomyopathy characterized by LV dilatation with global or regional wall motion abnormalities and aneurysm formation (15). Concentric LV hypertrophy is a key feature in Fabry disease (16).

The underlying mechanism for LV hypertrophy in Fabry disease patients is still unknown. Gb3 accumulation is unlikely to be directly involved in the development of Fabry cardiomyopathy, but it may induce cardiomyopathy by activating certain signalling pathways (17). The myocardial energy depletion in Fabry cardiomyopathy is similar to that found in other metabolic diseases and hypertrophic cardiomyopathies (18). The patients with Fabry cardiomyopathy may have mild diastolic dysfunction at the early stage, and they may evolve into exceptional restrictive cardiomyopathy at the late stage with a probable infiltrative pathogenesis of the endothelium of the arterioles (18).

In a majority of the patients, the LV hypertrophy is concentric; however, an asymmetrical variety with septal thickening and posterior wall fibrotic thinning may present in about 5% of the cases (14). Left ventricular hypertrophy in Fabry patients is usually not associated with significant systolic or restrictive diastolic dysfunction. Instead, the LV function correlates well with the severity of the disease (19). The deposits of Gb3 represent only about 1% of the increase in the LV mass (6). The fibrotic process in Fabry cardiomyopathy starts with intramural involvement with later transmural involvement. Fibrosis is invariably present in the basal posterolateral segments (20). Magnetic resonance imaging showed increased gadolinium uptake involving the basal segment of the LV posterolateral wall, typical for myocardial fibrosis in advanced Fabry cardiomyopathy patients, in whom the end-diastolic thicknesses of the LV septum and posterolateral walls were measured to be 16 mm and 15 mm, respectively (21). Gb3 accumulation had been observed in vascular endothelial and smooth muscle cells, cardiomyocytes, conduction tissues and valvular fibroblasts (22).

Sachdev *et al* (23) reported that about 6% of male patients with late-onset and about 1% of patients with early-onset hypertrophic cardiomyopathy had a low α-Gal activity and the incidence of Fabry disease was 4%. They screened for plasma α-Gal activity in male patients with hypertrophic cardiomyopathy diagnosed before and after 40 years of age, and noted that all six patients with low α-Gal values had α-Gal gene mutations. Monserrat *et al* (24) screened the genotype of 508 patients with hypertrophic cardiomyopathy and found that the prevalence of Fabry disease was 1% (0.9% in men and 1.1% in women). The prevalence of Fabry disease gene mutations in the patients with unexplained hypertrophic cardiomyopathy was 0.5%–4% (25, 26).

Valvular changes

Valvular changes in Fabry disease patients are believed to be caused by lipid storage and fibrosis in the valvular tissue (13). The incidence of valvular changes did not differ between the hemizygotes and the heterozygotes (27). The post-mortem examinations of the heart of patients with Fabry disease showed the maximal accumulation of the major glycosphingolipid substrate and Gb3 in the lysosomes of all the cardiac tissues examined; the greatest concentrations were found in the mitral

valve in addition to the LV myocardium (28). The valvular involvements in Fabry disease differed significantly between valves.

Minor structural abnormalities of the mitral valve were found in 57% of patients and the aortic valve was affected in 47% Valvular abnormalities were often associated with minor/mild degrees of regurgitation (14). Weidemann *et al* (29) reported no severe valvular disorders in a cohort of 111 patients with Fabry disease; instead, only a few cases of mild-to-moderate aortic, mitral or tricuspid disorders were noted. In addition, in Fabry cardiomyopathy, echocardiography might reveal very prominent papillary muscle associated with concentric LV hypertrophy (30). The thickening of the papillary muscle and mitral leaflet, along with mild mitral regurgitation, could be found in half of the Fabry disease patients (31). The findings of diffuse ballooning of the mitral valve and massive glycolipid storage in the valve tissue suggested that the abnormal storage process is responsible for the valvular insufficiency (32). Other authors proposed that there was a high frequency of mitral valve prolapse in Fabry disease patients (19, 33). Mitral valve thickening, deformity, or prolapse is often seen in young patients, whereas aortic disorders appear in older patients (17). But, findings in recent reports were not consistent with these arguments (31).

