Rare Metabolic and Endocrine Diseases with Cardiovascular Involvement: Insights from Cardiovascular Magnetic Resonance – A Review

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ABSTRACT

The identification of rare diseases with cardiovascular involvement poses significant diagnostic challenges due to the rarity of the diseases, but also due to the lack of knowledge and expertise. Most of them remain underrecognized and undiagnosed, leading to clinical mismanagement and affecting the patients' prognosis, as these diseases are per definition life-threatening or chronic debilitating. This article reviews the cardiovascular involvement of the most well-known rare metabolic and endocrine diseases and their diagnostic approach through the lens of cardiovascular magnetic resonance (CMR) imaging and its prognostic role, highlighting its fundamental value compared to other imaging modalities.

ABBREVIATIONS

BMI	Body mass index
CMR	Cardiac magnetic resonance
DCM	Dilatative Cardiomyopathy
ECV	Extracellular volume
EDWT	End diastolic wall thickness
ERT	Enzyme replacement therapy
FD	Fabry disease
GHD	Growth hormone deficiency
GCS	Global circumferential strain
GLS	Global longitudinal strain
HCM	Hypertrophic cardiomyopathy
IVS	Interventricular septum
LA	Left atrium
LGE	Late gadolinium enhancement
LV	Left ventricular
LVEDVi	Left ventricular end diastolic volume index
LVEF	Left ventricular ejection fraction
LVESVi	Left ventricular end systolic volume index
LVH	Left ventricular hypertrophy
LVM	Left ventricular mass
LVMi	Left ventricular mass index
LVPM	Left ventricular papillary muscle
LVSD	Left ventricular systolic dysfunction
RA	Right atrium
RV	Right ventricular
RVEF	Right ventricular ejection fraction
RVSD	Right ventricular systolic dysfunction

Introduction

A rare disease is defined as a condition that affects a small percentage of the population and is either life-threatening or chronic debilitating, and combined efforts are required to treat it. In terms of prevalence, there is no universal definition, as the numbers are affected by the size of each country's population, and even after adjustment it varies from 1 to 8 in 10 000 people [1]. Thus, in the USA it is defined as a disease that affects less than 200 000 people, in Japan less than 50 000, and in Australia less than 2000 [2]. According to the European Public Health Commission, the prevalence of rare diseases is estimated at 1:2000 [3]. Rare diseases are more than 8000, while about 30 million people are affected in Europe and 300 million worldwide [4].

The rarity of the diseases, but also the lack of knowledge and expertise make them a special entity, the treatment of which requires combined action with wide cooperation of many specialties and diagnostic approaches of all nations, so that there is a coordination of treatment at European level. Data for rare diseases are limited, especially those derived from cardiovascular magnetic resonance (CMR) imaging, as investigators struggle with limited patient data and scarce funding for research. Besides, small sample sizes are inevitable, especially when the primary end point is also uncommon and heterogeneity in the natural history of the disease and geographic dispersion also play an important role.

The goals of this paper are to review the applications of CMR in the spectrum of cardiovascular involvement of the most well-known rare metabolic and endocrine diseases and to suggest further methodological approaches, which can contribute to an early diagnosis and treatment of the disease.

Main Body

1) Storage diseases

Fabry disease

The superiority of CMR in terms of accuracy in the evaluation of cardiac structure and function in relation to echocardiography is well known, but what makes it unique, especially in infiltrative cardiomyopathies, such as Fabry disease, is its ability to characterize myocardial tissue [5].

Left ventricular hypertrophy (LVH) remains a key feature in Fabry disease, which requires extensive characterization. Primarily, cine sequences allow accurate measurement of left ventricular wall and mass and papillary muscles, ventricular volumes, left and right ventricular ejection fraction, and assessment of wall motion abnormalities. Data from recent years have demonstrated the importance of accurately calculating the left ventricular and papillary muscle mass, as patients undergoing enzyme replacement therapy have had a smaller increase in left ventricular mass [6], and the presence of disproportionate papillary muscle hypertrophy is also characteristic of the disease [7, 8]. CMR can detect cardiac involvement in almost one-half of the genotype-positive patients, even when the LVH severity is mild [9]. In addition, patients with elevated left ventricular mass index (LVMi) are more likely to have ventricular arrhythmias, as shown by Deva et al. [10]. In a study by Vijapurapu et al., LVMi correlated with impairment of all systolic strain parameters as well [11].

Myocardial tissue is characterized mainly by the method of late gadolinium enhancement (LGE) following intravenous administration of gadolinium and typically presents midmyocardial fibrosis in the basal and midventricular inferior-lateral wall of the left ventricle [9, 12–14]. However, atypical patterns of late enhancement in the basal anteroseptal and apical segment have also been observed in patients with asymmetric hypertrophy of the interventricular septum or with apical hypertrophy respectively [10, 11]. In addition, cases of patients with intramural and subepicardial LGE have been reported [15]. Finally, in advanced stages of the disease, late enhancement may be extensive and diffuse [10]. Interestingly, Niemann et al. showed that the onset of late enhancement may precede hypertrophy, especially in women [16]. Another study from Taiwan demonstrated that severe and irreversible cardiac fibrosis before development of LVH or other significant cardiac manifestations was also seen in a large portion of men with the IVS4 mutation, suggesting that it might be too late to start ERT after the occurrence of LVH or other significant cardiac manifestations in patients with late onset FD [17]. Furthermore, the prevalence of FD in patients with unexplained LGE has been reported as 2.5 % [18]. Recently, a strong association between the amount of late enhancement and cardiovascular events (arrhythmias, severe heart failure, cardiac death) has been suggested, demonstrating the importance of CMR in risk stratification in patients with Fabry disease [19].

