Anderson-Fabry disease

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Anderson-Fabry disease: Worthy to in-SPECT the nerves?

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Anderson-Fabry disease (AFD) is an X-linked disease and fatal if left untreated. The pathophysiological hallmark of the disease is the accumulation of substrates, mainly globotriaosylceramide (GB3), due to a mutation in the gene encoding for the lysosomal enzyme alpha-galactosidase A. This accumulation and storage of GB3 involve all human cells, and the process starts in early fetal life. Several organs can be damaged, mainly the heart, kidneys, and nervous system. The link of sphingolipids accumulation to cardiac disease is not well understood but might be primarily attributed to not only the storage of sphingolipids but also the release of circulating toxic metabolites.[1] Patients carrying the mutation might be asymptomatic, while cellular and organ damage is taking place, and this process if undetected and treated will eventually lead to an irreversible stage once fibrosis develops. The prevalence of AFD had been previously underestimated and believed to affect 1:117,000 live births;[2] however, newer newborn screening initiatives suggested a much higher prevalence ratio of as high as 1:3900.[3,4]

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Cardiovascular complications in AFD patients are the leading cause of death.[5] Cardiac manifestations include, left ventricular hypertrophy (LVH), chronic inflammation, myocardial fibrosis, ischemic heart disease due to coronary microvascular disease, valve disease, functional impairment, and arrhythmia.[6] Arrhythmia is mainly a complication of LVH, and fibrosis and is the cause of the substantial increase in morbidity and reduced life expectancy.[5]

Myocardial fibrosis first is limited to the mid-myocardial layers of the basal posterolateral wall, then starts spreading to transmural fibrosis, [7] and it is a sign of disease progression and irreversibility. The typical finding in AFD cardiomyopathy is LVH which affects almost 50% of patients, and the development of hypertrophy is owed to an active growth-promoting factor identified in the plasma of AFD patients named sphingosine-1-phosphate (S1P), and in vitro S1P induces hypertrophy of the cardiomyocytes. In vivo, the plasma level of S1P correlates strongly with the left ventricular mass. Thus, it appears that S1P has a significant contribution to the development of cardiovascular remodeling due to its proliferative mechanism of action.[1] Interestingly, due to the X-linked genetic nature, in female patients, the spectrum of the disease is broad, ranging from mild-to-severe disease; the presentation is usually later in life, around a decade later than in male patients; and it might be present without hypertrophy,[8] which could be an indication that fibrosis is not solely a consequence of hypertrophy and emphasizes the need for targeting new and early phenotypic (imaging) markers.

Early diagnosis of AFD is critical due to the existence of treatment with specific enzyme replacement

therapy (ERT), and the lately approved in Europe the pharmacologic chaperone migalastat, which can be administered orally and works on stabilizing certain mutant enzymes and eventually, Migalastat allows the catabolism of substrate by the α-galactosidase.[9] ERT, however, does neither reverse fibrosis nor entirely reverse the established LVH; it is expensive, and is given intravenous once every 2 weeks. For its approval for administration, a patient needs to show some phenotypic markers that need to be as early as possible in the course of the disease. The initiation of treatment after fibrosis is established might not be beneficial, and this is of special importance in the late onset AFD.[10] The consequences of delayed diagnosis include failure to deliver adequate treatment, downstream multiple testing, and devastation to the patient, and to the healthcare system. Once heart failure develops, management would be medical therapy, and insertion of intracardiac defibrillation devices to prevent sudden cardiac death due to malignant arrhythmia is usually indicated.[11]

In the past few years, several diagnostic steps have been implemented for early diagnosis; multiple imaging techniques have come to be employed to identify the earliest signs of the disease, as described below:

