

Cardiac magnetic resonance in Fabry disease

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Fabry disease (FD) is a rare X-linked inherited lysosomal storage disorder caused by deficient α -galactosidase A activity that leads to an accumulation of glycolipids, mainly globotriaosylceramide (Gb3) and globotriaosylsphingosine, in affected tissues, including the heart. Cardiovascular involvement usually manifests as left ventricular hypertrophy (LVH), myocardial fibrosis, heart failure, and arrhythmias, which limit the quality of life and represent the most common causes of death. Following the introduction of enzyme replacement therapy, early diagnosis and treatment have become essential in slowing down the disease progression and preventing major cardiac complications. Recent advances in the understanding of FD pathophysiology suggest that in addition to Gb3 accumulation, other mechanisms contribute to the development of cardiac damage. FD cardiomyopathy is characterized by an earlier stage of glycosphingolipid accumulation and a later one of hypertrophy. Morphological and functional aspects are not specific in the echocardiographic evaluation of Anderson-Fabry disease. Cardiac magnetic resonance with tissue characterization capability is an accurate technique for the differential diagnosis of LVH. Progress in imaging techniques has improved the diagnosis and staging of FD-related cardiac disease: a decreased myocardial T1 value is specific of FD. Late gadolinium enhancement is typical of the later stage of cardiac involvement but as in other cardiomyopathy is also valuable to predict the outcome and cardiac response to therapy.

Introduction

Fabry disease (FD) is an X-linked, rare, lysosomal storage disorder characterized by a deficiency of α -galactosidase A and progressive accumulation of complex glycosphingolipids, predominantly globotriaosylceramide (Gb3), in muscular, endothelial, and smooth muscle cells.

The main manifestations involve the nervous system, the heart, kidneys, and skin. Cardiac manifestations, which include cardiomyopathy, arrhythmia, and ischaemia, are common and are the leading cause of morbidity and mortality.¹

Heart involvement is characterized by left ventricular hypertrophy (LVH), progressively leading to heart failure and malignant arrhythmic events.²

Cardiac damage starts early in life, progresses subclinically before symptoms occurrence and usually manifest as LVH mimicking hypertrophic cardiomyopathy (HCM) with a prevalence of GLA pathogenic variants of 0.93% in males and 0.9% in females with LVH and/or HCM screened for FD.³

Echocardiography is important for the initial assessment and subsequent follow-up of FD cardiomyopathy; typical findings include LVH, mainly concentric, disproportionate hypertrophy of papillary muscles, loss of base-to-apex circumferential strain gradient and right ventricular hypertrophy with normal systolic function, but none of them are pathognomonic.⁴

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In patients with cardiac variant FD, differential diagnosis from other HCMs is more challenging in the absence of systemic manifestations, considering that all patterns of LVH have been reported in FD, CMR may be useful but in some cases genetic test can be necessary for final diagnosis since hypertrophic phenocopies can have similar aspect even in advance imaging.

CMR imaging is the leading non-invasive diagnostic techniques able to identify cardiac involvement in FD, as it allows a comprehensive assessment of cardiac anatomy, regional and global ventricular function, and tissue characterization. Detection and quantification of myocardial replacement fibrosis by late gadolinium enhancement (LGE) is a crucial prognostic feature in clinical risk stratification of FD patients, relating to hard cardiovascular outcomes.⁵

T1 mapping is an established and reproducible emerging CMR technique for the characterization of myocardial tissue by identification of myocardial oedema, intramyocyte lipids accumulation, and extracellular volume expansion (proteins or iron deposition).⁶ In particular, native T1 mapping estimates the intrinsic longitudinal relaxation time of myocardial tissue without the need for a contrast agent.

