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Minireview

Fabry disease revisited: Management and treatment recommendations for adult patients

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ABSTRACT

Fabry disease is an X-linked lysosomal storage disorder caused by mutations in the *GLA* gene leading to deficient α-galactosidase A activity, glycosphingolipid accumulation, and life-threatening complications. Phenotypes vary from the "classic" phenotype, with pediatric onset and multi-organ involvement, to later-onset, a predominantly cardiac phenotype. Manifestations are diverse in female patients in part due to variations in residual enzyme activity and X chromosome inactivation patterns. Enzyme replacement therapy (ERT) and adjunctive treatments can provide significant clinical benefit. However, much of the current literature reports outcomes after late initiation of ERT, once substantial organ damage has already occurred. Updated monitoring and treatment guidelines for pediatric patients with Fabry disease have recently been published. Expert physician panels were convened to develop updated, specific guidelines for adult patients. Management of adult patients depends on 1) a personalized approach to care, reflecting the natural history of the specific disease phenotype; 2) comprehensive evaluation of disease involvement prior to ERT initiation; 3) early ERT initiation; 4) thorough routine monitoring for evidence of organ involvement in non-classic asymptomatic patients and response to therapy in treated patients; 5) use of adjuvant treatments for specific disease manifestations; and 6) management by an experienced multidisciplinary team.

1. Introduction

Fabry disease (OMIM 301500) is an X-linked lysosomal storage disorder caused by mutations in the *GLA* gene. Markedly reduced or absent activity of the enzyme α-galactosidase A (α-Gal A, EC 3.2.1.22) [1,2] results in progressive accumulation of glycolipids, primarily

Abbreviations: ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; AV, atrioventricular; α-Gal A, α-galactosidase A; CKD, chronic kidney disease; CNS, central nervous system; CT, computed tomography; DBS, dried blood spots; ECG, electrocardiography; eGFR, estimated glomerular filtration rate; ENT, ear, nose, and throat; ERT, enzyme replacement therapy; GFR, glomerular filtration rate; GI, gastrointestinal; GL-3, globotriaosylceramide; IENFD, intra-epidermal nerve fiber density; IgG, immunoglobulin G; IV, intravenous; LV, left ventricular; LVH, left ventricular hypertrophy; LVMI, left ventricular mass index; lyso-GL-3, globotriaosylsphingosine; MBD, metabolic bone disorder; MRI, magnetic resonance imaging; TIA, transient ischemic attack; TOF MRA, time-of-flight magnetic resonance angiography (head and neck); TRPV1, transient receptor potential vanilloid 1; VUS, variants of unclear significance

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globotriaosylceramide (GL-3, Gb_3) and its deacylated form, globotriaosylsphingosine (lyso-GL-3), in plasma and in a wide range of cells throughout the body. This includes those particularly relevant to disease pathology (e.g., vascular endothelial cells, podocytes, cardiomyocytes, arterial smooth muscle cells) and other cell types in the kidneys, nervous system, and other organs [1,2]. Currently, there are 15 years of clinical experience with enzyme replacement therapy (ERT) [3,4] for Fabry disease.

Fabry disease was initially described in male patients with a severe clinical phenotype, now known as "classic" Fabry disease [1,2]. These patients are characterized by absent or severely reduced (< 1% of mean normal) α-Gal A activity, marked GL-3 accumulation in vascular endothelial cells, cardiomyocytes, smooth muscle cells, and podocytes, and childhood or adolescent onset of symptoms followed by progressive multi-organ failure, and eventually death [1,2]. However, a larger group of patients has later-onset phenotypes with varying levels of residual α-Gal A activity, age of onset, and manifestations [2]. Newborn screening (NBS) studies revealed frequencies of the classic and later-onset phenotypes of up to 1 in 22,570 males and 1 in 1390 males, respectively [5]. The spectrum of disease severity in heterozygous female patients ranges from asymptomatic to a severe phenotype that resembles that observed in male patients with the classic phenotype and is in part dependent on the mutation and the X chromosome inactivation (Lyonization) profile [2,6–8]. Severe clinical manifestations have been reported in at least 43% of obligate carrier women [7,9,10]. Numerous *GLA* mutations have been reported [11–15] and efforts are underway to correlate *GLA* mutations with the major phenotypic subtypes [16].

The past decade has witnessed an increased understanding of the pathogenesis, natural history, and prevalence of Fabry disease, and the effectiveness and limitations of ERT. The advances have changed our approach to disease monitoring and therapeutic intervention, necessitating an appraisal and update of monitoring and treatment guidelines for the multisystemic involvement in adult patients with Fabry disease published in 2006 [17]. The present document complements specific documents that have addressed controversial areas (KDIGO [18]) or aspects of diagnosis and management usually focused around individual organs [19–28]. Furthermore, these updated recommendations underline the importance of early treatment initiation in both males and females, and stress the importance of patient-specific care and a multidisciplinary approach to disease management. Recommendations for the cessation of treatment have not been included here as the clinical consequences of treatment cessation, compared with ERT continuation, remain to be clarified [29].

