New insights for early assessment of cardiac involvement in Anderson-Fabry disease

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Anderson-Fabry disease (AFD) is an X-linked recessive lysosomal storage disorder that is caused by the deficient activity of α -galactosidase A (α -Gal A)¹ with the resultant accumulation of globotriaosylceramide (Gb3) and related glycosphingolipids² in a variety of cells, including micro-vascular endothelial cells, renal tubular cells, and myocardial cells. In classically affected males, the progressive Gb3 accumulation leads to renal, cardiac, and cerebro-vascular manifestations and early death.³ Chronic renal failure represents the most frequent cause of morbidity, with cardiac involvement being the leading cause of death and premature mortality.⁴ It has been reported that the progressive accumulation of Gb3 in cardiomyocytes, cardiac valves, endothelial cells, and conduction system, leads to increased ventricular wall thickness and functional impairment,⁵ in addition to valvular and electrocardiographic abnormalities.⁶ The classic cardiac involvement is a form of hypertrophic cardiomyopathy, usually described as concentric left ventricular hypertrophy (LVH). The disease is progressive, with symptoms appearing with increasing age.

Myocardial fibrosis is generally considered a sign of disease progression, although it may also be present in female patients without LVH, suggesting that hypertrophy and fibrosis are not necessarily associated.⁷ Although the diagnosis of AFD is based on enzyme assay and genetic testing, there is an increasing need to identify potential phenotypic markers that can detect early cardiac involvement, preferably before the development of myocardial damage and fibrosis and potentially determine treatment response. Indeed, there

is agreement that early enzyme replacement therapy in pre-hypertrophic Fabry cardiomyopathy, prevents progression of the disease, strongly influencing life expectancy.

Conventional two-dimensional echocardiography is the standard imaging tool for identifying cardiac involvement in AFD but is not suitable to detect subtle myocardial dysfunction in the early course of the disease. Advanced echocardiographic techniques, including longitudinal strain, using speckle-tracking echocardiography, have recently been proposed as sensitive markers of myocardial deformation in patients with AFD, independently of the presence of LVH, as well in naïve AFD patients, mainly involving LV basal myocardial segments.⁸

Cardiac magnetic resonance (CMR) offers the unique possibility of measuring LV mass, dimensions, and wall thickness, together with a non-invasive tissue characterization for assessment of replacement fibrosis or inflammation. It has been largely demonstrated the usefulness of late-gadolinium enhancement (LGE) CMR technique, in the recognition of myocardial fibrosis in the setting of cardiac involvement of AFD disease.^{9–12} LGE occurs in up to 64% of patients with AFD, with the majority displaying LGE localized to the basal infero-lateral wall.^{13–16} Previous reports have also suggested that LGE in the context of normal mass is a phenomenon observed predominantly in women.¹⁷ T1 mapping is an additional and powerful diagnostic tool in AFD, that has been recently introduced in the diagnostic work up of these patients, to discriminate AFD from other causes of LVH.¹⁸ Pica et al.¹⁸ demonstrated that even in subjects without LVH, reduced myocardial T1 has a high prevalence and is associated with echocardiographic parameters of LV dysfunction, suggesting that a low T1 is detecting pre-hypertrophic or early cardiac involvement in AFD, as a consequence of the progressive Gb3

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storage in the myocardium¹⁹ and may be a starting criterion for early treatment.

Novel concepts that consider alternative molecular pathways linking Gb3 storage and fibrosis and integrated multimodality imaging using PET-MR acquisition have been shown to provide at the same time information on intra-myocardial fibrosis and areas of active myocardial inflammation in patients with AFD.²⁰ In particular, Spinelli et al.²¹ recently demonstrated in a prospective comparative study, using PET-MR and two-dimensional strain echocardiography, in 24 heterozygous females carrying α -Gal A mutation and without LVH, that focal FDG uptake represents an early sign of disease-related myocardial damage and is associated to LV longitudinal function impairment. These findings support the hypothesis that inflammation is likely to represent a clue of myocardial response to Gb3 storage and may be the pathological link in phenotype development of the disease. Further supporting these data, Frustaci et al.²² reported that Gb3 accumulation in Fabry cells, generate a pro-inflammatory response by the human immune system and found detectable myocarditis at histology in 56% of patients with AFD.

Another challenging field of research has also been recently proposed using ¹²³I-metaiodobenzylguanidine (¹²³I-MIBG) myocardial scintigraphy that allows to measure post-ganglionic pre-synaptic noradrenergic uptake in vivo and can therefore provide information on the sympathetic activity and its correlation with LV diastolic dysfunction.^{23,24} In particular, Imbriaco et al.²⁵ demonstrated that in patients with AFD there is reduced ¹²³I-MIBG uptake in the LV myocardium compared to controls; this reduced ¹²³I-MIBG uptake is significantly higher in the infero-lateral region, compared to the remaining myocardial walls and is also present in patients without evidence of myocardial fibrosis, as assessed on CMR. The authors showed that in 50% of patients with no evidence of myocardial fibrosis on LGE-CMR, a regional reduction of ¹²³I-MIBG uptake was observed in the infero-lateral wall, suggesting that degenerative changes in cardiac sympathetic nerves may precede the onset of myocardial fibrosis.²⁵ These data suggest that cardiac adrenergic denervation due to autonomic nervous degeneration accounts for alterations in ¹²³I-MIBG myocardial imaging and the impaired sympathetic function observed in patients with AFD.

In conclusion, although two-dimensional echocardiography remains the primary tool for initial evaluation and follow-up of patients with AFD, more advanced techniques such as CMR with T1-mapping and speckle tracking echocardiography can be particularly useful especially in patients with severe renal impairment, for whom intravenous contrast is contraindicated and as initial investigation of patients with α -Gal A mutation.

Further studies are mandatory to definitively establish the effectiveness of nuclear medicine techniques such as ¹²³I-MIBG myocardial scintigraphy and integrated multimodality PET-MR imaging, to assess early myocardial involvement in AFD.

Disclosure

A. Cuocolo, C. Nappi, V. Gaudieri, A. Pisani, M. Imbriaco declare that they have no conflict of interest.

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