Echocardiography is the most common imaging modality for screening for AFD due to its easy availability and cost, and when cardiac magnetic resonance imaging (CMRI) is contraindicated. Several parameters are addressed in an echocardiogram of patients with cardiac AFD: structure to identify LVH and specific feature of papillary muscle hypertrophy that potentially differentiates AFD from other hypertrophic diseases.[12] Assessment of both systolic and diastolic function, including the use of tissue doppler and speckle tracking echocardiography which allows the differentiation between active and passive movement of the myocardium, enabling evaluation of segments that cannot be visually assessed and thus providing a more reliable functional assessment. Global longitudinal strain (GLS) has a strong predictive value among well-known and established predictors of all-cause death in HF.[13] Studies have shown abnormal speckle tracking and strain imaging by echocardiography indicating impaired regional myocardial function despite normal ejection fraction. Therefore, these parameters will aid in the diagnosis of early occult systolic impairment. These regional abnormalities in AFD start at the basal segments of the posterolateral wall of the LV.[14,15]

CMRI is of special importance both in the diagnosis and the follow-up stages of patients with AFD. In the affected individuals with cardiac involvement, there is a myocyte replacement with fibrosis that is usually imaged by contrast enhancement of the intercellular space where Gadolinium accumulates due to slow distribution kinetics. Late gadolinium enhancement in the assessment of fibrosis is essential in staging of the disease and the follow-up response to treatment. Other sequences have been addressed and validated, such as native T1, T2, and T1 maps. T1 mapping has a high diagnostic value in myocardial involvement in systemic diseases and LVH; low T1 maps values are present in AFD patients, and this is likely attributed to the storage of GB3 in the myocytes.[16] Tissue tracking, strain, and strain rate by CMRI have emerged; however, they are still in use only for research purposes.

In the current issue of the journal, in a relatively small-sample-sized study, Spinelli, et al.,[17] describe nicely the use of a well-established, well-validated method for the detection of very early signs of cardiac involvement in AFD by means of 123I-metaiodobenzylguanidine (MIBG) against echo.

MIBG has been in use for decades in the evaluation of the integrity of the cardiac sympathetic innervations. This technique had been validated in cases of both ischemic and non-ischemic cardiomyopathy, hypertrophic cardiomyopathy, dilated cardiomyopathy, postcardiac transplantation, and cardiac amyloidosis.[18]

In this study, one would hope to see a breakthrough by demonstrating association between all myocardial segments with abnormal longitudinal strain on echo and denervation confirmed by MIBG; however, and as the authors emphasize, it seems that strain rate by echo might in fact precede the development of regional myocardial denervation. In this regard, limitations of imaging should be taken into account. The use of 2D speckle tracking is non-angle dependent and is only limited by image. Whereas, the nuclear imaging most important limitation in the current study is the exclusion of the inferior wall segments due to attenuation artifact, and therefore less reliable to assess. The results of the study were potentially affected by this, mainly because in the early appearance of AFD, the posterolateral wall is affected, and likely, we would have seen more denervated segments had the inferior wall been evaluated. Alternatively, the use of prone imaging or attenuation correction may have solved this obstacle. Most elegant, but most costly, is the application of the sympathetic innervation imaging with ^{11}C-mHED (*meta*Hydroxyephedrine) PET for optimal quantitation, and without the disadvantage of attenuation artifacts. Furthermore, 50% of the study population had LV hypertrophy, which is the hallmark of the disease, mainly in male patients. It would be worth investigating if this affects in particular the difference in the results between echo and MIBG, or is it applicable in all genders, including in all different phases of AFD?

Until we have that one specific test that provides the tools to confirm or rule out the diagnosis of AFD very

early in the course of the disease, prior to the development of LVH and fibrosis, the pleiotropic nature of the disease will still necessitate a comprehensive multidisciplinary, multimodality imaging approach for targeting the matched and mismatched morphological and functional abnormalities in AFD. Hybrid PET/MRI has also been used for the diagnosis of AFD. This technique is expected to better differentiate between patients with active inflammation versus scar, using FDG to facilitate the presence of inflammation and Gadolinium for the detection of fibrosis sand scar tissue.[19] Also, the combination with ^{11}C-mHED PET may clarify the autonomic cardiac function more accurately, by taking into account the different stages of AFD. We are convinced that multimodality imaging in cardiac AFD is needed; from early diagnosis to therapeutic targets, however, the place of nuclear imaging tests in the clinical care of Fabry patients still needs exploration.

Disclosure

S. Massalha has no conflict of interest. R.H.J.A. Slart has no conflict of interest.

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