

Multimodality imaging for pre-clinical assessment of Fabry's cardiomyopathy

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Anderson Fabry's disease (AFD) is a rare but underdiagnosed intracellular lipid disorder which can cause left ventricular hypertrophy (LVH). Pre-clinical diagnosis of Fabry's disease is important as it permits early stratification for enzyme replacement therapy, improving the patient's long-term prognosis, avoiding progression to irreversible fibrosis, and preventing cardiovascular complications. Combinations of imaging modalities that integrate the strengths of each modality and at the same time eliminate weaknesses of an individual modality can offer improved diagnostics, therapeutic monitoring, and pre-clinical assessment of Fabry's disease. This review discusses the advantages and challenges in developing multimodality imaging systems of Fabry's cardiomyopathy, highlights some successful combinations that are now routinely used in the clinic and in research, and discusses recent advances in multimodality instrumentation that may offer new opportunities for pre-clinical assessment of this disease.

Keywords Multimodality imaging • Molecular imaging • Fabry's disease

Introduction

Fabry's disease (AFD), also called as angiokeratoma corporis diffusum, is an X-linked lysosomal storage disease caused by mutations in the gene encoding the lysosomal enzyme α -galactosidase A.¹ The disease was firstly described by William Anderson in England in 1898.² However, it was not until 1963 when it was classified as a storage disorder.³ In 1967, the enzymatic defect was identified.⁴ The resultant deficiency in α -galactosidase A activity responsible for the hydrolysis of terminal α -galactosyl residues from glycolipids and glycoproteins leads to intralysosomal accumulation of neutral glycosphingolipids, specifically globotriaosylceramide (Gb3) in various organ systems. This accumulation leads to cellular dysfunction, particularly in the endothelium, resulting in hypoperfusion of tissues and inflammation. The disease affects kidneys, heart, peripheral nerves, and skin, and is characterized by progressive clinical manifestations and premature death from renal failure, stroke, and cardiac disease.⁵ Although it is an X-linked disorder, heterozygous females as well as hemizygous males can be affected. Hemizygous males have the most severe form of the disease and heterozygous females usually have a more benign presentation.⁶ The incidence of AFD is 1 in 55 000 male births.⁵ However, due to the constellation of presenting symptoms as well as some mutations allowing limited α -galactosidase A activity, the actual incidence of AFD, including atypical, subclinical, or late-variant phenotypes, is likely much higher.⁷ The α -galactosidase A gene consists of seven exons located on the long arm of the X chromosome (Xq22.1) that encode a

101 kDa homodimeric glycoprotein. Over 250 mutations have been described in all seven exons, the majority of which are missense point mutations. Depending on the mutation, the enzyme activity may be reduced or abolished. In the more benign mutations, the enzyme activity and stability are reduced but the active site is still capable of binding to the substrate. Reduced enzyme activity occurs by several mechanisms including abnormal or unstable protein folding, perturbation to active binding sites and defective enzyme tracking to the lysosome.⁶ More benign mutant forms of the protein may be stabilized by chemical chaperones such as galactose that bind to the active site of the enzyme.⁸ Therefore, in these mutant forms the enzyme active site is still capable of binding to the substrate galactose, which can be used to increase the enzyme activity and decrease the accumulation of Gb3.⁹

Cardiovascular involvement in AFD is common. The prevalence of AFD in patients with unexplained LVH ranges between 3 and 4%.¹⁰ In patients with cryptogenic stroke, the prevalence of AFD may be up to 5% in men and 2.8% in women.¹¹ Furthermore, heart can be the only organ involved in men with specific gene mutations and in women carriers provided by low enzymatic activity, the so-called 'cardiac Fabry variant'. This is characterized by conduction defects, supraventricular and ventricular arrhythmias, and progressive severe left ventricular (LV) hypertrophy that mimics obstructive or non-obstructive hypertrophic cardiomyopathy (HCM). These patients may develop heart failure symptoms associated with progressive LV dysfunction.¹² The right ventricle is often affected in patients with AFD without any major functional or clinical consequences.

