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Review

Cardiac Magnetic Resonance in Fabry Disease: Morphological, Functional and Tissue Features

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Abstract Fabry disease (FD) is a X-linked inheritable storage disease caused by deficiency of alpha-galactosidase causing lysosomal overload of sphingolipids. FD cardiomyopathy is characterized by left ventricular (LV) hypertrophy and should be considered in differential diagnosis with all the other causes of LV hypertrophy. An early diagnosis of FD is very important because the enzyme replacement therapy (ERT) may change the fate of patients by blocking both cardiac and systemic involvement and improving prognosis. Diagnosis may be relatively easy in young patients with the typical signs ans symptoms of FD, but in male patients with late onset of disease and in females, diagnosis may be very challenging. Morphological and functional aspects are not specific for FD, which cannot be diagnosed or excluded by echocardiography. Cardiac magnetic resonance (CMR) with tissue characterization capability, is the preferred technique for the differential diagnosis of LV hypertrophy. The finding of decreased myocardial T1 value in LV hypertrophy is very specific for FD. Late gadolinium enhancement (LGE) is found in late stage of disease but it is useful to predict the cardiac response to ERT and to stratify the prognosis.

Keywords: Fabry disease; Cardiac magnetic Resonance; T1 mapping; Late gadolinium enhancement; Feature tracking

1. Introduction

Anderson-Fabry disease or simply Fabry disease (FD) is a X-linked inheritable disease caused by deficiency of alpha-galactosidase-A enzyme. Deficiency of alpha-galactosidase causes lysosomal overload of globotriaosylceramide, which is responsible of the clinical manifestations of this disease (1). Male patients with pathogen mutation are all affected by disease, but the age onset of symptoms and the severity of presentation depends on the residual enzymatic activity of alpha-galactosidase. If the enzymatic activity is less than 3%, the onset of symptoms is early in childhood and with more severe presentation (2). Main manifestations involve the nervous system, the heart, kidney and skin. In childhood and teenage, symptoms of peripheral nervous system are frequent, presenting with neuropathic pain, anhidrosis (more rarely iperhidrosis) which is associated with febrile crisis and with self-limitation of physical effort, gastrointestinal symptoms and hearing loss (3). Some ophthalmologic signs as cornea verticillate and tortuous retinal vessels are often observed, as well as the presence of cutaneous angiokeratomas, often presenting a "swim-suit" distribution. Microalbuminuria is the first manifestation of renal involvement. For the natural history of FD, the involvement of organs becomes more evident in the second decade of life. Stroke or transient ischemic attack frequently occurs at this age. A progression from micro- to macroalbuminuria with decrease of glomerular filtration rate is observed, and chronic renal insufficiency is usually evident from the third decade of life (4). Heart involvement is characterized by left ventricular (LV) hypertrophy (actually a "pseudohypertrophy" caused by the sphingolipids overload), progressively leading to heart failure and malignant arrhythmic events.

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All the signs and symptoms of childhood and teenage should raise the suspicion of FD and induce clinicians to perform alpha-galactosidase enzymatic activity test on plasma or blood pool, and confirming diagnosis with genetic test. Enzymatic replacement therapy (ERT) is an etiological therapy that blocks the progression of disease often with a regression of LV hypertrophy and improving the prognosis of patients (5).

In some subgroups of patients, the diagnosis may be very challenging: a) Male patients with a residual enzymatic activity >3% and <30%; b) in females.

In male patients when the residual enzymatic activity is >3% and <30%, FD may have a late onset with the absence of the typical signs and symptoms of childhood (1). This subgroup of male patients, FD may be manifest in older age with complications of LV hypertrophy, stroke or renal insufficiency. All these manifestations may be considered typical of older ages and the diagnosis of FD never performed. This misdiagnosis could affect the patients itself and all the family members carrying the mutation.

In female patients, FD is even more insidious. The organs involvement in female patients is dependent to the Lyonization phenomenon: in each cell of females one X-chromosome is inactivated and compacted in the Barr body. By this phenomenon, female patients may be completely asymptomatic or present with severe organ involvement in case of inactivation of the normal chromosome (6). Heart involvement could be the only manifestation of this disease in females.

