Cardiac Involvement in Anderson-Fabry Disease

CHRISTOPH KAMPMANN, FRANK BAEHNER, MARKUS RIES, and MICHAEL BECK

Division of Cardiology and Division of Lysosomal Storage Diseases, University Children’s Hospital, Mainz, Germany.

Anderson-Fabry disease results from hereditary deficiency of the lysosomal enzyme α-galactosidase A. This disease is marked by progressive intracellular accumulation of globotriaosylceramide (Gb₃) and digalactosylceramide, the major glycosphingolipid substrates of α-galactosidase A. Many cell types are affected, including renal epithelial cells, myocardial cells and neuronal cells, endothelial cells, pericytes, and vascular smooth muscle cells (1). Cardiac involvement in Anderson-Fabry disease (AFD) is frequent, due to structural and functional changes related to glycosphingolipid deposition in the myocardium, valves, and conduction system. Deposition of Gb₃ in the heart is similar to deposition in other organs (2). It may be found in all cardiac tissues, with the greatest concentrations occurring in the left ventricular myocardium, the mitral valve, and the left atrium. In contrast, increased deposition of digalactosylceramide was found only in the lungs and right heart tissues (3). Accumulation of Gb₃ in the heart leads to an increase in ventricular wall thickness, mitral valve prolapse (4), and electrocardiographic abnormalities, including various degrees of atrioventricular conduction block, tachyarrhythmias, and ST-segment/T-wave abnormalities (5). Rarely, in the so-called “cardiac-variant,” cardiomyopathy is the principle manifestation of AFD (6).

Little is known about the timing of onset of cardiac involvement or its progression relative to other end-organ manifestations of AFD. This may be the result of the heterogeneous clinical symptoms leading to delayed diagnosis and because of uncertainty regarding the true incidence of the cardiac variant of AFD, which was mostly diagnosed by postmortem examinations. Indeed, AFD may account for up to 3% of men with hypertrophic cardiomyopathies, suggesting that the cardiac variant may be more common than previously thought (7).

Clinical manifestations of AFD have been reported in female heterozygotes, but these complications were felt to be uncommon and usually mild. For example, it has been estimated that severe manifestations occur in only approximately 1% of female carriers (8). In a recent study however, 12% of patients with AFD being treated with dialysis in the United States were female (9) (See Obrador et al. in this issue). Furthermore, pedigree examination in female carriers suggested that cardiac involvement by AFD was more frequent than previously expected. Of 21 carriers investigated by a questionnaire, 19% had left ventricular hypertrophy: 48% from valvular disease and 33% from arrhythmias (10). By comparison, 88% of hemizygous males had left ventricular hypertrophy, and 29% had valvular disease (11). In our own patient population of 20 heterozygous females, 55% had cardiomyopathy and 60% had electrocardiographic abnormalities (12). Although there are gender-related differences, cardiac involvement by AFD appears to increase with age in both hemizygotes and heterozygotes, and thus careful monitoring for cardiac disease in patients of both genders is warranted.

Cardiomyopathy

Early echocardiographic studies of AFD patients revealed increased left ventricular wall thickness, which was confirmed by magnetic resonance imaging (4,13). The presence of left ventricular hypertrophy, along with coexistent valvular changes, correlate with the severity of AFD (14). The increased wall thickness can be so marked that it may mimic hypertrophic cardiomyopathy (15). The left ventricular hypertrophy is, however, usually not associated with significant systolic or restrictive diastolic dysfunction. In later stages of hypertrophic disease, decreased left ventricular end-diastolic volume leads to progressive impairment of diastolic filling, resulting in reduced stroke volume and cardiac output and, therefore, to prerenal failure. Although prerenal failure may aggravate renal insufficiency, arterial hypertension will lead to a further increase in left ventricular mass.

The mechanism and pattern of cardiac hypertrophy in AFD is different from that seen in hypertensive cardiomyopathy or other forms of infiltrative cardiomyopathies. For example, among patients with cardiac amyloidosis, extensive interstitial infiltration is encountered, whereas in AFD, infiltration is caused by intracellular lysosomal deposits of Gb₃. Furthermore, in AFD patients with cardiac involvement there is electrocardiographic evidence of left ventricular hypertrophy marked by increased voltage, whereas low voltage is common in patients with other infiltrative cardiomyopathies (16). Of note, electrocardiographic voltage criteria for hypertrophy correlates with left ventricular mass assessed by echocardiography in AFD patients.

Importantly, lysosomal deposits represent only approximately 1% of the increase in left ventricular mass (11 mg/g wet weight) in AFD (17,18), suggesting that additional mechanisms, such as an absolute increase in contractile proteins,

Correspondence to Dr. Christoph Kampmann, Universitätskinderklinik Johannes Gutenberg Universität, Langenbeckstr. 1, D-55131 Mainz, Germany. Phone: +49-6131-177328; Fax: +49-6131-17477328; E-mail: christoph.kampmann@uni-mainz.de

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myocyte volume, and thereby in left ventricular muscle mass, might contribute to left ventricular hypertrophy. The underlying mechanism for such a trophic reaction of the myocardium as a “reactive” increase in muscle mass is unknown. One potential mechanism could be disruption of myocardial architecture by the deposited lipid leading to myocyte disarray. Neurohumoral factors such as increased plasma endothelin-1 levels also may contribute (19). Increased muscle mass rather than myocardial interstitial infiltration may explain the absence of restrictive filling patterns.

