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Fabry disease: Review and experience during newborn screening

Ting-Rong Hsu, M.D., Ph.D[a,b], *and Dau-Ming Niu, M.D., Ph.D*[a,b,*]

[a]*Department of Pediatrics, Taipei Veterans General Hospital, Taipei, Taiwan*
[b]*Institute of Clinical Medicine and Faculty of Medicine, National Yang-Ming University, Taipei, Taiwan*

ABSTRACT

Fabry disease (FD) is an X-linked lysosomal storage disease and is the result of mutation in the α-Galactosidase A gene; such mutations cause a deficiency in α-Galactosidase A enzyme and an accumulation of glycosphingolipid in tissue. Affected males with classic FD have little or no enzyme activity and have an early onset of symptoms and signs, including acroparesthesias, hypohidrosis, angiokeratomas, gastrointestinal dysfunction and/or a characteristic corneal dystrophy during childhood/adolescence. Males with late-onset FD who have residual enzyme activity develop progressive multi-systemic involvement that leads to renal failure and hypertrophic cardiomyopathy, as well as cerebrovascular disease; these events mostly occur during the fourth to seventh decades of life. Heterozygous females can develop vital organ damage that in turn causes severe morbidity and mortality; these symptoms may be as severe as those in affected males.

For the treatable disease, this review aims to raise awareness of early recognition and further management of FD based on newborn screening. As newborn screening for FD has been implemented worldwide, it allows the early detection of individuals with Fabry mutations. Based on screening studies, the prevalence of the later-onset type FD is much higher than that of classical type FD. Newborn screening studies have also revealed that patients with FD may develop insidious but ongoing irreversible organ damage. The timing of enzyme replacement therapy, which is able to stabilize the progression of disease, is important in order to prevent irreversible organ damage. Therapies that may become available in the future include pharmacological chaperones and substrate reduction therapy, both of which are still under investigation as ways of improving the health of individuals with FD.

Key words: Fabry disease, Newborn screening, Cardiomyopathy, Enzyme replacement therapy.

Introduction

Fabry disease (FD, MIM 301500), which is sometimes referred to as Anderson–Fabry disease, was first described in 1898 by two physicians, doctors Johannes Fabry and William Anderson. It was recognized early as a systemic vascular disease and later as a lipid storage disease. FD, an X-linked disorder, results from mutations in the α-Galactosidase A gene (*GLA*) that cause a deficiency in α-Galactosidase A enzyme activity; this results in the progressive systematic accumulation of globotriaosylceramide (Gb3) and related glycosphingolipids in a variety of different cell types. This continuous deposition starts as early as during the fetal stage of development and leads to the significant later cellular dysfunction and organ damage [1].

FD has been suggested to form two major phenotypes: the "classic" and the "later-onset" subtypes. The classical phenotype FD individuals have little or no residual enzyme activity and there is onset of acroparesthesias, hypohidrosis, angiokeratomas, and/or a characteristic corneal dystrophy during

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*Corresponding author at: Department of Pediatrics, Taipei Veterans General Hospital, No. 201, Section 2, Shih-Pai Road, Taipei 112, Taiwan. Tel./fax: +886-2-28767181.
E-mail address: dmniu1111@yahoo.com.tw (D.-M. Niu).

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childhood/adolescence. As they become older, affected males with the classic phenotype develop progressive multi-system involvement that results in renal failure, hypertrophic cardiomyopathy, and/or cerebrovascular disease [2]. Males with residual enzyme activities remain clinically asymptomatic during their first years of life. However, later as adults they develop progressive organ damage that includes end-stage renal disease, cardiovascular disorders, and/or cerebrovascular insult; these events largely occur during the fourth to seventh decades of life [3]. Interestingly, and without a current explanation, the later-onset phenotype tends to show mutation-specific cardiac or kidney involvement, although some males develop both phenotypes as they age.

FD shows X-linked inheritance and the clinical manifestations of the FD in heterozygous females range from being asymptomatic throughout a normal life span to as severe as many affected males, including severe morbidity and mortality [4]. This variation in the clinical manifestations of FD has been attributed to X-chromosome inactivation, which is random [5]. More severely affected females are more likely to have the X-chromosome with the *GLA* wild-type gene inactivated and the X-chromosome carrying the pathogenic variant remaining expressed in the affected organs. Most heterozygous females from families in which affected males have the classic phenotype have a milder clinical course and a better prognosis than affected males.