Gadolinium bases contrast media are an extracellular contrast that alters the image contrast following intravenous administration, predominantly shortening the T1 relaxation time of tissues and may be administered even in patients with advanced kidney disease and in haemodialysis since is a safe profile with very rare complication, mainly represented by rare anaphylactoid reaction, local necrosis in the site of injection, nephrotoxicity and very rare nephrogenic systemic fibrosis (NSF) in patients with kidney impairment. A recent consensus statement written together by radiologist and nephrologist conclude that depending on the clinical indication, the potential harms of delaying or withholding a magnetic resonance imaging in a patient with acute kidney injury or with advanced kidney disease, eGFR less than 30 mL/min per 1.73 m², should be balanced against and may outweigh the risk of NSF.⁷

CMR is a key tool for studying cardiac manifestations of FD and in early differential diagnosis and staging of cardiac FD.

Typical features of CMR in FD are low native T1 mapping in an earlier stage, reflecting glycosphingolipid myocyte storage, occurring before the development of significant LVH and LGE in the basal inferolateral wall with endocardium sparing in the later stage in up to 50% of affected patients.^{5,6}

CMR is a multi-parametric technique and has provided precious insights into myocardial biology of FD at different stages and on follow-up in enzyme replacement therapy (ERT) and chaperon therapies.

The model of FS as a simple storage disease caused mainly by sphingolipid accumulation has been challenged by endomyocardial biopsy and CMR with T1 and T2 mapping assessing myocardial lipid content and inflammation at different disease stages, suggesting a central role for inflammation in early FD progression.^{8,9}

The high levels of glycolipids in the cells and plasma of patients with FD are not sufficient to explain the pathophysiology of this disorder. Moreover, family members with GLA mutations can have very different clinical presentations (intra-familial phenotypic variability).⁹ It has been suggested that the anomalous accumulation of Gb3

or lyso-Gb3 due to alpha-galactosidase A deficiency in patients with FD could trigger different cellular mechanisms that contribute to the phenotypic expression of this disease.¹⁰

Nordin *et al.* proposed a three-phase model of myocardial FD involvement and progression: (i) *storage*, starting in childhood with progressive lowering of T1 with no LVH and LGE; (ii) *inflammation and/or hypertrophy*, with low T1, initial LVH (mostly in males), and T2 mapping evidence of inflammation in the basal inferolateral segment associated with LGE (sometimes preceding LVH in females); and (iii) *fibrosis and/or impairment*, with increasing T1 values (pseudo-normalization) and LGE with wall thinning in the basal inferolateral left ventricular segment.⁸

CMR consents a complete and accurate assessment of myocardial involvement in FD letting to 21% reclassification of genotype-positive patients as having cardiac involvement allowing improved risk stratification and targeting of a specific therapy.¹¹

Morphology in Anderson-Fabry disease

Cardiac involvement in FD is characterized by lysosomal storage of GB3 and other sphingolipids in myocytes of both ventricles at the cellular level and this accumulation in the left ventricle causes overt wall thickening and hypertrophy.

Sphingolipids deposit is homogeneous in myocardium, and hypertrophy is usually concentric. However, asymmetric LVH involving the inter-ventricular septum or the LV apex was also described in FD and in some cases even with outflow obstruction.^{10,12}

Patients with non-concentric wall thickening sub-group include asymmetric septal and apical hypertrophic patterns and these patients had greater wall thicknesses and LVMI than patients with concentric wall thickening.

CMR is the gold standard for the calculation of left ventricular mass (LVM) evaluation of regional wall thickness and to define the pattern of hypertrophy.⁶ Moreover, CMR does not suffer from the acoustic window limitations, it is a multi-planar technique allowing the measurement of wall thickness in planes orthogonal to myocardium and with a better depiction of both the endocardial and epicardial borders.

Nearly one-third of males and one-fourth of females had LVH among FD patients prior to ERT.¹³ The appearance of LVH was age-dependent, and the progression rate of LVM was higher in male patients than in female patients.¹⁴

CMR and echocardiographic studies reporting the pattern of LVH in FD,¹⁴ evaluated 736 patients with FD, and demonstrating a prevalence of LVH in 58% of cases (426 patients). The majority of patients ($n=388$ patients, 91%) had concentric hypertrophy, whereas an asymmetrical septal hypertrophy was found in 8% ($n=35$) and an apical pattern in 3 (1%).