As far as the role of CMR in monitoring response to therapy in FD patients is concerned, LV mass regression has only been demonstrated in AFD patients with either baseline LVH [19] or little or no LGE at baseline [20–24]. These findings suggest that treatment of Fabry disease with ERT should be started early before the development of myocardial fibrosis. Besides, it has been shown that myocardial fibrosis in Fabry disease is progressive, and not modified by ERT [25].

The characterization of myocardial tissue, however, is complemented by the new parametric mapping techniques. These techniques allow the quantification of changes in the composition of the myocardium, based on the relaxation times T1, T2, T2 * , and the extracellular volume by the addition of contrast agent [26]. Multiple studies have shown T1 mapping to be useful to differentiate patients with Fabry disease from other pathogeneses with increased wall thickness regardless of the sequence used [27–30]. The relaxation time T1 is typically very low (6 standard deviations lower than normal), even in the absence of hypertrophy [28, 29, 31–33]. This is more prominent in female patients, as the disease manifests in later stages. Therefore, this method contributes significantly to the differential diagnosis, as other diseases that present with left ventricular hypertrophy have a high relaxation time T1, except for athletes' heart. However, in this case there is a relatively small drop in T1 (up to only 2 standard deviations) [34]. Besides, the reduction of T1 relaxation time is not observed globally, since the basal posterior wall may have a high T1 time as part of the fibrosis and the surrounding segments may be normal. In any case, Deborde et al. demonstrated the importance of the value of T1 mapping for the identification of fibrosis foci, as it can be used in a large percentage of patients with Fabry disease and renal dysfunction without administration of gadolinium [35]. In addition, Réant et al. showed that T1 value along with other parameters was significantly predictive of occurrence of de novo atrial fibrillation or

stroke in these patients [36]. A recent study by Nordin et al. demonstrated that, although T1 values remained within normal limits, the values decreased with increasing age, reflecting a subclinical increase in sphingolipid accumulation in the myocardium. Furthermore, males demonstrated a more rapid decrease in T1 with age, which was then seen to increase after the development of LVH; women had a less rapid decrease in T1 and on the development of LVH demonstrated stabilization of T1 values [37]. Finally, another study presented that native T1 values correlated stronger with LV mass than CMR-derived GLS, emphasizing the potential use of native T1-mapping in the early detection of cardiac involvement and guidance of therapy timing [38].

Of interest, however, is the increase in T2 relaxation time observed in the basal posterior wall, as a surrogate marker of inflammation [39–41], while a reduction in T2 relaxation time has been correlated with the reversal of left ventricular mass in patients undergoing enzyme replacement therapy, which makes the method useful for monitoring the course of treatment [6, 42]. Specifically, Augusto et al. showed that when LGE was present, there were significant associations between increased T2 values in the LGE segments, an increase of troponin and N-terminal pro-B-type natriuretic peptide, electrocardiographic changes, and GLS impairment, whereas persistent T2 and troponin elevation over 1 year suggested chronic myocardial edema and injury, with associated clinical deterioration [41]. In addition, in some patients, myocardial edema increased together with LVH [42]. Another study showed that in up to 56 % of patients with Fabry disease myocarditis was detectable at histology. It was immune mediated, correlated with disease severity and contributed to disease progression and ERT resistance [43]. Finally, as the extracellular volume mainly reflects extracellular interstitial disease, it may miss intracellular lysosomal storage until diffuse fibrosis occurs [28].

Three stages of cardiac involvement have been proposed based on analysis of native T1 times, LVH, and LGE in a large cohort of patients with Fabry disease spanning all ages of life: 1) storage stage with normal or low native T1 times without LVH; 2) inflammation and myocyte hypertrophy with low native T1 times, presence of LGE with or without LVH; and 3) fibrosis and impairment with pseudonormalization of native T1 times and extensive LGE [39].

The technique of myocardial deformation, namely the newest feature tracking technique that does not require the acquisition of new sequences, but arises from the already obtained SSFP cine images, has also been proposed as a tool in the diagnostic quiver of Fabry disease. However, there is discrepancy regarding the strain values, maybe due to the different stages of the disease. Mathur et al. demonstrated that loss of base-to-apex circumferential strain gradient may be an early marker of cardiac involvement in Fabry disease, with independent and incremental value beyond native T1 [44]. Wilson et al. resulted in more positive CS values (CS) in patients with LVH [45], whereas Augusto et al. showed only a subtle impairment of GLS [46]. Recently, Zhao et al. presented that global longitudinal strain (GLS) was reduced significantly in all Fabry patients, while GCS was reduced only in patients with LVH or with LGE and heart failure [47]. The reduced GLS and global radial strain (GRS) were also confirmed in a recent study, which showed that GLS initially reduces with storage (low native T1 times and elevated LysoGb3 level, a specific biomarker of Fabry disease) and later with increasing LysoGb3 level and hypertrophy or scar (LGE) [48].

Regarding the myocardial perfusion imaging, positron emission tomography (PET) studies have showed coronary microvascular dysfunction, regardless of sex or the presence of left ventricular hypertrophy, with no improvement after enzyme replacement therapy [49, 50]. CMR data of recent years have shown a decrease in myocardial blood flow in the dynamic phase of the exam (myocardial blood flow) by the method of perfusion mapping, mainly subendocardial, with a greater reduction in patients with left ventricular hypertrophy, oedema and scar [51]. However, a reduction in perfusion was observed even in patients without left ventricular hypertrophy, thus making this sequence an early indicator of the disease [49, 51]. The same authors reported stress MBF to be lower in the endocardial than in the epicardial layers, but normal in controls. This was only in the subgroup with LVH. Indeed, in patients without any LVH, no difference between epicardial and endocardial stress MBF was detected. Besides, the presence of microvascular dysfunction before the onset of left ventricular hypertrophy has also been observed in hypertrophic cardiomyopathy [51, 52].