Valvular Disease

Valvular changes in AFD are believed to be caused by lipid deposition and fibrosis of valvular tissue (20). However, estimates of the incidence of valvular involvement in AFD differ significantly. Many authors have suggested, that there is a high frequency of mitral valve prolapse (4,21), but a recent report did not confirm these findings (14). Nevertheless, minor structural abnormalities on both mitral and aortic valves are frequent. Mitral valve thickening or prolapse are seen in younger patients, whereas aortic valve and aortic root abnormalities typically appear in older patients. Most of the patients with mitral valve abnormalities have thickened papillary muscles, accompanied by mild valvular regurgitation. In the advanced stage with progression of the cardiac involvement and left ventricular hypertrophy, there can be marked aortic root dilatation (4,13,14). There are no differences in the incidence of valvular changes among hemizygotes and heterozygotes; both genders are affected equally. Severe valvular disease requiring surgical treatment is rare.

Conduction System Disease

In addition to accumulation of Gb\textsubscript{3} in the myocardium and valves, deposits have been noted throughout the conduction system (22–24). This accumulation predisposes to both tachy- and bradyarrhythmias. For example, patients exhibit increased susceptibility to supraventricular tachycardias, complete heart block, premature ventricular beats, and in later stages, prolongation of the QRS complex (with or without a right or left bundle branch block morphology) may also be seen (24). Arrhythmias are implicated in the development of cardiac symptoms. For example, atrial fibrillation in association with diastolic left ventricular dysfunction can rapidly aggravate signs and symptoms of congestive heart failure.

Coronary Artery Disease

More than 50% of hemizygotes and heterozygotes complain of anginal chest pain (10,11). In many patients, there is electrocardiographic evidence of myocardial injury but no evidence of ischemic myocardial damage (20,24). Endothelial dysfunction may also play a major role in the development of these symptoms, as endothelial cells from cardiac capillaries are heavily infiltrated. Endothelial dysfunction may be related to coronary vasospasm. An additional cause of angina is decreased coronary reserve associated with left ventricular hypertrophy (14). When fixed coronary stenoses due to atherosclerosis occur, they are aggravated by dyslipidemia and hypertension, which frequently accompany chronic renal disease.

There are case reports of patients with AFD who required coronary revascularization. In our population of more than 100 patients with AFD, however, only one 56-yr-old female required coronary revascularization. This patient also had severe hypertrophic cardiomyopathy, smoked approximately 35 cigarettes per day, and had clinical evidence of myocardial infarction. Furthermore, of the three males older than 45 yr, each of whom were smokers with evidence of cardiomyopathy and valvular disease, who underwent cardiac catheterization, none had angiographically detectable coronary artery disease, although two complained of chest pain. Cardiac catheterization is not routinely performed in patients with AFD; therefore, the true incidence of large vessel coronary artery disease remains unclear. Likewise, whether there is a higher incidence of coronary disease among AFD patients compared with age-matched controls is unknown.

Therapy

In recent years, novel therapies for patients with AFD have been developed and are now available. These therapies could have significant impact on the cardiac manifestations of AFD. For example, a case of a patient with the cardiac variant of AFD who was treated with galactose infusion has been published. Galactose is a competitive inhibitor of α-galactosidase A, which increases or stabilizes residual enzyme activity (25). The patient improved, demonstrating decreased left ventricular mass, improved cardiac function, and diminished premature ventricular beats. The long-term benefits of galactose infusions remain to be determined.

Enzyme replacement therapy in AFD is now possible through the use of recombinant human α-galactosidase A enzymes. Two different enzyme preparations are available: Replagal (Transkaryotic Therapies, Cambridge, MA) made in human cells and Fabrazyme (Genzyme, Cambridge, MA) made in Chinese hamster ovary cells. These agents have been studied in two enzyme replacement trials of hemizygous males. In the study of Fabrazyme conducted by Mount Sinai (26), there was a significant reduction in endothelial deposits of Gb\textsubscript{3} in cardiac biopsy specimens after 20 wk of treatment. However, in that same study, there were no significant changes in echo- or electrocardiograms compared with baseline. In the Replagal study conducted at the National Institutes of Health (1), there was a statistically significant improvement in intraventricular conduction as measured by a decrease in an abnormally prolonged QRS complex duration after 24 wk of treatment. In two other Replagal studies, a significant decrease in cardiac mass was associated with therapy (27). Further investigation is needed to understand the long-term cardiac effects of treatment of AFD. The development of potentially effective therapies calls for additional systematic study of the natural history of cardiac disease in both heterozygotes and hemizygotes with AFD so that appropriate early therapeutic intervention may be possible in the future. Finally, when a nephrologist is confronted with a patient with AFD and kidney disease, coexisting cardiac disease should be excluded.
References