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Cardiac magnetic resonance imaging in patients with Fabry's disease

Obrazowanie serca za pomocą rezonansu magnetycznego u pacjentów z chorobą Fabry'ego

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Abstract

Fabry's disease (FD) is a rare hereditary disorder caused by the loss of alpha galactosidase A activity leading to accumulation of glycosphingolipids in various organs including hypertrophy of the heart. Most reports on cardiac involvement in FD focus on the left ventricular hypertrophy (LVH) and its relation to diastolic function. However, recent studies demonstrated large subset of patients with FD and right ventricle (RV) hypertophy. The accurate depiction of RV volumes, function and mass is possible with cardiovascular magnetic resonance (CMR). The CMR study can be also used to identify typically localised regions of intramyocardial fibrosis (infero-lateral segments of the LV), which have been shown to be a marker of inefficacious response to enzyme replacement therapy. We present series of 8 patients with genetically confirmed FD who underwent CMR study. We demonstrated a typical concentric and diffuse pattern of LVH with RV involvement in patients with the most severe LVH without significant impact on RV function and volumes. We showed that myocardial fibrosis can be observed not only in LV but also in RV. In 2 patients FD coexisted with symptomatic coronary artery disease with evidence of subendocardial myocardial fibrosis typical for ischaemic origin in one patient. The CMR confirmation of the presence of FD in one patient at an early stage of the disease, before the onset of advanced hypertrophy or failure of other organs, supports the value of this imaging technique in differential diagnosis of concentric and diffuse LVH.

Key words: Fabry's disease, left ventricular hypertrophy, right ventricle, magnetic resonance imaging

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INTRODUCTION

Fabry's disease (FD) is a rare X-linked hereditary disorder caused by the loss of alpha galactosidase A activity and leads to accumulation of glycosphingolipids in various organs including the heart [1]. Initial symptoms of heart involvement comprise conduction abnormalities, frequently leading to the pacemaker implantation. Cardiac hypertrophy which develops at the later age (5th–6th decade of life) is responsible for the onset of diastolic heart failure. Most reports on Fabry's disease focus on the patterns of left ventricular hypertrophy (LVH) and their relation to symptoms [2]. However, recent studies demonstrated that in a subset of patients with FD right ventricle (RV) may be also compromised [3, 4]. Therefore, accurate and reproducible assessment of RV parameters (volumes, function and mass) is also clinically important. This examination is typically difficult with 2-dimensional echocardiography, because of the low spatial resolution and complex geometry of the RV, but not with the cardiovascular magnetic

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resonance (CMR) imaging [5, 6]. The latter technique can be also used to identify the regions of myocardial fibrosis, which have been shown to be a marker of the ineffectiveness of the enzyme replacement therapy [7]. We present eight cases of CMR studies in patients with FD diagnosed and treated in our centre.

METHODS

Nine enzyme replacement therapy naive patients with genetically confirmed FD with or without echocardiographic features of heart involvement were referred to our centre for initiation of the enzyme replacement therapy as a part of clinical trial comparing the effect of various dosing regimens of alpha-galactosidase — Replagal® on regression of LVH (ClinicalTrials.gov Identifier NCT00864851). Seven patients underwent CMR as a part of the CMR substudy accompanying the main trial. Two patients were excluded from the CMR substudy because of the prior pacemaker implantation. Another patient (C.J.) was referred to the CMR unit for diagnosis of the LVH of unknown origin found on echocardiography. After CMR suspicion of FD the patient underwent genetic testing which revealed a typical mutation for the disease. Therefore, the whole study included 8 subjects.

All the CMR examinations were performed using a 1.5 Tesla scanner (Avanto, Siemens, Erlangen, Germany). Steady state free precession cine images for the assessment of RV and LV morphological and functional parameters were performed in accordance with the previously published protocol [8]. Subsequently, a gadolinium contrast agent was administered in 5 patients in order to assess the late gadolinium enhancement as described previously. Three patients did not receive gadolinium contrast for the safety measures due to the history of renal transplantation or end-stage chronic kidney disease. Images were analysed using dedicated software (MASS, Medis, Leiden, The Netherlands) as described previously [9]. The LVH and RVH were considered significant if LV or RV wall thickness exceeded 14 or 5 mm, respectively [10, 11]. The LV was divided into 16 segments per the American Heart Association classification (excluding the apex) and RV was divided into 3 subsequent segments (superior, anterior and inferior) of the free wall in each of the 3 sections (basal, mid-, apical).