The first suspicion of FD in male patients with late onset presentation and in females with lone cardiac involvement, is usually provided by cardiac magnetic resonance (CMR).

CMR is the preferred imaging technique to evaluate the phenotype of cardiomyopathies. CMR provides the differential diagnosis among the causes of LV hypertrophy through an accurate assessment of morphological, functional and tissue characteristics. In a recent study (7), CMR reclassified the initial echocardiographic etiologic suspicion in 43% of patients with LV hypertrophy. This reclassification of diagnosis has important implications for the clinical management of patients and for prognostic evaluation. CMR has the unique capability to detect sphingolipids overload by T1 mapping technique and to provide prognostic information through the assessment of myocardial fibrosis with Late Gadolinium Enhancement (LGE) technique (8). The aim of this review is to discuss the role of CMR in FD.

Morphological features of Fabry disease

As in other organs, cardiac involvement of FD is characterized by lysosomal overload of sphingolipids in myocytes. In left ventricle the effect of such sphingolipids overload causes wall thickening and hypertrophy (more correctly to be defined as pseudo-hypertrophy) (9). Sphingolipids deposit is homogeneous in LV myocardium, and hypertrophy is usually described as concentric (10). However, asymmetric LV hypertrophy involving the interventricular septum or the LV apex was also described in FD.

CMR is more accurate than echocardiography for the evaluation of regional wall thickness and to define the pattern of hypertrophy (11). CMR does not suffer from the acoustic window limitations, it is a multiplanar technique allowing measurement of wall thickness in planes orthogonal to myocardium and with a better depiction of both endocardial and

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epicardial border. In table 1 are shown all the CMR and echocardiographic studies reporting the prevalence of LV hypertrophy in FD. Globally 620 patients with FD were included, demonstrating a prevalence of LV hypertrophy of 56% of cases (347 patients). The pattern of LV hypertrophy was reported in 206 patients (6,10,12-23). The majority of patients (n= 178 patients, 87%) had concentric hypertrophy, whereas an asymmetrical septal hypertrophy was found in 12% (n=25) and an apical pattern in 3(1%). The practical information obtained by these data is that the finding of asymmetrical LV hypertrophy, that is generally considered a hallmark of the sarcomeric hypertrophic cardiomyopathy, cannot be used as a diagnostic criterion to exclude Fabry disease. Furthermore, considering the great prevalence of sarcomeric hypertrophic cardiomyopathy in the general population, the coexistence of both Fabry and sarcomeric diseases is also possible.

Table 1: Prevalence and pattern of left ventricular hypertrophy in Fabry disease

First Author, Journal, Year of Publication (ref.)	Patients with FD	LV hypertrophy	Concentric hypertrophy	Septal/apical hypertrophy
	n.	n.(%)	n.(%)	n.(%)
Bass JL, Am Heart J 1980(12)	32	15 (48%)	13 (87%)	2 (13%)/0
Nakao N, Eng J Med 1995 (13)	7	7 (100%)	7 (100)	0 (0%)/0
Linhart A, Am Heart J 2000(14)	30	14 (47%)	11 (79%)	3 (21%)/0
Sachdev B,Circulation 2002(15)	6	6 (100%)	5 (83%)	1 (17%)/0
Chimenti C, Circulation 2004(16)	4	4 (100%)	2 (50%)	1 (25%)/1(25%)
Kawano M, Am J Cardiol 2007 (17)	13	13 (100%)	4 (31%)	9 (69%)/0
Wu JC, European Heart Journal 2010 (18)	139	118 (85%)	115 (97%)	3 (3%)/0
Elliott P,Heart 2011 (9)	7	7 (100%)	4 (57%)	3 (43%)/0
Niemann M , JACC cardiovasc imag 2011(6)	104	40(38%)	N/A	N/A
Sado DM, Circ: Cardiovasc Imaging 2013 (20)	44	24 (55%)	N/A	N/A
Thompson RB,Circ: Cardiovasc Imaging 2013 (21)	31	16 (52%)	N/A	N/A
Kozor R, Heart 2016(22)	50	19 (38%)	N/A	N/A
Deva DP , JCMR 2016 (10)	39	22 (56%)	17 (77%)	3 (14%)/2(5%)
Augusto JB, Eur Heart Cardiovas J 2021(23)	114	42(37%)	N/A	N/A
Total	620	347(56%)	178(86.5%)	25(12.5%)/3(1%)