In conclusion, CMR with the new techniques it offers, plays a fundamental role in every stage of the course of Fabry disease, even in its early diagnosis.

Glucogen storage diseases (Pompe disease, Danon disease, Cori-Forbes disease, Anderson disease) and PRKAG2 syndrome

Given the rarity of the glucogen storage diseases, there is limited data regarding CMR. In the adult-form of Pompe disease (late-onset Pompe disease), a study has found that patients have normal ventricular dimensions and volumes in cine sequences, while a few have a non-ischemic late enhancement (LGE) or increased extracellular volume (ECV). The myocardial deformation feature tracking technique did not show any pathological changes in this group of patients. Therefore, the changes observed are mild and non-specific [53]. In a smaller study, CMR was performed in a subgroup of 12 patients with late-onset Pompe disease and no myocardial LGE was detected; how many patients underwent CMR, and cardiovascular comorbidities were not reported [54]. Otherwise, there are data from some case reports; a case of isolated severe nonischemic cardiomyopathy with an infiltrative process and heart failure [55], as well as a myocardial infiltration in a 54-year-old sportsman presented with syncope [56].

In contrast, patients with Danon's disease and PSKAG2 syndrome appeared to have a higher T1 relaxation time and extracellular volume (ECV), as well as late gadolinium enhancement, compared to patients with hypertrophic cardiomyopathy [57]. In particular, the pattern of late gadolinium enhancement in patients with Danon's disease is non-ischemic subendocardial or patchy and was observed mainly in the anterior/lateral/inferior wall of the midventricular or midventricular/apical myocardium or in the right ventricular insertion points, but not between them or in the interventricular septum [57–62], whereas a patchy midmyocardial LGE was documented in a case report with Danon's disease [63]. Case reports referred to the presence of apical hypertrophy with subendocardial patchy LGE, which was an atypical finding in apical HCM without an apical aneurysm or in an apical transmural pattern

[60, 64]. Although data regarding the phenotype of Danon disease have disproportionately focused on the severe findings in men because women appear to be less severely affected, a study showed a severe arrhythmogenic phenotype in women that includes a high risk of sudden death [65]. Of great interest is also the presence of perfusion deficits in the resting first-pass perfusion in almost all segments, partially transmural in the lateral and anterior ones [59, 60].

In the case of PSKAG2 syndrome, diffuse, concentric left ventricular hypertrophy is characteristic. However, asymmetric and eccentric forms of hypertrophy have also been observed [66, 67]. In addition to the already mentioned higher T1 relaxation time and extracellular volume (ECV) that characterize PSKAG2 syndrome, late enhancement (LGE) is observed globally subendocardial, subepicardial, and midmyocardial or patchy [57, 66, 68, 69]. T2 relaxation time has not been reported to show any significant changes [66]. Patients with late gadolinium enhancement required pacemaker implantation or had myocardial infarction [56, 68, 70]. Besides, extensive LGE in patients with hypertrophic cardiomyopathy has been shown to be an independent prognostic indicator for sudden cardiac death or appropriate ICD discharges [71]. Therefore, it has been proposed to be used as risk marker for sudden cardiac death and other adverse outcomes in patients with PSKAG2 syndrome [69].

Regarding Anderson disease or glycogenosis IV, a recent case report was presented with biventricular failure and increased right ventricular trabeculation with the presence of thrombus without evidence of late gadolinium enhancement [72].

Mucopolysaccharidoses

Cardiac involvement has been reported in all seven types of mucopolysaccharidoses as a common and early manifestation, especially in patients with MPS I, II and VI [73]. Valve thickening with dysfunction mainly of the left-sided valves and hypertrophy are characteristic [74]. Conduction abnormalities, coronary artery stenosis or obstruction, and stenosis or dilatation of the ascending aorta may also occur [75]. Heart disease occurs silently and contributes significantly to early mortality. In a retrospective case study of children with various forms of the disease, left ventricular hypertrophy and diastolic dysfunction occurred at an early stage, while left ventricular dilatation and systolic dysfunction occurred at older ages and in later stages of the disease [76].

Although data are scarce, CMR has been suggested, as the coexisting Pectus excavatum does not allow for optimal echogenicity. In a case report, normal left ventricular ejection fraction with paradoxical septal motion and dilated right ventricle with reduced ejection fraction were observed in the cine sequences. Valve pathologies were also observed, such as stiffened posterior mitral leaflet, while valve diseases were further characterized in the flow sequences. No late enhancement was observed [77]. However, the use of stress perfusion in these patients is also applicable, as they present a diffuse pattern of coronary heart disease [75]. In addition, since the disease is characterized by pathologies of large vessels, the application of magnetic angiography may also provide important clinical information.

Gaucher Disease

The cardiovascular form of Gaucher disease is characterized mainly by the presence of calcifications in the aortic and mitral valve [78], whereas cases of recurrent pericarditis [79] and dilated cardiomyopathy with reduced ejection fraction have been reported as well [80].

Although cardiovascular involvement is rare, there are CMR references. In a study of nine patients no late gadolinium enhancement was observed [81], while in one case report biatrial dilatation and dilatation of the right ventricle with preserved ejection fraction were observed, while the dimensions of the left ventricle were normal with normal ejection fraction and without hypertrophy. In addition, thickening of mitral leaflets was observed. Late gadolinium enhancement (LGE) sequences showed patchy intra-myocardial hyperenhancement with multiple foci in the basal and middle LV inferior and inferolateral segments, consistent with interstitial infiltrative fibrosis [82]. In fact, following these findings, the patient's enzyme replacement therapy was increased. The characteristic concomitant hepatosplenomegaly was also observed during the exam.