From all these previous data, we can conclude that the finding of asymmetrical LVH generally considered a hallmark of the sarcomeric HCM and cannot be used as a diagnostic criterion to exclude FD. Moreover, considering the great prevalence of HCM in the general population, the co-existence of both Fabry and sarcomeric diseases is also possible and estimated 1:200.¹²

The development of LVH is associated with the severity of the presentation of FD. It may occur later in a patient's life, particularly in females. In the study by Nieman *et al.*, evaluating a cohort of FD patients with an average age of 42 years, LVH was found in 17% of females and in 65% of males.¹⁵

Another morphological feature associated with FD is the hypertrophy of papillary muscles. The involvement of papillary muscles is more evident in FD than in other causes of LVH.¹⁶

Previous studies observed a greater LVH in FD in front of another form of LVH, and a significant increase in papillary muscle hypertrophy, even in the absence of increased LVM. Prominent papillary muscles have been proposed as typical of FD in the previous study but are not specific and are found in 14% of patients. The mechanism of this is unclear but may reflect sphingolipid deposition and the resultant hypertrophy preferentially occurring in papillary muscles prior to the onset of LVH.

Functional parameter in Fabry disease: ejection fraction, diastolic function, and strain

FD is not usually associated with LV systolic dysfunction but may evolve in progressive LV systolic dysfunction with overt heart failure in the terminal stage.

A more sophisticated, non-invasive tool for the evaluation of myocardial deformation and regional and global systolic function is performed by feature tracking analysis.

Tissue tracking is a post-processing technique using data of myocardial global longitudinal strain (GLS), global circumferential strain (GCS), and global radial strain (GRS) obtained from conventional cine images.

Only a few studies have evaluated myocardial strain with CMR in FD, even with conflicting results: no significant differences of GLS were found between patients with FD and healthy controls in a study by Mathur¹⁷ but a base-to-apex GCS discriminates between FD patients without hypertrophy or LGE and healthy controls independent of native T1, suggesting that loss of base-to-apex GCS gradient may be an early marker of cardiac involvement in FD.

A subsequent and larger study by Augusto *et al.* showed that FD patients had worse GLS than controls, even considering the group of FD patients without LVH and with normal T1 values postulating that slightly reduced GLS might be a primary cardiac phenomenon in a pre-hypertrophic stage of AD possibly reflecting altered myocardial coupling to the systemic vasculature due to systemic endothelial and smooth muscle changes.¹⁸ A loss of the base-to-apex CS and LS gradient was also described in the early stage of FD but this is not specific to FD but is found in other cardiomyopathies, such as in cardiac amyloidosis.

Diastolic LV dysfunction is also possible in FD, caused by the increased stiffness of hypertrophic myocardium, and may reflect an early structural change in the storage phase.

Pieroni *et al.* demonstrated that diastolic dysfunction already exist prior to the development of LVH or systolic dysfunction in patients with Fabry cardiomyopathy, suggesting that diastolic dysfunction might be an early sign of cardiac involvement in patients with FD.¹⁹

Echocardiography-derived diastolic dysfunction is closely linked to LGE in FD. Septal E/e' ratio is the best echocardiographic marker suggestive of LGE. Diastolic dysfunction is not a prerequisite for LGE in FD, since LGE can be detected in the absence of measurable cardiac functional impairments.¹⁹

T1 and T2 mapping in Fabry disease: from lipid storage to inflammation

T1 is the longitudinal relaxation time, that is, the time constant expressing the exponential recovery of longitudinal magnetization, passing from a high energy, non-equilibrium state, induced by the radiofrequency pulse, to a state of thermodynamic equilibrium.

