Fabry Disease
A Rare Condition Emerging From the Darkness

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Fabry (or Anderson–Fabry) disease—first described in 1898 by Johannes Fabry in Germany and William Anderson in England—is a lysosomal storage disease caused by mutations in the *GLA* gene located on the X chromosome (Xq22.1).[1] These cause deficiency of the enzyme aGal A (alpha galactosidase A) and the accumulation of glycosphingolipids, particularly globotriaosylceramide, in different cell types. Over 800 individual missense or nonsense point mutations, splicing mutations, deletions, and insertions are reported, the majority of which render the aGal A enzyme nonfunctional.[2] Some variants are associated with residual aGal A activity (typically 2%–20% of normal values) that results in attenuated forms of the disease. Although Fabry disease (FD) is an X–linked trait, women with *GLA* mutations can develop signs and symptoms of FD, which are usually milder than seen in affected men but cases of severe disease are well recognized, possibly as the result of skewed X chromosome inactivation.[3]

See Article by Adalsteinsdottir et al

In this edition of the journal, Adalsteinsdottir et al[4] describe the clinical phenotypes of 2 families—identified during genetic screening of Icelandic patients with a clinical diagnosis of hypertrophic cardiomyopathy. One family had severe enzyme deficiency associated with childhood onset and systemic symptoms, and the other had an attenuated form characterized by higher residual enzyme activity, later disease onset, and predominantly cardiac manifestations. Because all men >30 years of age had left ventricular (LV) hypertrophy, the authors conclude that cardiovascular disease occurs at similar ages, despite markedly different α-Gal A activities.

It has become the convention to divide FD into classical and nonclassical phenotypes.[1] Classical FD is characterized by childhood onset of neuropathic pain, gastrointestinal disturbance, cornea verticillata, and cutaneous angiokeratomata. In later decades of life, patients with classical disease develop cardiac disease, progressive renal failure, and stroke. In contrast, nonclassical FD is characterized by a more variable disease course in which patients are generally less severely affected with the exception of cardiac disease, which is often the sole manifestation. Individuals with this nonclassical presentation are often diagnosed incidentally after genetic or enzymatic screening of patients with ventricular hypertrophy.

In general, the findings in the study by Adalsteinsdottir et al[5] are broadly in line with those reported in much larger cohort studies. LV hypertrophy, arrhythmia, angina, and dyspnea are reported in ≈40% to 60% of patients with FD. Cardiac arrhythmias (atrioventricular block, atrial fibrillation, and ventricular arrhythmia) are common in patients with moderate-to-severe cardiac involvement and may be the cause of premature mortality.[6] As patients age, they often develop progressive myocardial fibrosis with a predilection for the posterior-lateral LV wall, which, in advanced disease, contributes to LV aneurysm formation and systolic impairment.[7]

The study by Adalsteinsdottir et al is at variance with the literature in 2 aspects. One is the apparently high incidence of asymmetrical patterns of LV hypertrophy, which are more typically seen in patients with mutations in cardiac sarcomeric protein genes. This observation has been reported previously,[8] but it is important to consider that the asymmetry may result from thinning of the posterior LV wall as a consequence of the characteristic pattern of scarring in FD. The practice point is to incorporate all aspects of the phenotype when considering differential diagnosis rather than a single parameter, such as LV wall thickness.

The second, and more important issue, concerns the natural history of heart disease in classical and nonclassical disease. This study is too small to address this point, but the question has been examined in larger cohort studies. In a recent multicenter study, sex, phenotype, and plasma lysoGb3 (the deacylated derivative of lysoglobotriaosylceramide) concentrations were all strongly associated with the rate of clinical events and the extent of cardiac, renal, and cerebral involvement (Figure).[9] Men with classical FD had an increased risk of developing complications and more severe cardiac and renal disease. Women with classical FD had a higher risk of developing complications compared with women with nonclassical FD. As observed in other studies, some women developed cardiac fibrosis in the absence of LV hypertrophy for reasons that as yet are unknown.

