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The Role of Enzyme Replacement Therapy in Fabry Disease in Cardiology Perspective

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Fabry disease is a hereditary lysosomal storage disorder caused by the reduction or absence of lysosomal enzyme alpha-galactosidase A and the accumulation of glycosphingolipids, such as globotriaosylceramide (Gb3), in various organs, including the heart. The prevention of cardiac involvement in Fabry disease can only be achieved by enzyme replacement therapy (ERT), and the method of assessing the efficacy of ERT should be confirmed. Changes in the electrocardiogram, such as the shortening of PQ interval, prolongation of QTc and repolarization abnormalities as well as left ventricular hypertrophy in voltage criteria, can be used to identify Fabry disease patients; however, the usefulness of electrocardiograms for evaluating the efficacy of ERT is limited. The assessment of left ventricular hypertrophy using echocardiography has been established to evaluate the efficacy of ERT during long-term period. A new technique involving speckled tracking method might be useful for detecting early cardiac dysfunction and identifying the effect of ERT for a relatively short period. The estimation of left ventricular hypertrophy using cardiac magnetic resonance (CMR) is also useful for assessing the efficacy of ERT. Identifying late gadolinium enhancement in CMR may affect the effectiveness of ERT, and the new technique of T1 mapping might be useful for monitoring the accumulation of Gb3 during ERT. Histopathology in cardiac biopsy specimens is another potentially useful method for identifying the accumulation of GB3; however, the use of histopathology to evaluate of the efficacy of ERT is limited because of the invasive nature of an endomyocardial biopsy.

Keywords: Electrocardiogram, Echocardiography, Cardiac magnetic resonance, Histopathology

Introduction

Fabry disease is an inherited metabolic disorder caused by the reduction or absence of lysosomal enzyme alpha-galactosidase A and the accumulation of metabolic substrates, such as globotriaosylceramide (Gb3), in various organs[1]. Because the inheritance of the disease is X-chromosome linked, only male hemizygous patients develop typical Fabry disease; however, female heterozygous patients also have various symptoms[2]. Enzyme replacement therapy (ERT) has been used to treat Fabry patients since early in the 21st century[3]. Although ERT can be effective for various symptoms, such as acroparesthesias and hypohidrosis, the major targets of the long-term ERT should be the prevention of serious complications in the heart (left ventricular hypertrophy [LVH] and heart failure), kidney (progressive renal dysfunction) and brain (transient ischemic attack and stroke), which are the main determinants of morbidity and mortality in Fabry disease[4-6]. Among these complications, heart involvement is especially important because the most frequent cause of death in Fabry disease is cardiovascular abnormalities[7]. In this mini-review, I will focus on the role of ERT in Fabry disease from a cardiology perspective.

Electrocardiogram (ECG) and ERT

Changes in various parameters in ECGs have been reported in Fabry disease patients[8]. The shortening of the PQ interval, which might be due to glycolipid infiltration[9], is thought to be a specific finding in Fabry disease; however, it's incidence is as low as 40%[10,11]. Because the shortening of the PQ interval can occur

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due to a the prolongation of the P wave duration, the PQ interval minus the P wave duration in lead II (Pend-Q) might be a more specific marker, and this new definition can be used to identify cases of Fabry disease among other LVH diseases, including amyloidosis, aortic stenosis and hypertrophic cardiomyopathy[12]. In the advanced stage, conduction abnormalities, such as prolongation of the QTc and PQ interval, are also observed[8]. LVH detected by voltage criteria and/or repolarization abnormalities are also reported to be associated with LVH detected by echocardiography, although the sensitivity and specificity of the ECG criteria to define LVH are generally not very high[13]. The effect of ERT on these parameters in ECG has been diverse. Some reports have suggested that the ERT can improve abnormal ECG parameters[14,15], while other reports have revealed no significant changes in the ECG parameters[16,17]. One report suggested that an abnormal ECG finding (shortening of PQ interval, prolongation of QTc and repolarization abnormalities) at the time of treatment initiation is significantly associated with the progression of LVH[17].