The development of LV hypertrophy is associated with the severity of the presentation of Fabry disease. It may occur later in patient life, particularly in females. In the study by Nieman et al, evaluating a cohort of FD patients with an average age of 42 years, LV hypertrophy was found in 17% of females and in 65% of males (6).

Another morphological feature often associated with FD, is the hypertrophy of papillary muscles. The involvement of papillary muscles is more evident in FD than in other causes of LV hypertrophy (22,24). The evaluation of papillary muscle hypertrophy may be difficult and different methods of measurement were proposed: maximal papillary muscle diameter, papillary muscle mass or transverse area, the ratio between papillary muscle

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area and the LV transversal circumference. However, papillary muscles hypertrophy is not specific of FD, and was reported in 14% of patients with other conditions (24).

Functional features of Fabry disease

FD is not usually associated with LV systolic dysfunction. A more complex evaluation of regional and global systolic function is performed by feature tracking analysis. By this technique, data of myocardial global longitudinal strain (GLS), global circumferential strain (GCS) and global radial strain (GCS) are obtained from conventional cine images. Only few studies evaluated myocardial strain with CMR in FD, even with discordant results. In the study by Mathur et al, no significant differences of GLS were found between patients with FD and healthy controls (25). On contrast, in the study by Augusto et al FD patients had worse GLS than controls, even considering the group of FD patients without LV hypertrophy and with normal T1 values (23). A loss of the base-to-apex CS and LS gradient was also described in early stage of FD (26). However, this finding is not specific for FD being found in other cardiomyopathies as in cardiac amyloidosis (25-27).

Diastolic LV dysfunction is also possible in FD, caused by the increased stiffness of hypertrophic myocardium. In advanced stage, left atrial dilation and atrial fibrillation may occur. For this, FD is not different from other causes of LV hypertrophy.

T1 and T2 mapping in Fabry disease

FD is probably the most important and robust indication for T1 mapping. Native T1 mapping consists in the measurement of myocardial T1 in basal conditions. T1 of normal myocardium should be constant at the same magnetic field intensity and any change of T1 is related to disease conditions (28). 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 shorter the T1, the faster is the recovery of longitudinal magnetization. T1 differences are based on the difference among the molecules containing hydrogen protons (spin-lattice): hydrogen protons in long-chain triglycerides of fat tissue have a very short T1, whereas the free-water hydrogen has the longest values. Myocardial T1 has intermediate values ranging from 880 to 1150 msec at 1.5T, depending on the sarcomeric protein concentration, glycogen content and water content (28).

Myocardial T1 is increased for oedema, for fibrosis/scar (collagen matrix of replacement scar increases the interstitial space and water content), and for amyloidotic protein deposit. On contrast, T1 is decreased in presence of iron overload (haemorrhagic infarction, hemochromatosis) or for fat infiltration\metaplasia (arrhythmogenic cardiomyopathy, metaplasia of old scar) (29). Lysosomal sphingolipids deposit of FD has low T1 values, similarly to fat (20). Among the cause of LV hypertrophy, FD is the unique condition associated with a short myocardial T1 (figure 1). In sarcomeric hypertrophic cardiomyopathy T1 is only patchy increased, usually in region with coexisting fibrosis (30). In cardiac amyloidosis myocardial T1 is diffusely and severely increased (31). FD may be also easily distinguished by hemochromatosis (usually not associated with LV hypertrophy) because iron overload causes a significant decrease of myocardial T2*.