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Early detection of cardiovascular involvement in patients with AFD is extremely important. Enzyme replacement therapy (ERT) improves these patients' long-term prognosis, helps avoid progression to irreversible fibrosis, and prevents cardiovascular complications. Myocyte and endothelial dysfunction can occur even during the pre-clinical stage of Fabry's disease, which can cause arrhythmias and thrombo-embolic complications. Combinations of conventional imaging modalities that integrate the strengths of each modality and at the same time eliminate weaknesses of an individual modality can offer improved diagnostics, therapeutic monitoring, and pre-clinical assessment of Fabry's disease. Multimodality imaging is widely considered to involve the incorporation of two or more imaging modalities, usually within the setting of a single examination using, for example, methodology based on nuclear medicine, positron emission tomography (PET) imaging, magnetic resonance imaging (MRI), and optical imaging. New tools such as micro-PET and matrix-assisted laser desorption/ionization (MALDI) spectroscopy, capable of combining *in vivo* imaging technologies with molecular and cell biology, are promising and they can provide functional and anatomical information of the target tissue before and after enzyme replacement treatment. In this review, we will discuss recent advances in multimodality imaging that may offer new opportunities for pre-clinical assessment of Fabry's cardiomyopathy (Figure 1).

Multimodality imaging tools for pre-clinical assessment of Fabry's cardiomyopathy

Echocardiography

Two-dimensional echocardiography

Two-dimensional (2D) echocardiographic evaluation is the most commonly used imaging tool in patients with AFD. These patients

usually have varying degrees of LVH with preserved systolic function which can easily be detected by 2D echocardiogram (Figure 2). Binary appearance of the endocardial border ('Binary sign') refers to hyper-echogenic appearance of the endocardial border of the interventricular septum that recalls the image of a binary (Figure 2). It is a characteristic sign of Fabry's cardiomyopathy with a sensitivity and specificity of 94 and 100%, respectively.¹³ Nevertheless, the accuracy of the binary appearance of the endocardium as a specific sign of the disease has been questioned.¹⁴ Mundigler *et al.*¹⁴ have shown that the binary sign has low sensitivity and poor reproducibility because of highly operator dependence. Furthermore, the specificity of this sign is low, since it can be found also in other forms of cardiomyopathy. Thus, the authors conclude that the binary sign is not helpful in the daily echocardiographic screening routine of Fabry's patients with LVH.

Diastolic dysfunction is usually not present in the absence of LVH. When LVH is present, diastolic dysfunction can be severe with mitral inflow velocities, suggesting restrictive pattern. Patients with Fabry's cardiomyopathy may have subtle mitral and aortic valvular abnormalities secondary to deposition of Gb3, fibrosis, and calcinosis without signs of severe regurgitation.

Tissue Doppler echocardiography

Early Fabry's disease is characterized by concentric remodelling and mild diastolic dysfunction, progressing later to concentric hypertrophy. The standard non-invasive tools for identifying patients with AFD and cardiac involvement, such as electrocardiogram, conventional echocardiography, and cardiac magnetic resonance (CMR), are useful in patients with established cardiomyopathy, but they are not suitable to detect subtle myocardial dysfunction early in the course of this disease or sensitive enough for the screening of relatives of patients with AFD. The addition of Doppler tissue imaging (DTI) allows to detect subclinical cardiac involvement