When studying patients with a rare disease, factors such as study design, sample size, patient characteristics, and disease severity must all be considered when drawing general conclusions about natural history and by inference treatment goals. This is particularly true of a phenotypically diverse

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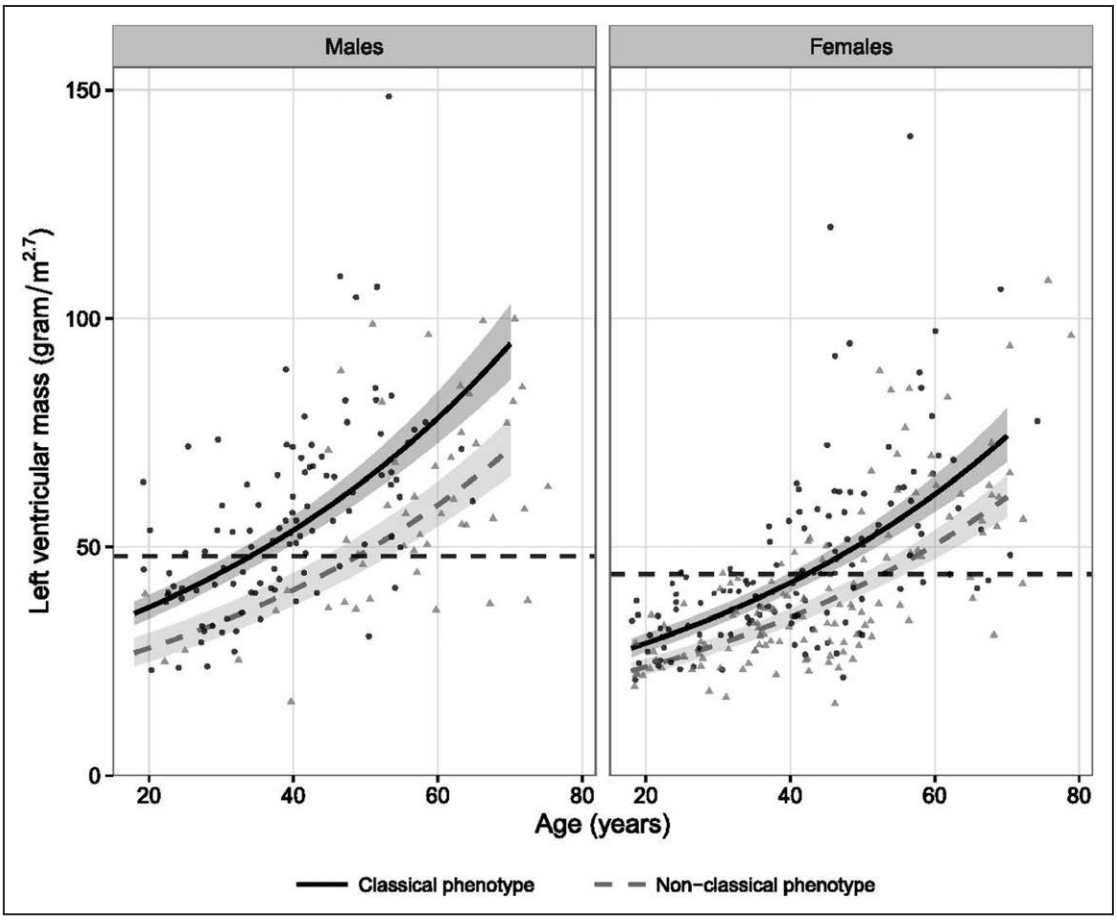

Figure. Log–linear regression curve of left ventricular mass measured by echocardiography corrected for height (meters$^{2.7}$). Shaded areas represent the 95% confidence intervals for the fitted curves. The dashed horizontal lines represent the upper reference limits (men, 48 g/m$^{2.7}$; women, 44 g/m$^{2.7}$). Black dots represent patients with classical Fabry disease (FD), and gray triangles represent patients with non-classical FD. Patients with classical phenotypes have earlier onset and more severe disease. Reprinted from Arends et al[9] with permission of the publisher. Copyright © 2017. Authorization for this adaptation has been obtained both from the owner of the copyright in the original work and from the owner of copyright in the translation or adaptation.

inherited disorder like FD, where it is increasingly recognized that subpopulations require tailored management and strategies.

Disclosures

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