Therefore, CMR can play a role in the assessment of cardiac involvement in Gaucher disease and treatment, as high doses of enzyme replacement therapy have been shown to improve the symptoms of heart failure and left ventricular ejection fraction [83].

2) RASopathies

RASopathies are a group of genetic disorders caused by mutations in Ras/mitogen-activated protein kinase (RAS-MAPK) waterfall, including Noonan Syndrome, Noonan syndrome with multiple lentigines, capillary malformation–arteriovenous malformation syndrome, Costello syndrome, cardio-facio-cutaneous syndrome, and Legius syndrome. In all diseases of this category, congenital heart defects mainly include hypertrophic cardiomyopathy and pulmonary valve stenosis. In particular, there is a higher degree of ventricular hypertrophy, and a more severe pattern of obstruction of the left ventricular outflow tract (LVOT) compared to non-syndromic forms [84]. Biventricular involvement is often described, due to the high prevalence of right ventricular hypertrophy. Myocardial ischemia is also common and is a major clinical problem in young adolescents [85]. Besides, coronary artery abnormalities have been reported in up to 30 % of patients [86].

Noonan syndrome typically presents with asymmetric septal hypertrophy, often obstructive, although isolated cases of apical hypertrophy have been reported [87, 88]. Also, pulmonary valve stenosis, and congenital heart disease such as atrial septal defect, atrioventricular canal, and rarely Fallot tetralogy, patent ductus arteriosus and mitral valve abnormalities are common [89]. Vascular abnormalities have been also described, mainly aortic dissection, aortic root dilatation and Valsalva sinus aneurysms [89].

In Noonan syndrome with multiple lentigines mitral valve prolapse is common, whereas atrial septal defect, non-compacted myocardium, and coronary artery anomalies have been reported [86]. Costello syndrome typically presents with subaortic septal hypertrophy, while concentric left ventricular hypertrophy and biventricular hypertrophy have been described [90]. In the case of cardio-facio-cutaneous syndrome, subaortic septal hypertrophy has also been observed in isolated cases.

Primarily, cine sequences demonstrate left ventricular hypertrophy with increased cardiac mass and any large atrial or atrioventricular septal defects. The presence of their hemodynamic importance, but also the assessment of valvular disease can be achieved with the flow sequences. In addition, important information can be extracted from the planimetry of the heart valve orifices.

In the late gadolinium enhancement (LGE) sequence, the presence of a patchy form of gadolinium enhancement in the anterior/anterior septal and lateral walls has been reported [91]. Another case report showed septal LVH, severe LA-dilatation secondary to severe mitral regurgitation and LGE in the antero- and infero-septal myocardial segments, as well as in the papillary muscles [92]. Finally, an 18-year-old girl presented with progressive ascending aortic aneurysm with histopathologically confirmed giant cell aortitis [93] and the reveal of double-chambered right ventricle in an adult patient with undiagnosed Noonan syndrome has also been reported [94]. Consequently, the use of angiography or whole heart sequences is recommended in order to rule out any coexisting congenital heart disease.

3) Endocrine disorders

Pheochromocytoma

Although the most common cardiovascular manifestation is hypertension, patients with pheochromocytoma may develop arrhythmias, hypotension, myocardial ischemia, cardiomyopathy, aortic dissection, peripheral ischemia, and shock [95]. In addition, excessive stimulation of catecholamines has been shown to lead to damage, manifested as Takotsubo or inverted Takotsubo cardiomyopathy, dilated cardiomyopathy, hypertrophic cardiomyopathy, and myocarditis [96–105].

Specifically, left ventricular systolic function may be normal or reduced [101–103]. However, the reduced systolic function is transient, as improvement has been observed after surgical treatment of pheochromocytoma. Left ventricular hypertrophy is not bigger than that seen in hypertensive patients and resolves with surgery as well. Pericardial effusion is also observed. The sequence of myocardial deformation feature tracking is also interesting, as global circumferential strain (GCS) and diastolic strain are reduced in these patients, and they remain reduced even in operated patients with normal left ventricular ejection fraction [101].

The late gadolinium enhancement (LGE) method sometimes detects a small localized myocardial fibrosis in a non-ischemic pattern (midwall, subendocardial or patchy) with no increase in follow-up [101, 102].

Furthermore, the mapping technique can reveal myocardial lesions that are not seen in other sequences. Specifically, T1 relaxation time is increased compared to both healthy and hypertensive individuals [104], and in fact while it relapses with treatment [106], it sometimes remains high compared to normal [101]. Furthermore, basal, but not apical, circumferential strain was significantly higher in the patients with catecholamine-producing tumors compared to patients with essential hypertension [104]. In T2 mapping, there is an increase in T2 relaxation time, reflecting the presence of diffuse myocardial edema that subsides after surgery [102, 107].