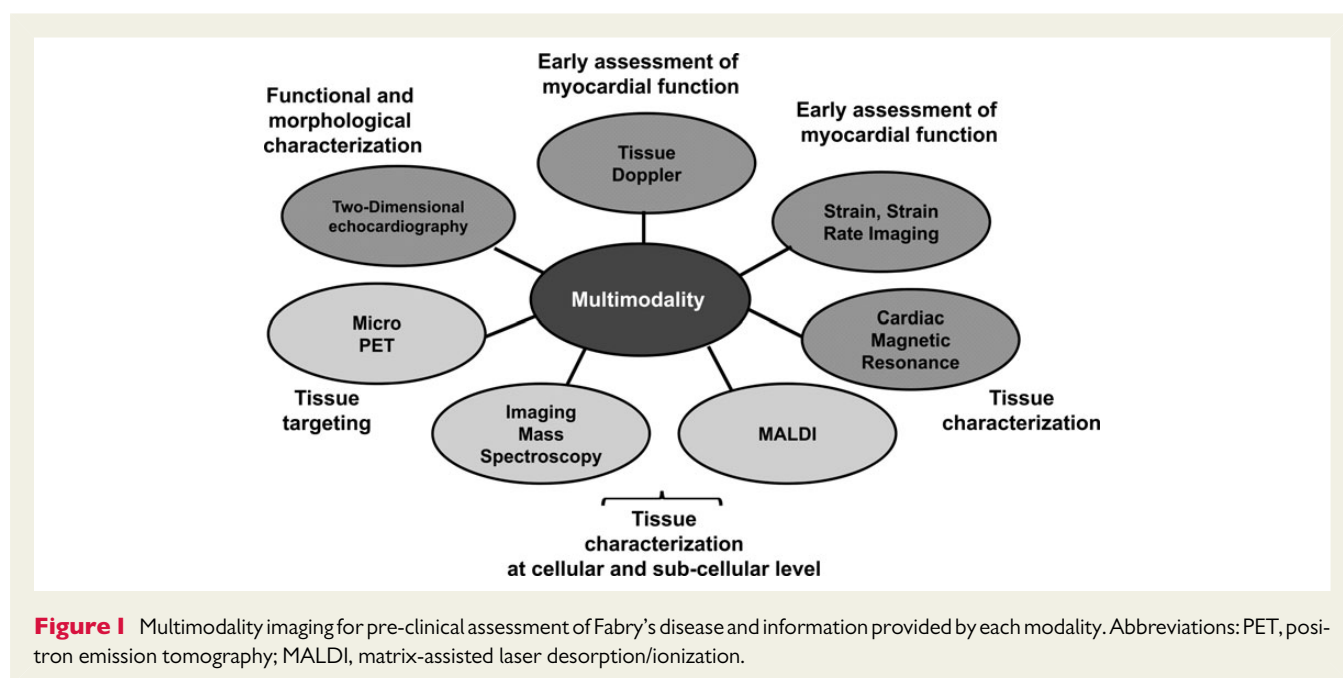


Figure 1 Multimodality imaging for pre-clinical assessment of Fabry's disease and information provided by each modality. Abbreviations: PET, positron emission tomography; MALDI, matrix-assisted laser desorption/ionization.

Strain, strain rate imaging, speckle-tracking echocardiography

Similarly to DTI, strain and SR imaging has emerged as a potentially useful technique for detecting early subclinical systolic dysfunction in patients with Fabry's disease and for monitoring the efficacy of the ERT. In recent analysis by Shanks *et al.*,¹⁹ systolic (longitudinal, circumferential, and radial systolic strain and SR) and diastolic [SR during isovolumic relaxation (SR_{IVR}) and early diastole and strain at peak transmitral E-wave] function was assessed in 16 patients with Fabry's disease and 24 healthy age-matched and gender-matched controls, using 2D speckle-tracking echocardiography. Compared with controls, patients with Fabry's disease had reduced longitudinal systolic strain and systolic SR, reduced longitudinal early diastolic SR, SR_{IVR}, and E/SR_{IVR}, while there were no differences in circumferential systolic strain and S', and no impairment of radial and circumferential diastolic function. Thus, strain and SR analysis is useful in identifying patients with Fabry's disease with reduced myocardial function.

CMRI

CMR provides complementary data to echocardiography through its ability to provide non-invasive evaluation of LV dysfunction, as well as to characterize tissue and assessing tissue abnormalities such as fibrosis, infiltration, and inflammation using contrast agent such as gadolinium enhancement.²⁰ Although the pattern of ventricular hypertrophy caused by Fabry's disease may be similar to that seen in HCM (Figure 3), the pattern of late gadolinium enhancement