In the study by Pica et al, low myocardial T1 was found in the majority of FD patients with LV hypertrophy and also in 50% of those without hypertrophy (32). By this finding,

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CMR may allow an early diagnosis of FD in case of LV hypertrophy when clinical signs and symptoms are consistent. However, caution should be exercised in patients with slightly reduced T1 values who do not have hypertrophy and neither clinical signs or symptoms of FD. Many factors, in fact, may influence the reliability of T1 measurement.

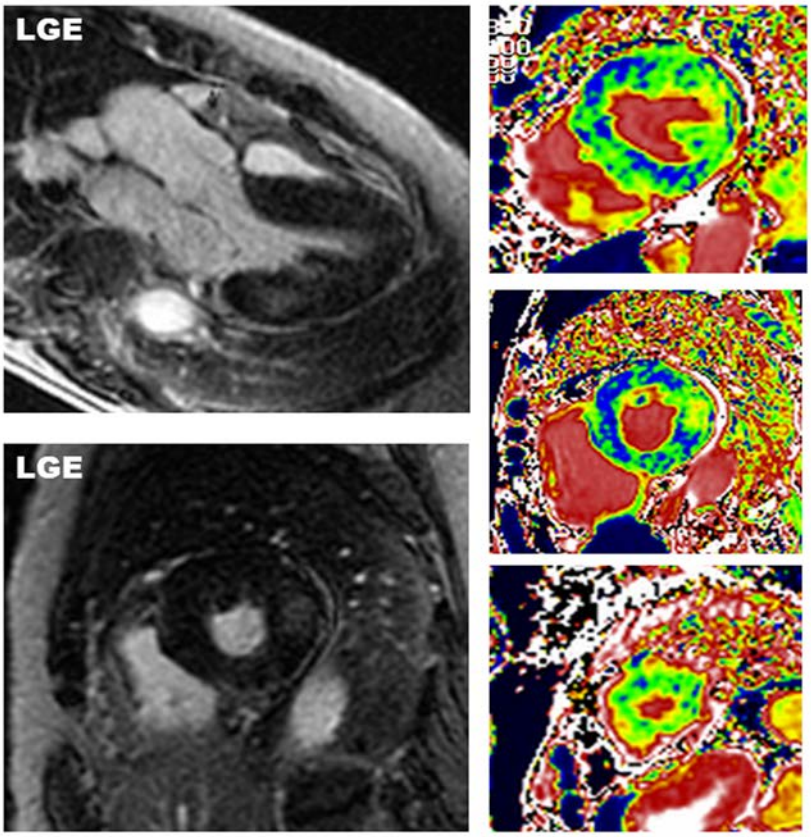

Figure 1: CMR of Fabry disease. Images of a 65 years old females with Fabry disease and concentric left ventricular hypertrophy and typical CMR presentation. On post contrast image (4-chamber and short axis views in left panels), area of late gadolinium enhancement (LGE) is found in the midwall layer of the inferolateral wall, which is the typical site of LGE in Fabry disease. At T1 mapping (short axis views in right panels) a diffuse decrease of native myocardial T1 (blue areas) is found.

T1 mapping pulse sequence are divided in 2 different methods: saturation recovery (SASHA) or inversion recovery (MOLLI, ShMOLLI). Differences in pulse sequence, in the setting of pulse sequence parameters, and in the algorithm used for the fitting of the SI/time analysis curve, may result in different T1 values. Patient's characteristics as heart rate, ability to keep breath-hold, body dimensions may also influence the measurement (28). Finally, different MRI machines (even by same vendors and of same model and release) may produce different T1 measurement because of shimming and magnetic field inhomogeneity that cannot be modelled and corrected. For these reasons, the Society for Cardiovascular Magnetic Resonance (SCMR) position paper indicates that every institution should have its on-site range of normality for myocardial T1 (as well as for T2 mapping) (33). The meta-analysis by Ponsiglione et al analysed all the studies with T1 mapping analysis in FD (34) and evaluated fourteen eligible studies including a total of 477 FD patients and 505 controls. In all the studies myocardial T1 was significant lower in FD than in controls. However, considering only the studies with 1.5T, the average values of