Epidemiology

FD is found in all races and regions throughout the world. Obtaining an accurate frequency for the diagnosis of FD is very difficult. Initially, the reported incidence was thought to be relatively low in the range from 1 in 476,000 to 1 in 117,000 of the general population. However, with the arrival of the large screening studies worldwide, the prevalence of FD has been found to be markedly higher than previously expected, with a rate of 1 in 3100 males being reported in northwestern Italy, 1 in 3000 males in Austria, 1 in 7800 males in Washington state (USA), 1 in 2900 males in Missouri (USA), and 1 in 1500 males in Taiwan [6,7]. However, most identified newborns are suspected to have the later-onset phenotype.

Newborn screening

The first pilot study related to newborn screening for FD was conducted in northern Italy [8]. In this study, the incidence of α-Gal A deficiency was high at 1/3100, and more than 90% of the identified newborns were suspected to have the later-onset phenotype. Thereafter, in Taiwan, our team found a surprisingly high incidence (approximately 1 in 1600 males) of a cardiac type *GLA* splicing mutation, IVS4 + 919G > A, in our newborn population and subsequently identified this mutation in a number of Chinese adult patients from Taiwan with idiopathic hypertrophic cardiomyopathy [7]. Furthermore, several other newborn screening centers have also started FD newborn screening and these groups have also revealed that the incidence of later-onset FD is much higher than previously expected. These findings indicate that later-onset FD could be a critical yet latent health issue in certain ethnic populations across the world.

Initially, lysosomal disease screening was performed by the fluorescence method using 4-methylumbelliferone (4-MU). In addition to the 4-U method, other technologies have also become available including immune-capture enzyme assays and tandem mass spectrometry (MS/MS). Our study has revealed that MS/MS is a more specific, powerful, and efficient tool than the 4-MU assay [9]. Furthermore, MS/MS is able to assay multiple lysosomal enzymes simultaneously in one single buffer. Recently, the U.S. Food and Drug Administration permitted marketing of a LSD Reagent Kit that is able to detect four lysosomal disorders, namely mucopolysarraridosis type I, Pompe disease, Gaucher disease, and FD.

As of July 2016, more than 916,000 newborns have been screened for FD by our team in Taiwan. However, by our own estimation, around 80% of female newborns are missed by our current enzyme-based screening approach. Nonetheless, a high percentage of heterozygous females may develop vital organ involvement, including the kidneys, heart and/or brain, and even females with normal plasma enzyme activity may still present with severe manifestations of the disease that affect various organs [4]. Therefore, it is important to develop a more reliable method for the detection of females who are heterozygous for FD and this method needs to become part of the newborn screening for FD. In our previous study, two molecular high-throughput methods, high-resolution melting analysis, and Sequenom iPLEX (Agena iPLEX), were investigated as part of a screening study for FD heterozygous females. Currently, an Agena iPLEX platform is being used in our FB newborn screening of female newborns. Out of 54,791 female infants screened, we found that around 83% of female newborns, including 113 IVS4 + 919G > A and one 656 T > C, are likely to have been missed by the current enzyme-based newborn screening system (unpublished data). This result supports the proposal that gene-based newborn screening method is much more reliable when detecting heterozygous female newborns. The algorithm of newborn screening of FD in our hospital is shown in Fig. 1.

Our current study has revealed that insidious and irreversible organ damage is likely to be progressing silently among patients with FD. These findings highlight the importance of newborn screening for the early detection of insidious but ongoing irreversible organ damage in FD patients. Through a family study of identified newborns, not only are we able to find many more undiagnosed patients that are showing disease-onset, but we also are able to identify individuals carrying a pathogenic mutation but as yet are without disease involvement. With appropriate and careful follow-up so that early disease involvement can be detected, these patients will be able to receive early intervention, which should help to prevent severe and irreversible tissue damage. Overall, this will result in better treatment outcomes.

Some ethical issues have been addressed especially regarding the newborn screening of later-onset disease. The optimal time for screening later-onset disease is still controversial. There were even some reports of patients feeling that they were being labeled and overmedicated once they had a presymptomatic diagnosis. However, early recognition, early diagnosis, and early intervention are the golden strategies of