(LGE) appears to be different. Moon *et al.*²¹ recently reported that 50% of patients with genetically confirmed Fabry's disease have LGE. LGE, also called delayed contrast enhancement, represents the distinguishing feature of cardiac hypertrophy due to Fabry's disease. Fibrosis causes increased intercellular space and therefore persistence of chelated gadolinium²¹ (Figure 4). LGE *per se* is not a specific finding of Fabry's disease and can be seen in any aetiology of LVH.²² However in Fabry's disease, fibrosis and therefore LGE may be more focal than other forms of cardiomyopathy. The earliest evidence of LGE in Fabry's disease is the basal infero-lateral wall (also known as the postero-lateral wall).²¹ A recent study comparing patients with symmetric HCM and Fabry's cardiomyopathy found LGE of the infero-lateral basal or mid-basal segments sparing the sub-endocardium to be specific for AFD.²³ This finding characterizes late stages of LV involvement and is associated with decreased regional functioning. In fact, in the absence of LVH, there is no LGE. In patients with LVH, LGE correlates with LV dysfunction. For example, males and females with LVH and LGE had severe longitudinal and radial dysfunction.²⁴ The final diagnosis of Fabry's disease is confirmed by biopsy, biochemical demonstration of a reduction in the activity of α -galactosidase A in peripheral blood cells and the detection of casual mutation. Despite this, LGE can provide information on the exact amount of irreversible myocardial damage, which is likely to be relevant for the patients' prognosis. Three lines of evidence point to the prognostic relevance of LGE in patients with Fabry's disease: (i) irreversible myocardial damage may cause adverse

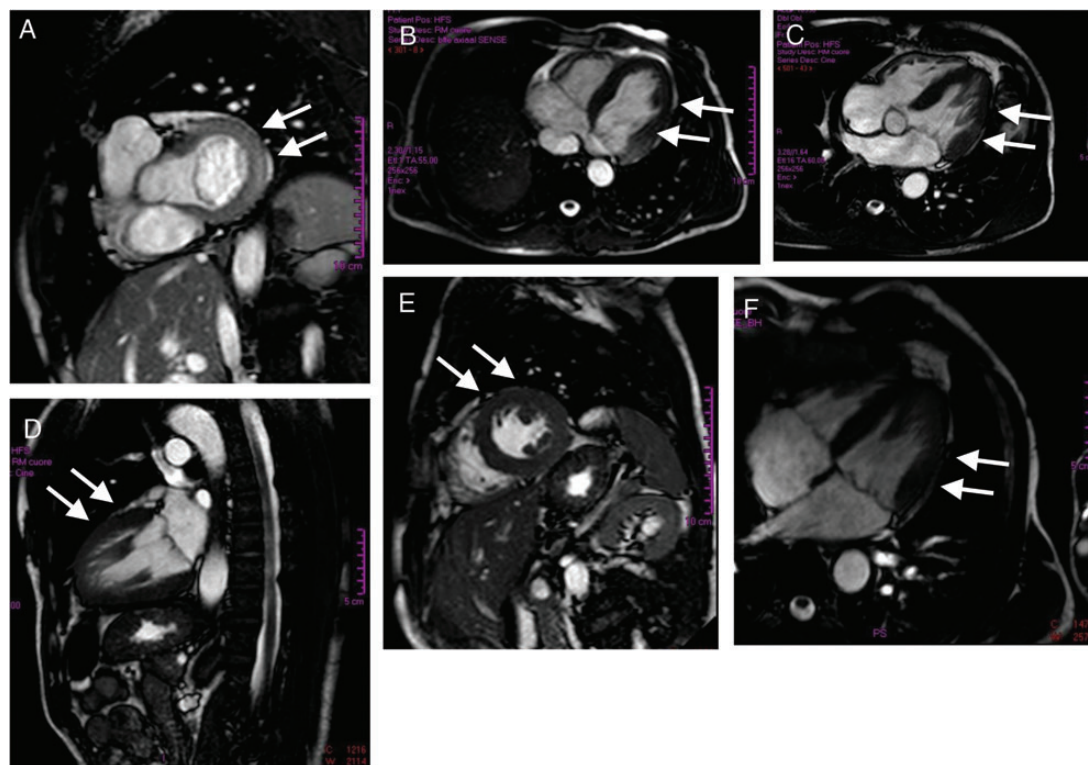


Figure 3 Cardiac magnetic resonance images illustrating findings of cardiac hypertrophy in patients with Fabry's disease. 44-year-old man is seen on a sagittal long-axis cine MRI views in diastole (A), on four-chamber (B) and five-chamber (C) in diastole, on longitudinal long axis in diastole (D), on short axis in diastole (E), and four-chamber in systole (F).