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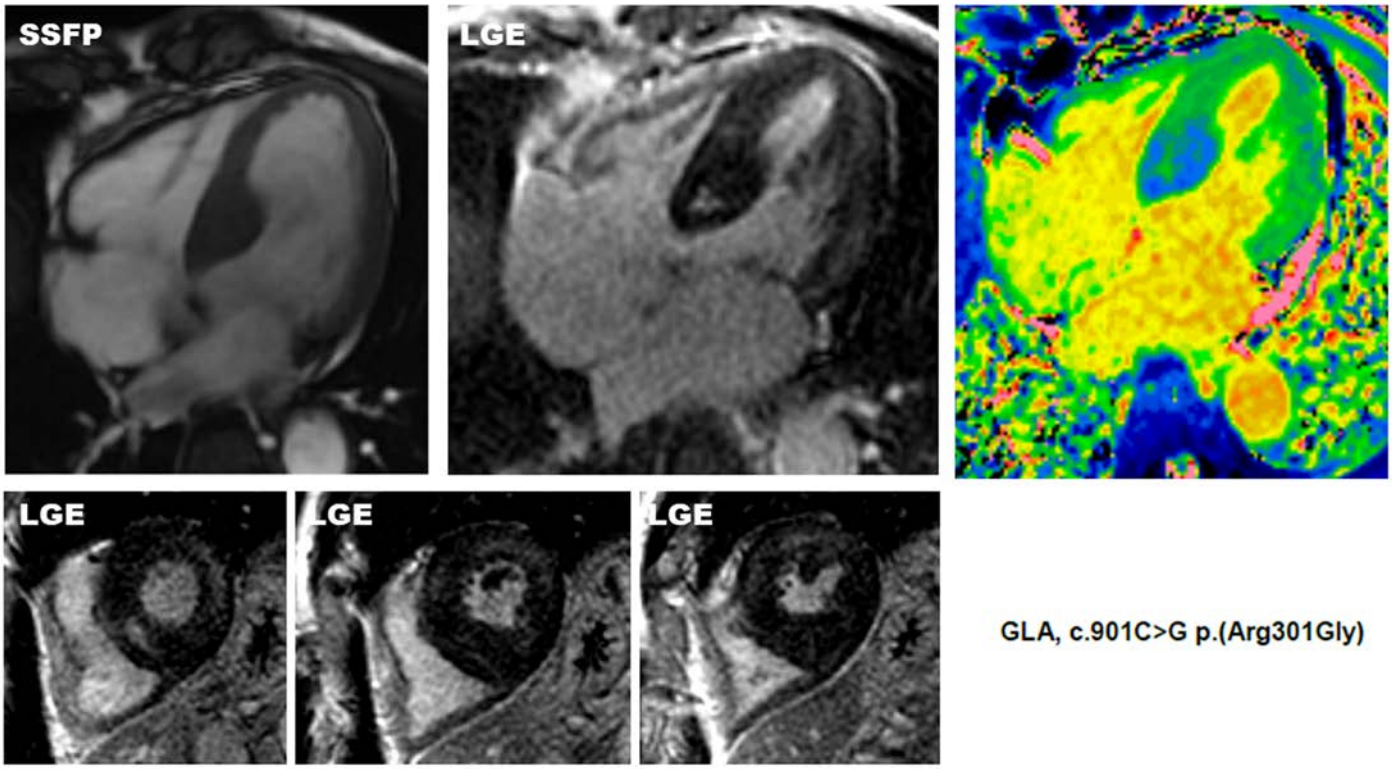
myocardial T1 ranged from 863±23 msec to 1070±50 msec in FD and from 938±21 to 1170±27 in controls with a great overlap of value between FD and controls.

T1 mapping technique may suffer for both false positive and negative results in the diagnosis of FD. Physiological hypertrophy of athletes is associated with the increase of sarcomeric proteins and decrease of intracellular and interstitial water content. This may result in a slight reduction myocardial T1, that, summed to concentric hypertrophy may mimic FD (35). In that case, clinical history helps for differential diagnosis because patients with FD can hardly have training levels of elite athletes.