As some patients present with symptoms of acute coronary syndrome without obstructive coronary artery disease findings on coronary angiography [108, 109], applying a stress perfusion sequence may rule out significant obstructive coronary heart disease, unless patients have significant risk factors for coronary heart disease or objective evidence of acute myocardial infarction [110]. In many cases, CMR plays a key role in order to eliminate other potential causes of regional LV systolic dysfunction, providing a comprehensive evaluation of both ventricles, and supporting the final diagnosis of the etiology. For example, in case reports, the presentation of phaeochromocytoma was as a biventricular Takotsubo cardiomyopathy [111] or Takotsubo cardiomyopathy and hypertrophic cardiomyopathy [112]. Two reports presented cases of myocarditis with T1 and T2 elevation with no evidence of LGE, where CMR revealed a pheochromocytoma [113, 114]. Another case report referred to the presence of asymptomatic pheochromocytoma in a patient with Holt – Oram syndrome, where CMR showed dilated right heart chambers with moderately severe RV systolic dysfunction, a patent RV-PA conduit with mild conduit regurgitation and extensive LGE of the RV myocardium and interventricular septum [115]. Finally, there is a report referring to a cardiac pheochromocytoma presenting during pregnancy; the tumor was in the right atrioventricular (AV) groove in the RCA (right coronary artery) territory, closely attached to the myocardium with LGE at its core [116].

Early recognition of different clinical symptoms that indicate this diagnosis is of great importance in the successful treatment of cardiomyopathy caused by pheochromocytoma. CMR allows an accurate diagnosis of cardiomyopathy and can monitor patients, as early recurrence of the disease can be detected even if patients are asymptomatic [110].

Growth hormone deficiency (GHD)

Growth hormone deficiency patients have been shown to have a normal or decreased left ventricular mass index (LVMi) [117–120], which increases one year after replacement therapy [117, 118]. On the contrary, in another study LVM was greater than in normal subjects, even when corrected for the body surface area [121]. The authors explained this difference due to higher blood pressure in the patients with GHD than in the normal subjects. Decreased left right ventricular stroke volume index, LV end-diastolic volume index and end-systolic volume index, as well as reduced ascending aortic diameter have also been reported [117, 119]. Although cardiac fibrosis is not a typical feature of the disease, isolated cases of late gadolinium enhancement (LGE) have been reported, which nevertheless were eventually attributed to ischemic heart disease [117].

As subjects with growth hormone deficiency have high cholesterol levels and therefore a higher risk of cardiovascular disease [122] or myocardial ischemia [117], further investigation is possible with the application of the stress perfusion sequence.

Acromegaly

In patients with acromegaly, dilatation of heart cavities, hypertrophy, and normal or reduced ejection fraction [123–128] are observed, while most of these changes are reversed with surgical treatment of the disease [124]. Interestingly, these changes are more pronounced in men than in women [125]. In this study right ventricle systolic dysfunction and mid-wall late gadolinium enhancement of the IVS and of the basal anterior LV myocardium were also demonstrated. Reported differences in the extent of LVMi or

▶ **Table 1** Summary of studies of CMR in patients with rare metabolic and endocrine diseases with cardiovascular involvement.

Disease	Investigators [Ref] and Study Design	Number of cases	Comparator	Findings
Fabry Disease (FD)	Imbriaco M et al. [6], Prospective observational study	11	None	LV mass and LV wall thickness were significantly reduced after 45 months of ERT, no significant change in LVEF
	Kozor R et al. [7], Prospective observational study	20	20 healthy control individuals	Inclusion of papillary muscles & trabeculations in LV mass contributed to a greater percentage of LVM in Fabry subjects
	Kozor R et al. [8], Retrospective observational study	478	125 Fabry disease, 85 hypertrophic cardiomyopathy (HCM), 67 amyloid, 82 aortic stenosis (AS), 40 hypertension, 79 controls	Disproportionate hypertrophy of LVPMs in FD, regardless of LVH. Low T1 not always present
	Kozor R et al. [9], Prospective observational study	50	39 healthy control individuals	Detection of cardiac involvement in 48 % of the FD cohort, despite the overall mild disease phenotype. Of those not on ERT, 21 % were reclassified as having cardiac involvement allowing improved risk stratification and targeting of therapy
	Deva DP et al. [10], Retrospective observational study	39	None	Concentric LVH, inferolateral mid-myocardial scar the most common manifestations of FD, but apical and asymmetrical of forms of LVH having more apical and mid-ventricular LV scar than cases with concentric thickening also observed. Patients with elevated LVMi had a greater incidence of ventricular arrhythmia
	Vijapurapu R et al. [11],Cross-sectional, international multicenter study	166	None	Low T1 in LVH patients, no significant correlation between LVEF – LVMi; LVMi correlated with impairment of all systolic strain parameters
	Moon J et al. [12], Prospective observational study	26	None	In 92 % of the patients, LGE was seen in the basal infero-lateral wall and was not sub-endocardial. 50 % of the male patients had LGE and its percentage was related to LVMi but not to EF or LV volumes
	De Cobelli F et al. [13], Retrospective observational study	13	10 patients with symmetric HCM, matched for age (7 males)	FD patients with LVH consistently showed LGE in the inferolateral basal or mid basal segments in a mesocardial distribution sparing the subendocardium
	Nojiri A et al. [14], Prospective observational study	26	None	LGE localized at the mid-wall in the infero-lateral area of LV. LGE-positive patients were older, and tended to have a larger LVMi
	Weidemann F et al. [15], Clinical cross-sectional study	39	25 healthy control individuals	31 % (2 females, 10 males) of the FD patients had LGE in the inferolateral wall, two of them showed additional LGE in antero-septal segments. 23 % had intramural and 7.7 % had subepicardial LGE
	Niemann M et al. [16], Prospective observational study	104	None	LGE and loss of myocardial function can occur without LVH in females
	Hsu TR et al. [17], Prospective observational study	129	None	Severe, irreversible cardiac fibrosis before development of LVH was seen in a large portion of men with the IVS4 mutation
	Moonen A et al. [18], Retrospective observational study	79 patients with unexplained LGE	None	Prevalence of FD in patients with unexplained LGE was 2.5 %; patchy mid-wall pattern in the inferoseptum
	Hanneman K et al. [19], Retrospective observational study	90	None	LVH and LGE were independent predictors of adverse cardiac events; patients with extensive LGE were at highest risk
	Arends M et al. [20], Retrospective observational study	73	None	Increased cardiac mass at baseline was associated with decrease in cardiac mass during treatment; presence of cardiac fibrosis predicted a stronger increase in cardiac mass

▶ **Table 1** (Continued.