Conduction abnormalities and arrhythmias

Gb3 deposits have been found in the conduction system in addition to the deposit in the myocardium (34). This predisposes to rhythm disturbances resulting in tachy- and mostly bradycardia. The typical electrocardiogram findings of Fabry disease include short P-R intervals (The P-R interval refers to the time from the beginning of the P wave to the beginning of the ventricular wave, representing the time from the beginning of atrial depolarization to the beginning of ventricular depolarization) in the early stage, and P-R interval prolongation, atrioventricular block, electric LV hypertrophy, ST (the ST segment represents the period from the end of the QRS complex (J) to the beginning of the T wave on electrocardiogram) depressions and T-wave inversions at the late stage (14). Fabry disease is often associated with P-R interval shortening, QRS (the QRS complex reflects the changes of left- and right-ventricular depolarization potential and time) interval prolongation, positive Sokolow Lyon index, pseudo-myocardial infarction pattern and repolarization dispersion (35). Cryptogenic ventricular ectopic beats are frequent (36). P-R interval shortening and first-degree atrioventricular block were found in 14% and 1.4% of Fabry disease patients, respectively (37). Electron microscopy of the myocardial biopsy of Fabry cardiomyopathy patients revealed the prominent involvement of cardiac conduction tissue, which was largely occupied by vacuoles (36).

Aortopathy

In patients with Fabry disease, inflammatory and neurohormonal mechanisms were identified in the vascular dysfunction predisposing to tissue ischaemia, hypertrophy and fibrosis (38). The echocardiographic evidence of aortic root dilatation was noted in 30%–56% of male patients with Fabry disease (14, 19, 33, 39). The aortic dilatation at the sinus of Valsalva was found in 32.7% of the male and 5.6% of the female patients; aneurysms were present in 9.6% of the male and 1.9% of the female patients (40). In the advanced stage, with progression of cardiac involvement and LV hypertrophy, marked aortic root dilatation could be seen (41). Additionally, a high prevalence of ascending aorta dilatation and aneurysms in the male patients with Fabry disease compared with the normal population was noted. Females with Fabry disease also developed dilatation of the sinus of Valsalva and ascending aorta, but with a significantly lower rate than males. The dilatation seemed to be independent of cardiovascular risk factors. The lower prevalence and delayed onset of aortic dilatation in the female patients was consistent with the previous arguments of milder female involvements (40).

Coronary artery disease

The true incidence of coronary heart disease in Fabry disease remains unclear, because cardiac catheterization is not routinely performed in such patients (13). Angina was frequent in 13%–23% of the Fabry disease patients, but myocardial infarction is uncommon (42, 43). According to the Fabry Outcome Survey database, the incidence of myocardial infarction was < 2% (13/752) in Fabry disease patients (14). The pathogenesis of angina might be coronary vasospasm due to endothelial infiltrates and dysfunction, decreased coronary reserve, and LV hypertrophy (14). A double-blind, randomized, placebo-controlled trial showed Gb3 deposits in the interstitial capillary endothelial cells in the myocardiocytes, which was considered to be the true mechanism of the coronary lesion in Fabry disease patients (44). There was electrocardiographic evidence of myocardial injury but no evidence of ischaemic myocardial damage (13). Elevated troponin I levels were noted in 46.2% of the patients with Fabry disease with angina pectoris

(13). Coronary and ventricular angiography revealed slow coronary flow and slow runoff of the contrast medium in normal coronary calibres in those presenting with angina (13). Revascularization of stenotic coronary arteries was required in < 1% of the Fabry disease patients (14). The post-mortem examination of the hearts of Fabry disease patients revealed accumulation of Gb3 in the lysosomes of the vascular endothelium in addition to marked accumulation of the major glycosphingolipid substrate Gb3 in the lysosomes of all the cardiac tissues (28).

Isolated cardiac variant

Although Fabry disease may involve many systems, including neurological, metabolic, gastrointestinal and renal, isolated cardiac variants have been described (45). This is because Gb3 deposit occurs almost exclusively in the heart in quite a number of patients (6, 46, 47). The isolated cardiac variant of Fabry disease was present in about 3% of male patients with LV hypertrophy (48). Significantly reduced plasma α-Gal activity, missense mutations in the α-Gal gene and low α-Gal mRNA amounts were noted in at least some of the patients (48).

Diagnosis

The protean clinical manifestations of Fabry disease often lead to delayed diagnosis for many years (49). A known familial history of Fabry disease may lead to an early diagnosis and prompt treatment (50). The diagnosis is primarily biochemical, based on determination of enzymatic activities in different biological tissues (such as plasma, leukocytes, fibroblasts and most recently dried blood spots on filter paper) (51), and on histological studies, i.e., a significant Gb3 deposit in the capillary endothelium of the skin (2). Prenatal diagnosis is possible by measuring the α-Gal A activity in the tissue or the fluid taken from around the foetus. This test may be offered to expectant mothers who have Fabry disease. Diagnosis through DNA testing to identify specific gene mutations is also an option (50). In female patients, α-Gal A mutation is more a reliable indicator than clinical symptoms or laboratory findings (2). The prominent papillary muscle that is positively correlated with LV wall thickness could be an echocardiographic marker for the detection of Fabry patients with concentric LV hypertrophy (52). Electrocardiogram is helpful in the diagnosis of not only the conduction of the abnormalities and arrhythmias, but also the diagnosis of LV hypertrophy by displaying a typical giant negative T wave in leads $V_{2\text{-}5}$ (35).

