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Later Onset Fabry Disease, Cardiac Damage Progress in Silence

Experience With a Highly Prevalent Mutation

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ABSTRACT

BACKGROUND Recently, several studies revealed a much higher prevalence of later onset Fabry disease (FD) than previously expected. It suggested that later onset FD might present as an important hidden health issue in certain ethnic or demographic populations in the world. However, the natural history of its phenotype has not been systemically investigated, especially the cardiac involvement.

OBJECTIVES The study analyzed a large-scale newborn screening program for FD to understand the natural course of later onset FD.

METHODS To date, 916,383 newborns have been screened for FD in Taiwan, including more than 1,200 individuals with the common, later onset IVS4+919G>A (IVS4) mutation. Echocardiography was performed in 620 adults with the IVS4 mutation to analyze the prevalence of left ventricular hypertrophy (LVH), and gadolinium-enhanced cardiac magnetic resonance imaging was performed in 129 patients with FD, including 100 IVS4 adults.

RESULTS LVH was observed in 67% of men and 32% of women older than 40 years. Imaging evidenced significant late gadolinium enhancement in 38.1% of IVS4 men and 16.7% of IVS4 women with the IVS4 mutation but without LVH. Seventeen patients underwent endomyocardial biopsies, which revealed significant globotriaosylceramide substrate accumulation in their cardiomyocytes.

CONCLUSIONS Significant cardiomyocyte substrate accumulation in IVS4 patients led to severe and irreversible cardiac fibrosis before development of LVH or other significant cardiac manifestations. Thus, it might be too late to start enzyme replacement therapy after the occurrence of LVH or other significant cardiac manifestations in patients with later onset FD. This study also indicated the importance of newborn screening for early detection of the insidious, ongoing, irreversible cardiac damage in patients with later onset FD. (J Am Coll Cardiol 2016;68:2554–63)

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Fabry disease (FD), an X-linked lysosomal storage disorder (MIM 301500), results from mutations in the α-galactosidase A gene (*GLA*) that cause deficient α-galactosidase A (α-Gal A) activity and the progressive systematic accumulation of globotriaosylceramide (Gb3) and related glycosphingolipids, particularly in lysosomes of the heart, kidneys, skin, and brain.

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The disease has 2 major phenotypes, the classic (type 1) and the later onset (type 2) subtypes (1–5). On the basis of recent newborn screening studies, the incidence of patients with the later onset phenotype is much higher than that of the classic phenotype (6–12). Affected boys with the type 1 classic phenotype have little or no α-Gal A activity and have onset of acroparesthesias, hypohidrosis, angiokeratomas, or a characteristic corneal dystrophy in childhood or adolescence (13). As they age, affected men with the type 1 phenotype develop progressive multisystemic involvement leading to renal failure, hypertrophic cardiomyopathy (HCM), or cerebrovascular disease (1). Men with the type 2 later onset phenotype have residual α-Gal A activity, little or no vascular endothelial Gb3 accumulation, and lack of the early clinical manifestations of patients with the type 1 phenotype (1–3,14). However, type 2 men develop severe cardiac disease or renal failure in the fourth to seventh decades of life (1–3,14). Of interest, and without a current explanation, the type 2 phenotype tends to have mutation-specific cardiac or kidney involvement, although some men develop both with age (15).

Here, we report the findings in patients with the type 2 mutation IVS4+919G>A (IVS4) that primarily presents with progressive cardiac involvement, leading to HCM and eventual heart failure. In Taiwan, we initiated newborn screening for FD, and found the IVS4 mutation was unusually frequent, occurring in about 1 in 1,600 boys (7). As of December 2015, more than 1,200 individuals with the IVS4 mutation had been identified at our center.

The natural course of the type 2 phenotype with primary cardiac disease is largely unknown, but understanding the early signs of cardiac involvement is relevant to determining when to initiate enzyme replacement therapy (ERT) to improve the cardiac outcome. Moreover, there are no well-established treatment guidelines for type 2 cardiac patients. In Taiwan, ERT can be initiated only after presence of HCM or significant cardiac impairment. However, recent studies revealed that for long-term improvement in myocardial morphology and function, ERT should be initiated before myocardial fibrosis has developed (16,17). To further our understanding of the pathogenesis of the type 2 cardiac phenotype and to update treatment guidelines, we used gadolinium-enhanced cardiac magnetic resonance (GE-CMR) imaging to investigate the development of myocardial fibrosis in patients with or without cardiac hypertrophy.

ABBREVIATIONS AND ACRONYMS

CAD = coronary artery disease
ERT = enzyme replacement therapy
FD = Fabry disease
Gal A = galactosidase A
Gb3 = globotriaosylceramide
GE-CMR = gadolinium-enhanced cardiac magnetic resonance
GLA = α-galactosidase A gene
HCM = hypertrophic cardiomyopathy
IVS4 = IVS4+919G>A
LGE = late gadolinium enhancement
LVH = left ventricular hypertrophy
LVM = left ventricular mass
LVMI = left ventricular mass index

METHODS

The methodology and results of the newborn screening program for FD in Taiwan have been previously described (7,18). From January 1, 2008, to December 31, 2015, a total of 916,383 newborns were screened.

Since 2008, 620 adults with the IVS4 mutation—identified through screening the families of newborns with the IVS4 mutation—were enrolled in this study. All participants were examined by 2 experienced cardiologists who were blind to those with a *GLA* mutation. Echocardiography was performed in accord with the recommendations of the American Society of Echocardiography using ACUSON equipment (Antares, Siemens AG, Munich, Germany; Sono 7500, Hewlett-Packard Company, Palo Alto, California). Left ventricular mass (LVM) was calculated according to the Devereux cube formula (19). LVM was normalized to height (m) to 2.7 power (left ventricular mass index [LVMI] = LVM/height$^{2.7}$) (20). Left ventricular hypertrophy (LVH) was defined as LVMI >51 g/m$^{2.7}$ in men and LVMI >48 g/m$^{2.7}$ in women (21).

Since 2010, a total of 129 patients with FD have been enrolled in GE-CMR studies (57.4% men; 54.0 ± 12.3 years of age, range 19 to 83 years of age). There were 100 IVS4 patients (64 men), 22 type 1 patients (5 men), and 7 type 2 patients with primarily renal involvement (5 men). All of the IVS4 participants

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