ventricular remodelling, as described by Moon *et al.*²¹ showing that in the setting of Fabry's disease, the extent of LGE is associated with ventricular dilation and clinical symptoms of heart disease;²¹ (ii) myocardial areas affected by LGE do not respond to heart failure drug therapy; and (iii) irreversible myocardial damage with LGE may trigger arrhythmic events causing sudden cardiac death, which is consistent with several reports of a progressive stepwise relationship between the amount of scarring and the clinical risk for sudden death in the setting of Fabry's disease. However, despite the

obvious diagnostic utility of LGE in Fabry's disease, its independent prognostic value needs to be determined.

Molecular imaging for pre-clinical assessment of Fabry's cardiomyopathy

Pre-clinical Fabry's cardiomyopathy can be also diagnosed using several molecular imaging techniques, including measuring α -galactosidase A activity in leucocytes or plasma, analysing genotype, and examining the histopathology of biopsied specimens.¹ Recently, MALDI and imaging mass spectrometry (IMS) have been developed that are able to detect Fabry's disease at early stages. MALDI is a technique of mass spectrometry that profiles biological molecules based on their molecular masses²⁵ (Figure 5). IMS can analyse specimens as small as biopsy samples and visualize the distribution of microscopically observed substances.²⁵

A recent study reported that MALDI and IMS of Gb3 in endomyocardial biopsy specimen from human and mouse are useful to diagnose Fabry's cardiomyopathy.²⁶ By using MALDI, the authors found spectrophotometric extra peaks that were not observed in the control specimens from non-Fabry patients.²⁶ Using information from the database, the authors determined that these peaks were consistent with Gb3 molecules. By using IMS, the authors showed that the distribution of Gb3s was consistent with that of cardiomyocytes, especially in areas that were affected by vacuolar degeneration, while GB3 was not detected in the control hearts.²⁶

Since PET imaging can monitor the bio-distribution of therapeutic enzymes, PET in principle can be useful in providing information related to ERT, in terms of appropriate dosing regimens, the ability of recombinant proteins to target key tissues, the *in vivo* half-lives of recombinant proteins in specific tissues as well as long-term efficacy.

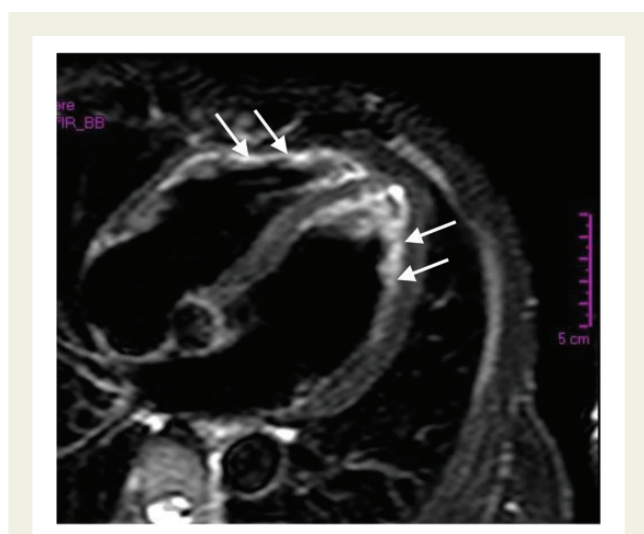


Figure 4 Cardiac magnetic resonance images illustrating typical findings of myocardial fibrosis in patients with Fabry's disease. 44-year-old man is seen on five-chamber in diastole, showing evidence of myocardial fibrosis by hyperenhancement signal (arrows). Arrows indicate late gadolinium enhancement (LGE).

