Significance of Cardiac Involvement in Fabry Disease

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Mini Review

Fabry Disease (FD) is a rare form of progressive genetic disorder, which results on damages to multi-organs especially cardio-renal system [1]. As for the genetic origin, FD is occurred due to the specific mutation of the GLA gene, which is routed on X Chromosome, where currently more than 800 types of different GLA mutations have been reported [1,2].

The accurate incidence and prevalence of Fabry disease has ranged between different populations from 1:336,000 in males (11) and 1:339,000 in female carriers in U.K. (12), and more common to 1:1,250 in males and 1:40,840 in females in Taiwan accordingly (13). As the true prevalent rates in females are still unknown, however due to the involvement of X-linked inheritance the female prevalence estimated at approximately 1:20,000 (14), which is twice folds to male incident rate on Fabry disease was expected in 1:40,000 in reported study (15).

Based on the genetic mutated forms, even a single-point mutation for GLA gene is pathogenic to develop the manifestation of Fabry Disease [3]. GLA mutation consequence the altered metabolism of specific glycosphingolipid known as Gb3, this will also cascade to glycolipid Gb3 accumulation in lysosomes of various cell types in organ systems including cardiac, renal, ophthalmology or nervous system, and dermatological blood vessel lining cells in complication [4-9], causing lysosomal α-Gal A enzyme deficiency in net effects of increase level of plasma degrading substance of lyso-GB3 [1,5,6,10-14].

Due to the complex relationship with their association with genotype and morphological features, the classical clinical presentation of Fabry disease varies within patients population with even identical gene mutation, which makes a simultaneous heterogeneity on multi-organ facets on clinical symptoms [1,15,16], where residual α-Gal A enzyme activity tend to resemble fewer symptomatic progressions as a slow progressive pathology [16,17].

One of the most commonly involvement vital organ as cardiac components is known to be the major source of the Fabry disease mortality and their co-morbidities [18]. Cardiac involvement of Fabry Disease is typically manifested by inflammatory nature of the late-stage complication of the organ damage, which lead by pathogenic oxidative stress, endothelial dysfunction, and multi-systematic inflammatory vasculopathy mimicking the tissue remodeling as fibrosis and sclerosis of cardiac tissue [19-22].

With debilitating inflammatory changes in cardiac tissue results predominantly in left ventricle of the cardiac chambers, which leads to increased oxidative stress could manifest hypertrophic cardiomyopathies from left ventricular dysfunction, left ventricular hypertrophy, and abnormalities of signal conduction system, and adjacent valve dysfunctions [22-26]. The cardiac manifestation is also accounted for almost 60% of all mortalities in Fabry disease population [27,23], whereas cerebrovascular complications such as stroke and TIA are also accounted in 21% and 25% of female/male FD in ratio [28].

The diagnosis of cardiac complications is assessed by cardiography methodology including ECG, Echocardiography, cardiac function test, and 24-hours Holter for accurate determination of disease extents [29]. With either symptoms indicative of FD or family member with known Fabry disease patients are also referred to biochemical and genetic tests, which segmented to males for measurement of plasma α-Gal A activity with urinary/plasma Gb3 or degradation product lyso-Gb3, accompanying with confirmatory GLA gene mutation by genetic
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analysis [29]. In females, due to the X-linked chromosome, genetic analysis and testing on GLA gene is essential methods to diagnose Fabry disease [29].

The important aspects on diagnosis of Fabry disease is based on the duration undertaken in prior to confirmatory findings on the genetic assessment which commonly lead to delays by the characteristic on symptomatic non-specificity and diverse presentation with less acknowledgement on disease state [27,29]. The average delay expected from first symptom presentation to diagnosis was reported in ranges from 12 years to 16 years, and even exceeding a long-term diagnostic delay more than 20 years were frequently seen with sequential consultations from multi-specialists including potential risks of differential or misdiagnosis [27,30]. In contrary to diagnostic delay, the quality of life in Fabry disease when early in life is significantly compromised with deteriorating consequences [31].

The treatment of Fabry disease requires a multi-disciplinary approach, which most essential treatment is the management of underlying enzyme deficiency by Enzyme Replace Therapy (ERT) such as Agalsidase alfa to slow the progression of the disease by their mechanism of action in supplement of exogenous enzyme intravenously to target lysosome via receptor-mediated endocytosis at cellular level with net effects of reduction of substrate amounts leading to inhibit glycosphingolipid synthesis [32,33]. ERT is also indicated as a long-term correction of enzyme deficiency of Fabry Disease with tolerance [33].

In combination to ERT, supportive treatment for specific cardiac symptoms are also adjuvant with Fabry disease, which the common treatments of ACE inhibitors, ARBs, anti-arrhythmics, diuretics, and Pacemaker at late cardiac complication are common treatments of ACE inhibitors, ARBs, anti-arrhythmics, cardiac symptoms are also adjuvant with Fabry disease, which the deficiency of Fabry Disease with tolerance [33].

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In combination to ERT, supportive treatment for specific cardiac symptoms are also adjuvant with Fabry disease, which the common treatments of ACE inhibitors, ARBs, anti-arrhythmics, diuretics, and Pacemaker at late cardiac complication are considered [34,35]. Thus, the principle of comprehensive management would be key to prevent the further organ damage and disease progression of Fabry disease, early involvements of multi-disciplinary contribution would enhance the patient’s long-term modalities and their further improvement in quality of life within rare condition on Fabry disease [1,34,35-39].

References


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