Disease	Investigators [Ref] and Study Design	Number of cases	Comparator	Findings
	Koeppe S et al. [21], Prospective observational study	25	43 healthy control individuals	Highest degree of hypertrophy and hypokinesia if LGE was detectable. Significant decrease of the EDWT under ERT in LGE negative patients and decline of hypokinesia with regional differences
	Weidemann F et al. [22], Prospective observational study	32	20 healthy control individuals	FD patients with mild or severe fibrosis showed a minor reduction in LVH despite ERT
	Beer M et al. [23], Prospective observational study	17	None	LGE was associated with increased LVM, failure of significant regression of LVH during ERT and worse segmental myocardial function
	Hughes DA et al. [24], Randomized, controlled study	15	None	ERT resulted in regression of LVH
	Krämer J et al. [25], Prospective observational study	57	None	In patients with established fibrosis, there is an increase in the degree of fibrosis despite ERT, as the only independent predictor of ventricular arrhythmias
	Walter TC et al. [27], Prospective observational study	25	14 patients with HCM, 21 healthy control individuals	T1 shortening in FD patients in a varying degree, segment-specific
	Thompson RB et al. [28], Prospective observational study	31	21 subjects with concentric remodeling or hypertrophy and 23 healthy controls	Reduced myocardial T1 values are the most sensitive and specific cardiovascular MRI parameter in patients with FD irrespective of sex and LV morphology and function
	Sado DM et al. [29], Prospective observational study	44	67 healthy volunteers, 41 patients with hypertension, 34 patients with HCM, 21 with severe aortic stenosis and 20 patients with definite amyloid light-chain (AL) cardiac amyloidosis	Septal T1 was lower in FD and higher in other diseases. Pseudonormalization or elevation of T1 was showed in the left ventricular inferolateral wall, correlating with the presence or absence of LGE
	Karur GR et al. [30], Prospective observational study	30	30 patients with HCM	Significantly lower native T1 values at 3.0 T in patients with FD compared with those with HCM - independent and incremental diagnostic value beyond age, sex, and conventional imaging features
	Pica S et al. [31], Prospective observational study	63	None	T1 reduction in FD happens prior to the onset of LVH and is associated with early diastolic and systolic changes measured by echocardiography
	Camporeale A et al. [32], Prospective observational study	44	None	In prehypertrophic FD, low T1 values correlate with early electrocardiographic, morphological cardiac changes, and worsening of global disease severity but not associated with functional abnormalities
	Deborde E et al. [35], Prospective observational study	17	36 patients with HCM, 70 healthy control individuals	Significantly lower native T1 values in patients with FD in comparison with those with HCM and healthy volunteers
	Réant P et al. [36], Prospective observational study	35	20 healthy control individuals	T1 value was significantly predictive of occurrence of de novo atrial fibrillation or stroke in FD patients
	Nordin S et al. [37], Prospective observational study	182 (15 children)	None	T1 values remained within normal limits, but decreased with increasing age; more rapid decrease in T1 with age, which was then seen to increase after the development of LVH in males; less rapid decrease in T1 and stabilization of T1 values on the development of LVH in females
	Reid AB et al. [38], Prospective observational study	66	None	T1 values correlated stronger with LV mass than CMR-derived GLS

▶ **Table 1** Continued.

Disease	Investigators [Ref] and Study Design	Number of cases	Comparator	Findings
	Nordin S et al. [39], Prospective observational study	47	28 patients with HCM, 30 patients with chronic myocardial infarction, 60 healthy control individuals	Lower T1 values and lesser T1 elevation in LGE in FD patients, normal remote area T2, but elevated LGE T2
	Augusto JB et al. [41], Prospective observational multicenter study	186	29 patients with HCM, 30 patients with chronic myocardial infarction, 59 healthy control individuals	Chronic local T2 elevation in LGE in FD, strongly associated with chronic troponin elevation; slight global T2 elevation. Association with ECG and mechanical changes and clinical worsening over 1 year
	Messalli G et al. [42], Prospective observational study	16	None	ERT leads to significant reduction in T2, maximal myocardial thickness and total LV mass
	Frustaci A et al. [43], Retrospective observational study	78	None	Myocarditis histologically detectable in 56 % of patients with FD, immune mediated, correlated with disease severity and contributed to disease progression and ERT resistance
	Mathur S et al. [44], Prospective observational study	38	8 healthy control individuals	Loss of base-to-apex CS gradient is an early marker of cardiac involvement in FD, with independent and incremental value beyond native T1
	Wilson HC et al. [45], Retrospective observational study	18	None	FD patients with LVH have reduced native T1 and more positive circumferential strain compared to those without
	Augusto JB et al. [46], Prospective observational study	114	76 healthy control individuals	Pre-LVH FD with normal T1 had reduced GLS, microvascular changes, subtle T2 elevation, limited LGE
	Zhao L et al. [47], Prospective observational study	20	20 healthy control individuals	GLS was reduced significantly in all Fabry patients, GCS was reduced only in patients with LVH or with LGE and heart failure
	Roller FC et al. [48], Prospective observational study	28	28 healthy control individuals	T1, GLS, and GRS were significantly reduced in FD patients. T1 and GLS were significantly lower in Lyso-Gb3 positive FD patients
	Elliott PM et al. [49], Prospective observational study	10	24 healthy control individuals	Resting and hyperemic MBF and CFR were reduced in FD patients compared with controls
	Knott KD et al. [50], Prospective observational study	44	27 healthy control individuals	FD patients have reduced perfusion, particularly in the subendocardium with greater reductions with LVH, storage, edema, and scar
Glucogen Storage Disease				
Late-onset Pompe Disease	Boentert M et al. [53], Prospective observational study	17	18 healthy control individuals	Mild, non-specific cardiac abnormalities can be detected by CMR only in a small proportion of patients with late-onset Pompe disease
	Morris DA et al. [54], Prospective observational study	subgroup of 12 (not reported)	187 healthy control individuals	No evidence of myocardial fibrosis in late-onset Pompe disease
	Mori M et al. [55], Case report			Isolated severe nonischemic cardiomyopathy with infiltrative process and heart failure
	Walczak-Galezewska M [5], Case report			Isolated infiltrative cardiomyopathy with syncope
Danon Disease & PSKAG2 syndrome	Fang T et al. [57], Prospective observational study	2	None	Higher T1, ECV, and LGE in patients with Danon's disease and PSKAG2 syndrome, compared to patients with HCM
	Dara BS et al. [58], Case reports	2	None	Patchy LGE in the lateral wall, and one or both RV insertion points in Danon's disease