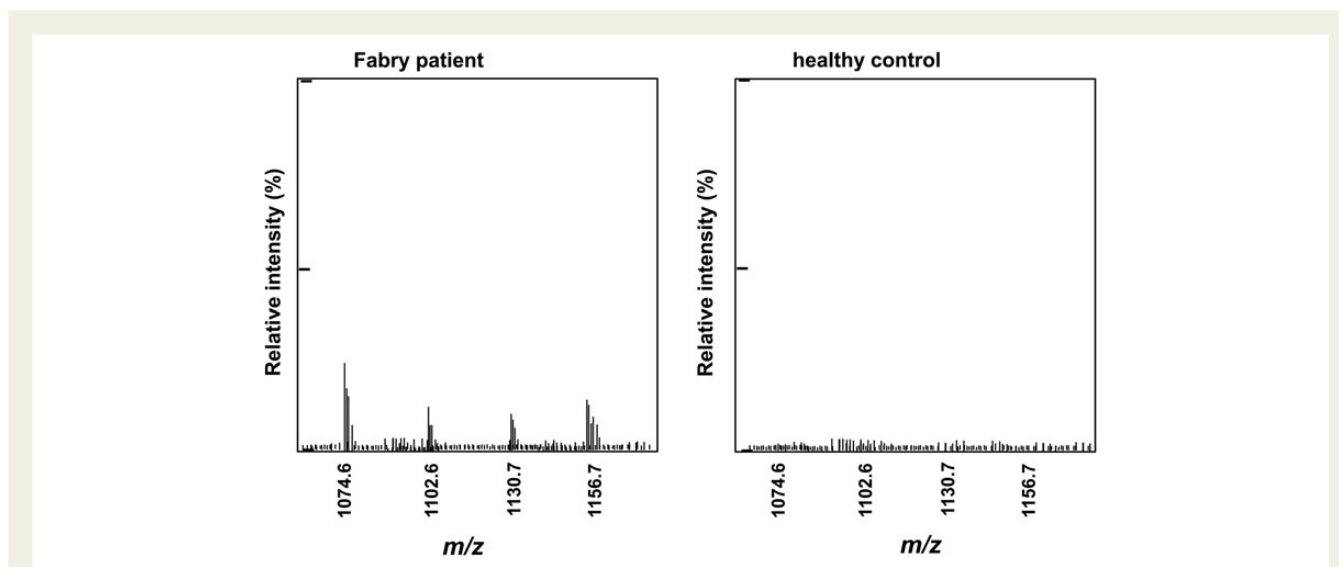


Figure 5 Representative imaging of a mass spectroscopy of endomyocardial biopsy in patients with Fabry's disease and healthy control. The patient's heart (A) produces unique peaks at mass charge (m/z) 1074.6, 1102.6, 1130.7, and 1156.7 corresponding with globotriaosylceramides (Gb3 s). These peaks are not observed in the control human heart (B).

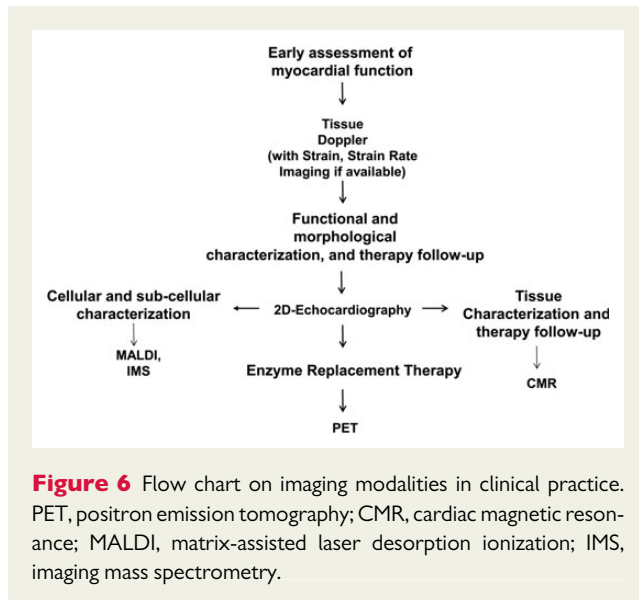


Figure 6 Flow chart on imaging modalities in clinical practice. PET, positron emission tomography; CMR, cardiac magnetic resonance; MALDI, matrix-assisted laser desorption ionization; IMS, imaging mass spectrometry.

