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 alpha galactosidase A (aGal A) and the accumulation of glycosphingolipids, particularly globotriaosylceramide (Gb3), 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 non-functional [2]. Some variants are associated with residual aGal A activity (typically 2 to 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 recognised, possibly as the result of skewed X chromosome inactivation [3].

In this edition of the journal, Adalsteinsdottir and colleagues describe the clinical phenotypes of two families—identified during genetic screening of Icelandic patients with a clinical diagnosis of hypertrophic cardiomyopathy [4]. One family had severe enzyme deficiency associated with childhood onset and systemic symptoms and the other had an attenuated form characterised by higher residual enzyme activity, later disease onset and predominantly cardiac manifestations. As all males over 30 years of age had left ventricular 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 non-classical phenotypes [1]. Classical FD is characterised 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, non-classical 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 non-classical presentation are often diagnosed incidentally following genetic or enzymatic screening of patients with ventricular hypertrophy.
In general, the findings in the study by Adalsteinsdottir et al are broadly in line with those reported in much larger cohort studies. Left ventricular hypertrophy, arrhythmia, angina and dyspnea are reported in approximately 40-60% of patients with FD [5]. Cardiac arrhythmias (AV 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 left ventricular wall which, in advanced disease, contributes to LV aneurysm formation and systolic impairment [7].

The study by Adalsteinsdottir and colleagues is at variance with the literature in two aspects. One is the apparently high incidence of asymmetric patterns of left ventricular 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 left ventricular 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 left ventricular wall thickness.

The second, and more important issue, concerns the natural history of heart disease in classical and non-classical disease. This study is too small to address this point, but the question has been examined in larger cohort studies. In a recent multicentre study, sex, phenotype, and plasma lysoGb3 (the deacylated derivative of Gb3) concentrations were all strongly associated with the rate of clinical events and the extent of cardiac, renal, and cerebral involvement [9], figure 1. 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 non-classical FD. As observed in other studies, some women developed cardiac fibrosis in the absence of left ventricular 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 inherited disorder like FD, where it is increasingly recognised that sub-populations require tailored management and strategies.

References

1. Germain DP. Fabry Disease Orphanet Journal of Rare Diseases 2010, 5:30


Figure Legend

Log–linear regression curve of the LVM measured by echocardiography corrected for height (meters$^2$). Shaded areas represent the 95% CIs for the fitted curves. The dashed horizontal lines represent the upper reference limits (men: 48 g/m$^2$; women: 44 g/m$^2$). Black dots represent patients with classical FD, and gray triangles represent patients with nonclassical FD. Patients with classical phenotypes have earlier onset and more severe disease.

From reference 9 Arends et al.