Treatment

Enzyme replacement therapy with agalsidase α (0.2 mg/kg body weight every 2 weeks); and agalsidase β (1 mg/kg every 2 weeks) has been administered to patients and proved to be effective in the LV structural and functional improvements (11, 53). symptomatic treatments include: analgesics, antihypertensives, antiplatelet agents and anticoagulants where indicated for patients with Fabry disease (54). Symptomatic bradycardia and atrioventricular conduction abnormalities frequently warrant pacemaker implantation. Implant indications included symptomatic bradycardia, non-sustained ventricular tachycardia, conduction abnormalities, palpitations and syncope (55). The patients with proven malignant arrhythmias may benefit from an implantable cardioverter-defibrillator (56).

Only 3/752 (0.4%) valvular disorders in Fabry disease required a surgical operation (14). Fernandez *et al* (57) reported a 59-year-old male patient with Fabry disease with severe mitral regurgitation by echocardiography. He received a successful mitral valve repair with a P_2 resection and ring annuloplasty via a right minthoracotomy. Choi *et al* (58) reported aortic mechanical valvular replacement and heart biopsy in a 31-year-old male patient during enzyme replacement therapy. The surgical indication for aortic valve replacement was a more thickened, severely degenerative aortic valve with severe aortic regurgitation. The histology of the aortic valve showed myxoid degeneration of the valve leaflets. Significant LV outflow tract obstruction caused by asymmetric hypertrophy can be cured by alcohol ablation, which may result in complete relief of the obstruction (59).

For the coronary lesions in Fabry disease, coronary angioplasty and coronary artery bypass might achieve less than satisfactory results. Marcì *et al* (60) reported a Fabry disease patient who had a recurrent angina two years after successful coronary angioplasty when the diagnosis of Fabry disease was overlooked. Chimenti *et al* (61) reported coronary artery bypass performed in a 54-year-old man with untreated Fabry disease. The man's left internal mammary artery graft was occluded while his saphenous vein grafts were patent at 1-year follow-up. They proposed that the vein graft might be free of glycosphingolipid accumulation due to low-pressure load. Septal alcohol ablation may be effective in patients with LV outflow tract obstruction. Kunkala *et al* (62) reported successful septal myectomy in two patients with Fabry disease. Their post-operative echocardiography revealed no or minimal residual LV outflow

tract obstruction and no systolic anterior motion of the mitral valve apparatus. Cardiac transplantation has been recommended and performed for end-stage cardiomyopathy secondary to Fabry disease (63, 64). Furthermore, patients with the advanced stages of heart disease, such as congestive heart failure, may be candidates for heart transplantation, as the intrinsic enzyme production within the graft could prevent its rapid deterioration (63). Concurrent heart and kidney transplantations were successfully performed in a Fabry disease patient who was complicated by end-stage renal disease and severe heart failure that responded poorly to enzyme replacement therapy (65).

Outcomes

The patients' prognoses with enzyme replacement therapy relied on the severity of baseline hypertrophy and fibrosis and on the timing of treatment (66). Plasma Gb3 declined by 50% after 10 weeks of treatment with agalsidase α (67). There was a significant reduction in LV mass, an improvement in myocardial function and a higher exercise capacity in comparison with the baselines (68). The histological analyses of the vascular endothelial cells in the patients receiving enzyme replacement therapy demonstrated intracellular Gb3 clearance following treatment (69). Pathological studies revealed cardiomyocyte Gb3 accumulation in baseline biopsies and clearance of Gb3 from cardiac capillaries after enzyme replacement therapy with recombinant human α-Gal A (44). Similarly, Hughes et al (70) discovered a significant decrease in the myocardial Gb3 content in myocardial biopsies and a remarkably, reduced LV mass as measured by magnetic resonance imaging after a 6-month treatment.

Despite the good early and mid-term results of the surgical intervention in Fabry disease patients with simultaneous enzyme replacement therapy, ongoing follow-up is imperative.

CONCLUSION

Cardiac involvements, typically LV hypertrophy, are frequent in Fabry disease. The protean clinical manifestations often lead to delayed diagnosis. The diagnosis is primarily based on laboratory testing for the determination of enzymatic activities or histological studies. Enzyme replacement therapy with agalsidases α or β is effective for Fabry disease. Very few patients with cardiac involvements warrant cardiac surgical procedures.

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