Using an ^{18}F -labelled substrate analogue that becomes trapped within the active site of the defective enzyme, Phenix *et al.*²⁷ have shown micro-PET capable to detect the tissue distribution of injected enzyme, therefore allowing to monitor pharmacokinetic changes effected by receptor blocking. The ability to ^{18}F -labelling to monitor the enzyme distribution and tissue half-life *in vivo* by PET provides a powerful research tool with an immediate clinical application to Gaucher disease and a clear path for application to ERT in other lysosomal diseases including Fabry's disease. Genotyping analyses and measurement of α -galactosidase A activity are suffering from some limitations: (i) there may be residual enzymatic activity in patients with variants of Fabry's disease or in patients who are heterozygous; (ii) the α -galactosidase A gene has high genetic heterogeneity with >400 mutations and novel mutations that must be checked to determine whether the mutation truly results in Fabry's disease; and (iii) vacuolar degeneration or lamellar inclusion bodies observed on a light or electron microscopy are not specific for Gb3.

Future directions

AFD has serious cardiovascular complications that can be preventable with ERT. Treatment should be started before the development of myocardial fibrosis. Therefore, it is crucial to detect these patients at the earliest stage. The strategy of routine screening of any unexplained LVH in patients with a conventional or advanced echocardiographic tool to rule out Fabry's cardiomyopathy needs to be clarified. The diagnostic utility of molecular imaging with novel modalities such as MALDI, IMS, and PET in addition to the conventional tools is promising. Specific CMR findings such as LGE and their diagnostic implications in these patients warrant detailed investigation with large studies. Similarly, different mapping sequences in CMR may detect early cardiac involvement in AFD and potentially improve outcomes. Multimodality imaging can aid in the differential diagnosis of these patients from other cardiomyopathies by demonstrating specific pattern of involvement and its expression in patients with AFD (Figure 6). Furthermore, certain imaging findings that may arise

before the development of LVH or fibrosis can even alert the clinician to consider AFD in the diagnosis. The role of genetic testing and its effect on clinical outcomes of these patients needs more study.

Conclusions

Although recent advancement in our understanding of diagnosis and management of clinically manifested Fabry's cardiomyopathy, a number of important questions remain in early diagnosis of this disease at pre-clinical stage, before the development of LVH. This is particularly important since treatment with ERT may decrease the frequency of cardiac events, reverse hypertrophy, and, if started early before the development of fibrosis, may improve cardiac function and prevent deterioration in functional capacity. The advent of several molecular and imaging techniques and the use of novel echocardiographic tools such as DTI, strain, and SR imaging can help detect pre-clinical disease, institute treatment to prevent life-threatening complications and set the stage for potential clinical trials considering such subjects for ERT.

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Conflict of interest: none declared.

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IMAGE FOCUS

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Coronary sinus atrial communication in a 58 year old

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A 58-year-old male with myelodysplastic syndrome presented with dyspnoea. A transthoracic echocardiogram demonstrated an enlarged coronary sinus with colour Doppler, suggesting flow from the coronary sinus into the right atrium (Supplementary data online, Figure S1 A and B). Transoesophageal echocardiography (Figure, Supplementary data online and Movies S1–S3) revealed a dilated and partially unroofed coronary sinus (2.7 cm × 1.7 cm) with left to right flow (shunt fraction Q_p/Q_s 1.5). The right atrium and right ventricle were moderately dilated, right ventricular function was normal and the inter-atrial septum was otherwise intact. There was no persistent left superior vena cava.

Unroofed coronary sinus is a rare congenital anomaly that involves communication between the left and right atrium through a defect in the atrial aspect of the coronary sinus. The open or 'unroofed' coronary sinus results in an intracardiac shunt at the level of the atrial septum that may be mistaken for an atrial septal defect. These defects can be classified based on their extent (complete or partial) and the presence or absence of a left superior vena cava. Although frequently asymptomatic, clinical manifestations range from dyspnoea to overt right-sided heart failure. In the setting of reversed (right-to-left) shunt, these may provide substrate for paradoxical embolization.

In the present case management, options including surgical correction were discussed. A conservative approach was employed due to the size of the shunt and absence of right heart failure. His dyspnoea resolved over a period of weeks with treatment myelodysplastic syndrome. Subsequent echocardiograms have not revealed progression in the shunt fraction, right atrial, or ventricular dilation.

Supplementary data are available at *European Heart Journal – Cardiovascular Imaging* online.

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