As discussed in details in the next paragraph, the occurrence of myocardial fibrosis may alter the measurement of T1 in FD (20). Myocardial fibrosis increases T1 and pseudo-normalizes the measurement. This is particularly evident in female, where fibrosis is often seen even before the development of LV hypertrophy (6). The finding of "normal" T1 values despite extensive fibrosis should raise the suspicion of FD. Areas of low T1 may be distributed within myocardium, particularly in females, in early stage of disease or in late stage with coexisting fibrosis. Current SCMR position paper, suggests to acquire only 3 short axis views of T1 mapping. With such approach, areas of abnormal T1 could be missed (34). The example of figure 2, in a patient with FD and extensive fibrosis shows areas of decreased T1 only in basal septum of 4-chamber view which was missed in short axis image (not showed). We strongly suggest to cover all the LV with a complete dataset of short axis images of T1 mapping from mitral annulus to LV apex or by acquisition of short axis and long axis images.



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T2 mapping may have a role in the evaluation of FD. Few studies reported a diffuse increase of myocardial T2 in FD, whereas other studies found abnormal T2 only the inferolateral wall, associated with consensual LGE (36,37). This increased of myocardial T2 was explained as an inflammatory phenomenon accompanying myocardial damage . T2 increase is not a specific for FD. In sarcomeric hypertrophic cardiomyopathy, focal increase of myocardial T2, as well as areas of hyperintensity in conventional T2-weigthed FSE, were reported (38). Moreover, myocardial edema is seen in acute phase of myocardial damage from many different conditions as ischemic heart disease, cocaine-induced myocardial damage, sarcoidosis etc.

Both T1 and T2 mapping are useful to evaluate myocardial response to ERT. Imbriaco et al demonstrated that ERT can normalize myocardial T2 in region with abnormal values at basal evaluation (39). Nordin et al, demonstrated a significant increase of myocardial T1 in patients naïve for therapy and in those with initiated ERT, whereas a substantial stability of values was found in those with long-time established therapy (40).

Late Gadolinium Enhancement and Extracellular volume mapping n Fabry disease

Late gadolinium enhancement (LGE) is the most important CMR feature. Gadolinium based media are interstitial agents, and they are not specific for fibrosis. However, the collagen matrix of scar, replacing dead myocyte, increases interstitial space and the myocardial distribution volume of gadolinium. For this reason, LGE is generally considered a valid marker of myocardial fibrosis. Patten of presentation of LGE is very useful for the differential diagnosis among the different causes of LV hypertrophy, as well as for differential diagnosis between ischemic and non-ischemic heart disease (41). In cardiac amyloidosis the pattern of LGE is very specific permitting a definite diagnosis in most of cases (42). Although less specific, the LGE pattern help also for the diagnosis of sarcomeric Hypertrophic cardiomyopathy, where LGE has an important prognostic role being a strong predictor of malignant ventricular arrhythmias (43,44).

In FD, as explained above, the intracellular overload of sphingolipids, increases myocyte dimensions and decreases interstitial space. LGE is only seen in late stage of FD when a sufficient mass of necrotic myocytes causes macroscopic fibrosis (6). In FD LGE is usually located in the inferolateral basal wall of LV, with a mid-wall distribution (10). However, this pattern of LGE is not specific of Fabry disease, being found in other conditions as myocarditis, arrhythmogenic cardiomyopathy, sarcoidosis etc (45) In table 2 are shown data of LGE presentation reported in FD studies (10,23,24,26, 46-52). The overall prevalence of LGE in FD was 33% (in 145 out of 442 patients). Eight studies also reported the distribution of LGE in LV myocardium (10,24,46-51). LGE was non-ischemic in all the cases, 113 patients (94%) presented inferolateral basal midwall LGE, and 7 (6%) a different pattern. All the patients of this latter group had asymmetrical LV hypertrophy and LGE was located in hypertrophic segments (mostly in interventricular septum). Multiple myocardial areas of LGE were reported in 29 patients (24%). Interestingly, Nieman et al demonstrated that LGE may be detected earlier than LV hypertrophy in female patients (6).