The T1 recovery time can be spatially varying and depends on the local environment of the protons and can be used to characterize variations in tissue composition. The shorter the T1, the faster the recovery of longitudinal magnetization. T1 differences are based on the difference among the hydrogen protons (spin-lattice): hydrogen protons in a long-chain of fat tissue have a very short T1, whereas the free-water hydrogen has the longest values.

The result is a quantitative map where each pixel's colour represents the average T1 relaxation time within the voxel. Myocardial T1 has intermediate values ranging from 880 to 1150 ms at 1.5 on the sarcomeric protein concentration, glycogen content, and water.¹⁹

Myocardial T1 is increased for oedema, for fibrosis/scars (collagen matrix of scars increases the interstitial space and water content), and for amyloidotic deposit.

In contrast, T1 is decreased in the presence of iron overload (haemorrhagic haemochromatosis) or for fat infiltration/metaplasia (arrhythmogenic cardiomyopathy, metaplasia of old scars).

In HCM, T1 is only patchily increased, usually in a region with coexisting fibrosis.⁶

In cardiac amyloidosis, myocardial T1 is diffusely and severely increased. The primum movens of cardiac damage in patients with FD is the myocardial intra-cellular accumulation of glycosphingolipids by α -galactosidase A enzyme deficiency, with direct consequences on tissue T1 relaxation times. Protein and fat have shorter T1 relaxation times by their low inherent energy and slow molecular tumbling rate, underlying the differences in T1 mapping between AD patients and healthy control subjects.

A meta-analysis by Imbriaco *et al.* on 14 articles, 982 subjects showed a mean native T1 value of 984 ± 47 ms in FD patients and 1016 ± 26 ms in controls ($P < 0.0001$). In AD patients, there was also an inverse correlation between native T1 values and male gender ($P = 0.002$) and LVH ($P < 0.001$), confirming a reduction of native T1 values in FD patients compared to healthy controls and point out that the degree of T1 shortening in FD is influenced by gender and LVH²⁰ (Figure 1).

The first papers published on CMR and myocardial involvement in FD were focused on LVH and LGE in the basal inferolateral wall,²¹ thought initially to reflect only fibrosis.

Later, multi-parametric CMR has been able to measure sphingolipid infiltration (T1 mapping, low native T1) (39) and apparent oedema (T2 mapping, high native T2) with blood troponin elevation suggesting inflammation, albeit histological validation is lacking.²²

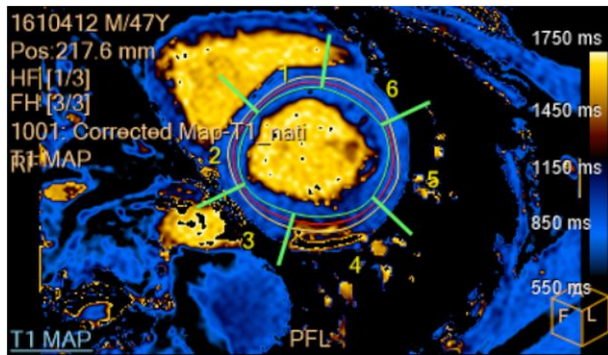


Figure 1 CMR T1 mapping in AD. At T1 mapping (short axis views) a diffuse decrease of native myocardial T1 is found.

A pre-LVH phase of cardiac FD was subsequently defined by a low T1 phenotype, occurring in up to 60% of FD patients; slightly elevated LV ejection fraction and electrocardiographic changes were also observed pre-LVH.

Sphingolipid storage starts before birth,²³ and T1 mapping presumably has a detection threshold, a ‘silent’ sphingolipid accumulation stage before T1 lowers must also occur.

A new parameter, T1 dispersion, as the standard deviation of the extracted T1 times, has been included together with age and indexed LVM in a risk prediction model that accurately predicts 5-year risk of adverse cardiac outcome for individual patients with FD.