▶ **Table 1** Continued.

Disease	Investigators [Ref] and Study Design	Number of cases	Comparator	Findings
	Piotrowska-Kownacka D et al. [59], Case report			LGE in the anterior/lateral/apical segments, and RF inferior insertion point; first pass perfusion defects in Danon's disease
	Tada H et al. [60], Case report			Subendocardial inferior LGE, intramyocardial lateral LGE and RF inferior insertion point
	Nucifora G et al. [61], Case reports	2		Subendocardial anterior, lateral, posterior LGE, transmural apical, IVS and RF inferior insertion point
	Rigolli M et al. [62], Prospective observational study	12	None	In males, LVH was typically concentric with normal LVEF. Females had impaired LVEF, asymmetrical LVH, RVH, and 2 different phenotypes: HCM or DCM. 3 patients showed no LGE. Various LGE patterns and distributions but always sparing the mid-septum. Extensive LGE consistently sparing the mid-septum may represent a specific sign of DD cardiomyopathy
	Vago H et al. [63], Case report			Patchy midmyocardial LGE in Danon's disease
	Yu L. et al. [64], Case report			Apical hypertrophy with subendocardial patchy LGE in Danon's disease
	Miani D et al. [65], Prospective comperative study	5 female patients	2 male patients	Severe arrhythmogenic phenotype in women with high risk of sudden death in Danon's disease
	Pöyhönen P et al. [66], Prospective comperative study	6		At earlier stages of PSKAG2 syndrome, without LGE, T1 values may be reduced, while in the advanced disease stage T1 values are higher. Patchy LGE
	Fabris E et al. [67], Case report			Asymmetric LVH in PSKAG2 syndrome
	Yogasundaram H et al. [68], Case report			Patchy, subepicardial, midmyocardial LGE in PSKAG2 syndrome
	Yang KQ et al. [69], Prospective comparative study	6		Concentric LVH, subendocardial or transmural LGE in PSKAG2 syndrome
	Sternick EB et al. [70], Case report			Myocardial infraction in a teenager with PRKAG2 gene mutation
	Lyo S et al. [72], Case report			Severe biventricular failure with presence of intraventricular thrombi with increased RV-trabeculation and no LGE in heterozygous glycogen storage disease type IV
Mucopolysaccharidoses	Mostefa-Kara M et al. [77], Case report			Normal LVEF, paradoxical septal motion, dilated RV with reduced EF; valve pathologies, no LGE
Gaucher Disease	Roghi A et al. [81], Prospective observational study	9		Two patients with valvular disease, three patients with mild LA-enlargement, no LGE
	Solanich X. et al. [82], Case report			Biatrial dilatation,RV-dilatation with preserved EF, normal LV-dimensions and LVEF, no LVH; Patchy intra-myocardial LGE with multiple foci in the basal and middle LV inferior/inferolateral segments
Rasopathies	Hudsmith LE et al. [91], Case report			Patchy LGE in the anterior/anterior septal and lateral segments in a patient with Noonan syndrome
	O'Neill AC et al. [92], Case report			Septal LVH, severe LA-dilatation secondary to severe MR;LGE in the antero- and infero-septal myocardial segments and papillary muscles in Noonan syndorme
	Menon S et al. [93], Case report			Progressive aneurysmal dilatation of the ascending aorta with histopathologically confirmed giant cell aortitis in an 18-year old girl with Noonan syndrome
	Patel AM et al. (94), Case report			Reveal of double-chambered RV in an adult patient with Noonan syndrome

▶ **Table 1** Continued.