LGE is useful for the identification of the "pseudo-normalization of myocardial T1" in FD (20). Briefly, as mentioned above, in FD native myocardial T1 is decreased because of intracellular sphingolipids deposition. On contrast myocardial fibrosis increases myocardial T1, compensating the decrease of T1 by sphingolipid deposition. Then, myocardial regions containing both islands of viable myocytes (loaded with sphingolipids) and both areas of fibrosis may have average T1 values within the range of normality (example in

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Table 2: Prevalence and pattern of Late Gadolinium Enhancement in Fabry disease					
First Author, Journal, Year of Publication (ref.)	Patients with FD	Late gadolinium enhancement (LGE)	Classic pattern (basal inferolateral non ischemic LGE)	Other patterns	Multiple site of LGE
	n.	n.(%)	n.(%)	n.	
Moon, Eur Heart J, 2003 (46)	26	13 (50%)	12(93%)	1 inferior	-
Beer, Am J Cardiol, 2006 (47)	35	8 (31%).	6 (75%)	1 anterior /1 septal	-
Pieroni, J Am Coll Cardiol, 2006 (48)	40	10 (25%)	10 (100%)	-	1
De Cobelli, Am J Roentgenol, 2009 (49)	13	10 (77%).	10 (100%)	-	2
Niemann, JACC: Cardiovasc Imaging, 2011 (6)	104	41 (39%).	41(100%)	-	13
Kozor Heart 2016(50)	44	. 15(34.1%)	14 (93%)	1 anteroseptal	13
Deva, JCMR 2016 (10)	39	17 (44%).	14(76%)	2 apical/ 1 inferior	-
Nojiri J Cardiol 2020(51)	26	6(23%)	6(100%)	N/A	-
Roller, J Clin Med 2021 (26)	28	8(28%)	N/A	N/A	N/A
Zhao, Cardiovasc Diagn Ther 2021 (52)	20	4(20%)	N/A	N/A	N/A
Augusto, Eur Heart J Cardiovasc Imaging 2021 (23)	67*	13(19%)	N/A	N/A	N/A
Total	442	145(33%)	113(94)	7(6%)	29(24%)

figure 2). The identification of LGE in regions with apparently "normal" T1 values should raise the suspicion of "pseudo-normalization" of T1. Myocardial fibrosis usually does not involve all the myocardial segments, and it is very important to measure myocardial T1 in regions spared from LGE.

LGE has an important prognostic role in FD. In patients treated with the ERT, the studies by Weidemann et al (53) and Beer et al (47) demonstrated that the presence of LGE was associated with a low likelihood of regression of LV hypertrophy, and with a scarce improvement of exercise capacity. Moreover, the presence of LGE was associated with greater risk for malignant arrhythmic events, including sudden cardiac death (54).

Extracellular volume mapping (ECV) consists in the measurement of the distribution volume of gadolinium in myocardial tissue. Since gadolinium is an interstitial contrast agent, its distribution volume corresponds to the ECV of myocardium (interstitial space plus blood vessel). ECV is calculated as the ratio between myocardial and blood pool variation of R1 (that is 1/T1) induced by gadolinium injection, corrected by the haematocrit (31). ECV is increased in many conditions as amyloidosis, myocardial infarction and generally fibrotic myocardium of any causes. In Fabry disease, interstitial spaces are reduced by the intracellular overload of sphingolipids. Then, in absence of fibrosis, ECV is normal or even decreased and its role is limited to more advanced stages disease.

CMR protocol.

The proposed CMR protocols of pulse sequence for FD is showed in table 3.