The development of these recommendations was initiated in July 2014 at a meeting of an international panel of Fabry disease experts from seven subspecialties, including nephrology, cardiology, neurology, genetics, genetic counseling, pediatrics, and metabolic disorders convened in Atlanta, GA, USA, to review existing treatment guidelines for adults with Fabry disease [17]. Subsequent discussions were held during a panel meeting in February 2015 in Orlando, FL, USA. Treatment of pediatric patients was not part of the discussions; recommendations for the monitoring and management of pediatric/adolescent patients were being developed by a panel of experts in pediatric Fabry disease and have recently been published [30]. Based on these face-to-face panel discussions, an independent coordinator prepared a draft set of updated recommendations for clinical management of adult patients with Fabry disease. Each member of the panel amended the recommendations based on his/her long clinical experience and in-depth knowledge of the literature; therefore, no systematic review of the literature on clinical outcome was performed, and the recommendations were not graded. Several revision rounds were performed until a consensus was reached by all panelists, taking important newly published data and perspectives into account.

2. Disease manifestation

In classic Fabry disease, the first symptoms, including chronic neuropathic pain and episodic severe pain crises, typically emerge during childhood (Table 1). Symptoms such as hypohidrosis, skin abnormalities (angiokeratomas), gastrointestinal (GI) disturbances (bloating, diarrhea, abdominal pain), and a characteristic asymptomatic corneal opacity (cornea verticillata) are additional common early manifestations [1,2]. Occult kidney injury may occur at a young age, including albuminuria (a defining feature of chronic kidney disease [CKD]) and glomerulosclerosis [33,43,44]. Symptomatic organ complications typically emerge in young adult patients, including CKD progression to renal failure and left ventricular hypertrophy (LVH) associated with myocardial fibrosis and arrhythmias, auditory loss, transient ischemic attacks (TIAs), strokes, and eventually premature death [7,32,45–50]. Accumulation of GL-3 in cardiac tissues, as well as inflammatory and neurohormonal mechanisms leading to cardiac cellular and vascular dysfunction are likely contributors to cardiac manifestations [45]. Lung manifestations have been reported (e.g., dyspnea, wheezing, dry cough) [39]. In patients with the later-onset phenotype, typical cardiac symptoms (e.g., LVH, arrhythmia, abnormalities on cardiac magnetic resonance imaging [MRI]) and, exceptionally, decreased glomerular filtration rate (GFR) present in the fourth to seventh decades of life, reflecting delayed onset and slower disease progression [2,51,52]. The spectrum of disease in heterozygous female patients ranges from being asymptomatic or having mild, later-onset phenotypes that usually affect only a few or one organ(s) to the severe phenotype (as observed in male patients with the classic disease phenotype) [2,6–8]. Registry data provide evidence that cardiomyopathy and strokes are also common among female patients, and that female patients typically develop disease complications at older ages than male patients, although renal failure may manifest at a similar mean age [53,54] in female patients with a skewed X inactivation pattern and predominant expression of the mutant *GLA* allele [6,7,34,46–48,53,54]. More detailed descriptions of the clinical signs and symptoms of Fabry disease are provided in Table 1 and online Appendices A, B, C, D, and E (renal, cardiac, peripheral nervous system, central nervous system (CNS), and other organ systems, respectively).

3. Genetics

α-Gal A is a homodimeric glycoprotein encoded by the *GLA* gene which is located on the long arm of the X chromosome [1,2]. Numerous *GLA* mutations are currently reported in gene mutation databases [11–15] Missense, nonsense, consensus splice site, cryptic splicing, and frameshift mutations (small and large deletions and insertions) cause Fabry disease (Fig. 1). In general, nonsense, consensus splice site, and most frameshift mutations result in little or no α-Gal A enzyme activity, and are associated with the classic phenotype. In contrast, a proportion of the missense mutations and rare cryptic splicing mutations can encode enzymes with residual α-Gal A activity, which may explain the later-onset phenotypes. Except in the most recent publications [55], general registries and clinical studies have not stratified Fabry patients by genotype.

Random X chromosome inactivation occurs in heterozygous female patients, and prediction of their ultimate disease course is challenging. A largely skewed X chromosome inactivation pattern (reported in 29% of a female Fabry patient population in a recent study [6]), either preferentially expressing or suppressing the disease-causing Fabry mutation, significantly contributes to phenotypic variability, in addition to other factors [6]. Thus, heterozygous female patients who preferentially express the normally functioning *GLA* ("wild-type") allele will experience few, if any symptoms, while female patients who preferentially express the mutant *GLA* allele have a disease course which may mimic the male disease phenotype (either classic or later-onset), depending on the underlying *GLA* mutation in their family [2,6].