Echocardiography and ERT

Echocardiography is the most useful non-invasive tool for evaluating the cardiac morphology and function. In Fabry disease, the progressive LVH is an important feature during the disease course, although diastolic and systolic dysfunction as well as mitral and aortic valve dysfunction are also observed at various stages of disease[18]. The left ventricular mass (LVM), which is usually used to evaluate LVH, is dependent on age, and the age-dependent progression of LVH is reported in both male and female Fabry patients[19,20]. One report clearly showed that most of male as well as female Fabry disease patients developed LVH at a relatively old age, although the progression of LVH appeared at an older age in female patients than in male patients[2]. Some studies have found that ERT prevented or ameliorated LVH in a relatively short period (within a few years)[14,21]. Recent reports on the effect of the long-term ERT (10 years) showed the initial improvement of LVH following slow increase in LVM[22,23]. A very recent report also showed the beneficial effects of long-term ERT (median 10 years) to prevent LVH progression in Fabry patients, although the initial improvement was not observed[20]. That study found that the effect of the long-term ERT were also observed in the patients with LVH prior to the initiation of ERT. There have been no reports of the recovery from systolic dysfunction in the advanced stage using ERT. However, one report using the speckled tracking method showed that short-term ERT was able to recover the global strain rate in patients without myocardial fibrosis as assessed using cardiac magnetic resonance (CMR), which indicated that early systolic dysfunction can be normalized by ERT[24]. However, this finding should be confirmed over a long-term course of ERT. Diastolic dysfunction can be resolved by ERT[16], but a number of different methods for assessing the diastolic function have been proposed, and this effect should also be evaluated over a long-term period.

Cardiac Magnetic Resonance (CMR) and ERT

Recent advances in CMR have made it possible to achieve a more accurate estimation of LVM than can be achieved with echocardiography. However, the follow-up period of ERT using CMR in Fabry disease patients is relatively short compared with reports using echocardiography. The amelioration or prevention of LVH by short-term ERT has also been reported in studies performing CMR evaluations[25,26]. Another important assessment using CMR involves using late gadolinium enhancement (LGE) to detect myocardial fibrosis, and the pattern of LGE in various myocardial diseases has been reported[27,28]. In Fabry disease, LGE is specifically observed at the postero-lateral area of the left ventricles, in which the regional wall motion abnormality can be started[29]. Gender differences in the appearance of LGE have also been reported, and female patients have a higher prevalence of LGE even without LVH as estimated by the left ventricular wall thickness[30]. Another study reported a similar tendency in the early detection of LGE in female patients with late-onset type Fabry disease[31]. LGE can be used to identify the early benefits of ERT in improving early systolic dysfunction as evaluated by speckled tracking echocardiography, as describe above[24]. However, the existence of LGE cannot be cleared by using ERT[32]. Recently, native T1 mapping in non-contrast CMR has been reported as an effective way of identifying Fabry patients among the patients with LVH[33]. This new modality may also be used to examine the efficacy of ERT in resolving the accumulation of Gb3 in the myocardium.

Histopathology and ERT

Histopathological examinations are an important tool for the diagnosis of Fabry disease[34,35]. Biopsy specimens from various organs, including the heart, kidney and skin, can be used to examine typical morphological changes (vacuolization on light microscopy and zebra body on electron microscopy) due to the accumulation of glycosphingolipids, such as Gb3[35]. The diagno-

sis of male Fabry patients can be made by measuring the alpha-galactosidase A activity in their white blood cells; however, the diagnosis of female Fabry patients cannot be achieved in this manner. Instead, a genetic mutation analysis of the gene encoding alpha-galactosidase A (GLA) is necessary for the definitive diagnosis especially for female patients. However, a genetic analysis may be difficult given the hereditary nature of the disease and may not be able to be performed for all the patients. In addition, the existence of a mutation in GLA cannot always confirm a diagnosis of Fabry disease; for example, functional polymorphisms such as the E66Q mutation have been reported[35]. Therefore, the additional information on histopathology can be very helpful for making a diagnosis of Fabry disease. Late-onset Fabry disease is difficult to diagnose because of the lack of typical symptoms observed in classical Fabry disease. Indeed, typical histopathological findings could help the identification of an atypical variant of Fabry disease (late-onset type)[34]. In Taiwan, the indications of ERT must be determined by the histopathological examination of an endomyocardial biopsy specimen in patients with an IVS4+919G>A mutation, which is commonly observed in late-onset Fabry disease in Taiwan[36]. A histopathological examination can also be used to assess the effects of ERT; however, the use of histopathology is limited because of the invasive nature of an endomyocardial biopsy[37]. The successful clearance of Gb3 from the kidney had been reported in the patients treated with ERT[38]. In cardiac tissue, the clearance of Gb3 by ERT has also been reported; however, it takes a relatively long time to remove Gb3, and the role of this clearance in improving the cardiac involvement is questionable[39].

Conclusion

It has been more than a decade since ERT was first made available to treat Fabry patients, and the long-term beneficial effects of ERT have been reported. Cardiac involvement in Fabry disease can be assessed by various methods, including new modalities, such as speckled tracking in echocardiography and T1 mapping in CMR. Therefore, the long-term efficacy of ERT should be evaluated using a combination of various methods.

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