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Table 3: CMR protocol in Fabry disease

techniques	**Recommended Acquisition planes**	**Pulse sequence**	**Scope**
3-plane localizer	Axial, coronal, sagittal	Vendor specific	Heart localization, image planning
Cine-SSFP	2- 4- 3- chamber views or Radial acquisition	SSFP (FIESTA, True-FISP, Balance).	LV morphology, regional wall motion assessment
Cine-SSFP	Short axis views from mitral valve plane to LV apex	SSFP (FIESTA, True-FISP, Balance).	LV morphology, regional wall motion, quantification of ventricular volumes, mass and functional parameters
T1 mapping	3-short axis views + 3 long views (2- 4- 3-chamber views) or full coverage of LV by short axis views	MOLLI, ShMOLLI, SASHA, SMART-T1	Measurement of native myocardial T1
T2 mapping	3-short axis views	GRASE, T2-Prep SSFP, MESE	Measurement of native myocardial T2/edema detection
Gadolinium-based contrast media injection			
TI- scout	4-chamber view	TI-scout, Cine-IR, Lock-Locker	Choice for appropriate TI for LGE
Late gadolinium enhancement	2- 4- 3- chamber views (or radial acquisition). or full coverage of LV by short axis views	2D-LGE, 3D-LGE, PSIR	Detection of Fibrosis, search for specific pattern for differential diagnosis

Conclusions

Despite FD cardiomyopathy is a rare cardiac disease, it should be considered in the differential diagnosis with all the conditions causing LV hypertrophy (table 4). An early diagnosis of FD is very important because the instauration of ERT may change the fate of the patients, reversing or blocking the development of cardiac involvement as well as of the other systemic manifestations. Moreover, the detection of a FD proband allows the screening of other family members.

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The diagnosis may be straightforward in males when specific signs and symptoms are present from childhood. However, in male patients with late onset disease and in females, the diagnosis is more challenging. Morphological and functional features don't permit to exclude the diagnosis. Decreased myocardial T1 associated with LV hypertrophy is probably the only imaging feature permitting to suspect FD. The assay of alpha-galactosidase enzymatic activity and the genetic evaluation confirm the diagnosis. Finally, LGE is important in FD to predict cardiac response to ERT and for prognostic evaluation.

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Table 4: CMR for differential diagnosis in left ventricular hypertrophy

Cause of LV Hypertrophy	Morphological and Functional features	Native myocardial T1	Myocardial T2 or signal at T2w STIR	Late Gadolinium Enhancement (LGE)	Extracellular Volume (ECV)
Fabry Disease	Concentric LVH (87%) Asymmetrical septal (12%) Asymmetrical apical (1%)	Decreased (segment without LGE) Pseudo-normal (segment with LGE)	Slight diffuse increase (inflammatory phase) Focal increase in inferolateral wall (associated with LGE)	Only in advanced stage of disease. Inferolateral midwall (or subepicardial) (94%), other site (6%)	Normal or slight decrease in absence of LGE. Increased in LGE areas.
Sarcomeric HCM	Asymmetrical LVH Secondary phenotype: -LV outflow obstruction with SAM -LAD bridge -crypts -elongation of AML -papillary abnormalities -RV hypertrophy -Apical aneurysms	Increased only in areas with fibrosis	Increased in acute damage associated with LGE	Midwall distribution in hypertrophic segments	Increased only in areas with LGE
Cardiac Amyloidosis	Concentric LVH	Diffusely and highly increased	Heterogeneous pattern	Typical pattern (spec 100%, sens 85%): -Diffuse subendocardial enhancement - early darkening of blood pool - nulling defect of myocardium	Diffusely and highly increased
Acromegaly	Concentric LVH	No data available	Normal	Negative	Normal
Mitochondrial disease	Concentric mild LVH	Increased only in areas with fibrosis	Increased only in areas with LGE	Small areas of focal LGE	Increased only in areas with LGE
Aortic stenosis	Concentric LVH. Severe aortic valve stenosis	Slight diffuse increase	Normal	Negative	Slight diffuse increase
Athlete's heart	Mild concentric LVH , LV and RV balanced dilation	Normal (or slight decrease in elite athletes)	Normal	Negative	Normal(or slight decrease in elite athletes)

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