Disease	Investigators [Ref] and Study Design	Number of cases	Comparator	Findings
Pheochromocytoma	Ferrerira VM et al. [101], Prospective observational study	29	31 patients with previously surgically cured pheochromocytoma, 51 healthy control subjects and 14 hypertensive control subjects	In newly diagnosed pheochromocytoma impaired LVEF, peak systolic CS, diastolic strain rate, higher T1, areas of myocarditis and focal fibrosis (nonischemic LGE)
	Roghi A et al. [102], Case report			Myocardial edema and intramyocardial LGE in a middle-aged woman with non-specific clinical presentation suggesting ACS or subacute myocarditis. Resolution of both after surgical excision.
	De Lazzari M et al. [103], Case report			Heart failure (normal LV-dimensions and mild LVSD with akinesia of mid inferolateral wall and hypokinesia of mid anterolateral and inferior walls). Myocardial edema and midwall LGE in the inferolateral wall
	Higuchi S et al. [104], Retrospective observational study	16	16 patients with essential hypertension	Native T1 values and basal, but not apical, circumferential strain were significantly higher in the CPT than the EH patients
	Gervais MK et al. [105], Case report			Pheochromocytoma presenting as inverted Takotsubo cardiomyopathy and DCM
	Nam MCY et al. [106], Case report			Transient regional myocardial edema in endocrinopathy-Induced Takotsubo cardiomyopathy
	de Miguel V et al. [107], Case report			Catecholamine-induced myocarditis (increased LV wall thickness and diffuse intramyocardial edema with focal midwall LGE)
	Martínez A et al. [111], Case report			Biventricular Takotsubo Cardiomyopathy as the Initial Manifestation of a Pheochromocytoma
	Gravina M et al. [112], Case report			Pheochromocytoma mimicking Takotsubo cardiomyopathy and HCM
	Khattak S et al. [113], Case report			Myocarditis (T1 and T2 elevation, no evidence of LGE), where CMR revealed a pheochromocytoma
	Wong TS et al. (114), Case report			Catecholamine-mediated myocarditis complicated by LV thrombus
	Ng P et al. [115], Case report			Asymptomatic pheochromocytoma in a patient with Holt–Oram syndrome: dilated right heart chambers, moderately severe RVSD, patent RV-PA conduit with mild conduit regurgitation, extensive LGE of the RV myocardium and IVS
	Fraser LA et al. [116], Case report			Cardiac pheochromocytoma presenting during pregnancy; tumor located in the right atrioventricular groove in the right coronary artery territory, closely attached to the myocardium with LGE at its core
Growth hormone deficiency (GHD)	Thomas JD et al. [117], Prospective observational study	10	10 healthy control subjects	Trend towards reduced LVMi and significantly reduced aortic area observed in GHD patients at baseline; lost by 1 year of GH treatment. Fibrosis and ischemia in some patients
	Dattani A et al. [118], Prospective observational study	10	6 healthy control subjects	Patients with adult-onset GHD have an LVMi at or below the lower limit of normal, which improves with one year of GH replacement
	Andreassen M et al. [119], Prospective observational study	16	16 healthy control subjects	Patients had significantly smaller LVEDVi & LVESVi; GHD not associated with LVSD or reduced LVMI
	De Cobelli F et al. [120], Prospective observational study	15	15 healthy control subjects	Reduced LVM in patients with GHD without major structural/metabolic alterations
	Gonzalez S et al. [121], Double-blind, placebo-controlled randomized, cross-over trial	17	16 healthy control subjects	Patients with GHD had significantly higher systolic BP, EF, LVMi than the control group; treatment with rGH normalized the insulin-like growth factor 1 concentration failed to normalize the functional and structural cardiac differences

▶ **Table 1** Continued.

Disease	Investigators [Ref] and Study Design	Number of cases	Comparator	Findings
Acromegaly	Guo X et al. [124], Prospective observational study	50	None	LV and RV EF of acromegaly patients were higher than the healthy reference values. Male patients had thicker LV myocardia, wider ventricular diameters and more dilated pulmonary artery roots than female patients. Postoperative cardiac reversibility was observed in male but not in all female patients.
	Guo X et al. [125], Prospective observational study	61	None	LVH, LV, and RV systolic dysfunction and mid-wall LGE of the IVS and of the basal anterior LV myocardium. Gender might influence cardiac parameters via its impact on BMI
	Bogazzi F et al. [126], Prospective observational study	14	None	LVH present in 72 % of the patients, which was only detected in 36 % patients by echocardiography. Cardiac fibrosis was absent in all patients
	dos Santos Silva CM et al. [127], Prospective observational study	40	None	No clinically relevant differences in cardiac variables were observed before and after treatment, no difference in LVMi and LVEF among patients with and without disease control
	Warszawski L et al. [128], Prospective observational study	36	None	No sustained arrhythmias and lack of arrhythmia-related symptoms in a contemporary cohort of acromegaly patients with low frequency of structural heart changes
	Gouya H et al. [129], Prospective observational study	15	None	Increased T2 values in patients with acromegaly, which decrease soon after treatment, reflecting reversible myocardial edema. T2 value is more sensitive than LVMi in the detection of early reversal of acromegalic cardiomyopathy
	Kim MS et al. [130], Case report			Acromegaly presenting as dilatative cardiomyopathy with patchy LGE

LVEF are maybe due to different degree of development and ethnicities of the enrolled patients (e. g., Asian vs. Caucasian). Another study showed that patients with acromegaly have increased myocardial T2 values, which decrease soon after treatment, reflecting reversible myocardial edema. The authors suggested that T2 value is more sensitive than left ventricular mass index in the detection of early reversal of acromegalic cardiomyopathy [129]. Finally, in a case report, acromegaly presented as dilatative cardiomyopathy with patchy LGE [130].

A tabular survey of studies of CMR in patients with rare metabolic and endocrine diseases with cardiovascular involvement is presented in ▶ **Table 1**.

Conclusion

Cardiovascular magnetic resonance through its ability to assess with great accuracy the anatomy, function, inflammation, (dynamic) perfusion of the myocardium, fibrosis, vascular structures, iron and/or fat deposition plays a key role in the early diagnosis of cardiac involvement, risk stratification, treatment evaluation, and long-term follow-up of patients with metabolic cardiomyopathy [131]. In the case of rare diseases specifically, its role should be considered fundamental, as it allows an early diagnosis of cardiovascular involvement, leading to the determination of the therapeutic strategy and affecting the patients' prognosis.

Conflict of Interest

The authors declare that they have no conflict of interest.

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