Myocardial fibrosis increases T1 and pseudonormalizes the measurement. This is particularly evident in females, where fibrosis can even precede LVH.¹⁶

Late gadolinium enhanced and extracellular volume in Fabry disease

In HCM, LGE has been shown to represent myocardial fibrosis, and the extent is linked to markers of adverse clinical outcomes. In FD, LGE is found in up to 50% of patients, but in a unique pattern affecting the basal inferolateral mid-wall²¹ (Figure 2).

The presence and the progression of fibrosis is an important prognostic determinant for ventricular arrhythmias and sudden cardiac death in FD²⁴ and is also associated with a low likelihood of regression of LVH.

LGE in FD usually involves the inferolateral wall sparing the sub-endocardium: a hypothesis is that the basal inferolateral segment is the most mobile of the basal segments and likely faces the most junctional stresses transmitted from the fibrous skeleton into the mesocardial layer.

Pattern of presentation of LGE is very useful for the differential diagnosis among the different causes of LVH.

In cardiac amyloidosis the pattern of LGE is very specific, permitting a definite diagnosis in most cases.²⁵ Although less specific, the LGE pattern also helps in the diagnosis of (HCM), where LGE has also an important prognostic role, being a strong predictor of malignant ventricular arrhythmias.

LGE may be detected earlier than LVH in female patients,¹⁶ myocardial fibrosis increases myocardial T1, balancing for the decrease of T1 by sphingolipid deposition. Then, myocardial regions containing both areas of viable myocytes (loaded with sphingolipids) and areas of fibrosis

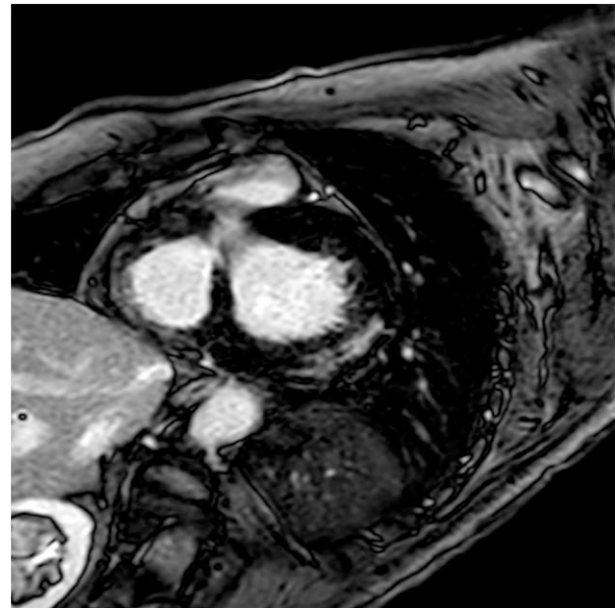


Figure 2 On the post-contrast image (short axis view), the area of LGE is found in the mid-wall layer of the inferolateral wall, which is the typical site of LGE in Fabry disease.

may have average T1 values within the range of normality, showing a ‘pseudo-normalization’ phenomenon of T1.

LGE has an important prognostic role in FD in terms of response to ERT since has been demonstrated that the presence of LGE was associated with a low likelihood of regression of LVH.²⁶

Extracellular volume mapping (ECV) consists of the measurement of the distribution volume of gadolinium in myocardial tissue. Since gadolinium is an extracellular contrast agent, its distribution volume corresponds to the ECV of myocardium (interstitial space plus blood vessel) and can assess both focal and diffuse fibrosis.

ECV is increased in many conditions, such as amyloidosis because of the deposit of protein, myocardial infarction, and generally, fibrotic myocardium of any cause or oedema. In FD, interstitial spaces are reduced by the intracellular overload of sphingolipids. Then, in the absence of fibrosis, ECV is normal or even decreased, and its role is limited to more advanced stages of the disease.

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Data availability

No new data were generated or analysed in support of this research.

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