RESULTS

Baseline characteristics of the studied group are presented in Table 1. Most patients were in the 5th or 6th decade of life and were males which is typical for X-linked mutations. Most often found abnormalities included the following futures: angiokeratomas and hypohidrosis, corneal changes and chronic kidney disease. Results of the CMR studies are presented in Table 2 [12, 13]. Left ventricular hypertrophy was found in 7 patients and RVH in 4. Left ventricular wall was not thickened in the youngest subject. Examples of ventricular hypertrophy are presented in Figure 1. Two patients had an evidence of intramyocardial fibrosis typical for non-ischemic origin (Fig. 2A–C) and one patient had an almost transmural postmyocardial infarction scar responsible for the reduction of muscle thickness and systolic heart failure (Fig. 3).

DISCUSSION

Our findings confirm that the LVH in FD is generally symmetric and diffused which is characteristic of storage diseases [1, 14] in contrast to most typically asymmetric pattern found in sarcomeric hypertrophic cardiomyopathy [10]. It is also fre-

Table 1. Baseline characteristics of the studied patients

	M.P.	M.W.	C.J.	G.P.	J.P.	M.R.	J.T.	G.S.
Age [year] at the time of CMR, gender	54, male	44, male	33, male	55, female	52, female	25, male	55, male	49, male
Renal disease	Post-RT	Post-RT CKD stage 4	–	CKD stage 2	CKD stage 2	CKD stage 4	CKD stage 3	Post-RT
Prior stroke	+	–	–	–	–	–	+	–
History of CAD	PCI of Cx PCI of ISR	–	–	–	–	–	Post-MI	–
Neuropathic pain	Severe	Moderate	–	–	Mild	–	–	–
Gastrointestinal manifestations	Moderate	–	–	Mild	–	–	–	–
Confirmed corneal changes	+	+	+	+	+	+	+	+
Angiokeratoma/ /hypohidrosis	Severe	Moderate	Mild	Mild	Mild	Mild	Mild	Mild
Tinnitus	+	–	–	–	–	–	–	–

CAD — coronary artery disease, CKD — chronic kidney disease, CMR — cardiac magnetic resonance, Cx — circumflex artery, ISR — in-stent restenosis, MI — myocardial infarction, PCI — percutaneous coronary intervention, RT — renal transplantation

Table 2. Cardiac magnetic resonance findings in studied patients

	M.P.	M.W.	C.J.	G.P.	J.P.	M.R.	J.T.	G.S.
LVEDVI [mL/m^2]	72 [62–97]*	93 [64–99]	100 [66–101]	77 [56–90]	76 [56–90]	66 [68–103]	121 [62–97]	111 [64–99]
LVEF [%]	57 [58–76]	59 [58–75]	73 [57–75]	69 [59–77]	81 [59–77]	75 [57–74]	31 [58–76]	64 [58–75]
IVSDmax [mm]	21	22	15	16	18	14	12	29
LVMI [g/m^2]	134 [57–91]	182 [58–91]	88 [59–92]	102 [48–78]	102 [48–78]	66 [59–93]	133 [107–184]	224 [58–91]
LVH	+	+	+	+	+	+	–	+
No. of hypertrophied LV segments (max. 16)	8	10	2	4	3	2	0	16
LGE in the LV and its type	NA	NA	+ intramyocardial	+ intramyocardial	–	–	+ subendocardial	NA
RVEDVI [mL/m^2]	50 [67–111]*	59 [67–111]	106 [74–134]	78 [42–118]	81 [42–118]	85 [74–134]	47 [67–111]	106 [67–111]
RVEF [%]	62 [49–73]	79 [49–73]	67 [47–67]	63 [50–78]	69 [50–78]	58 [47–67]	67 [49–73]	68 [49–73]
RVMI [g/m^2]	37 [14–26]	42 [14–26]	19 [14–30]	22 [13–25]	35 [13–25]	23 [14–30]	17 [14–26]	63 [14–26]
RVH	+	+	–	–	+	–	–	+
No. of hypertrophied RV segments (max. 9)	3	5	0	0	2	0	0	7
LGE in the RV	NA	NA	–	–	+	–	–	NA

*Reference values for sex and age for left and right ventricular parameters are cited after references [12] and [13]; IVSDmax — maximal interventricular septal diameter, LGE — late gadolinium enhancement, LV — left ventricle, LVEDVI — left ventricular end-diastolic volume index, LVEF — left ventricular ejection fraction, LVH — left ventricular hypertrophy, LVMI — left ventricular mass index, NA — not applicable, RV — right ventricle, RVEDVI — right ventricular end-diastolic volume index, RVEF — right ventricular ejection fraction, RVH — right ventricular hypertrophy, RVMI — right ventricular mass index

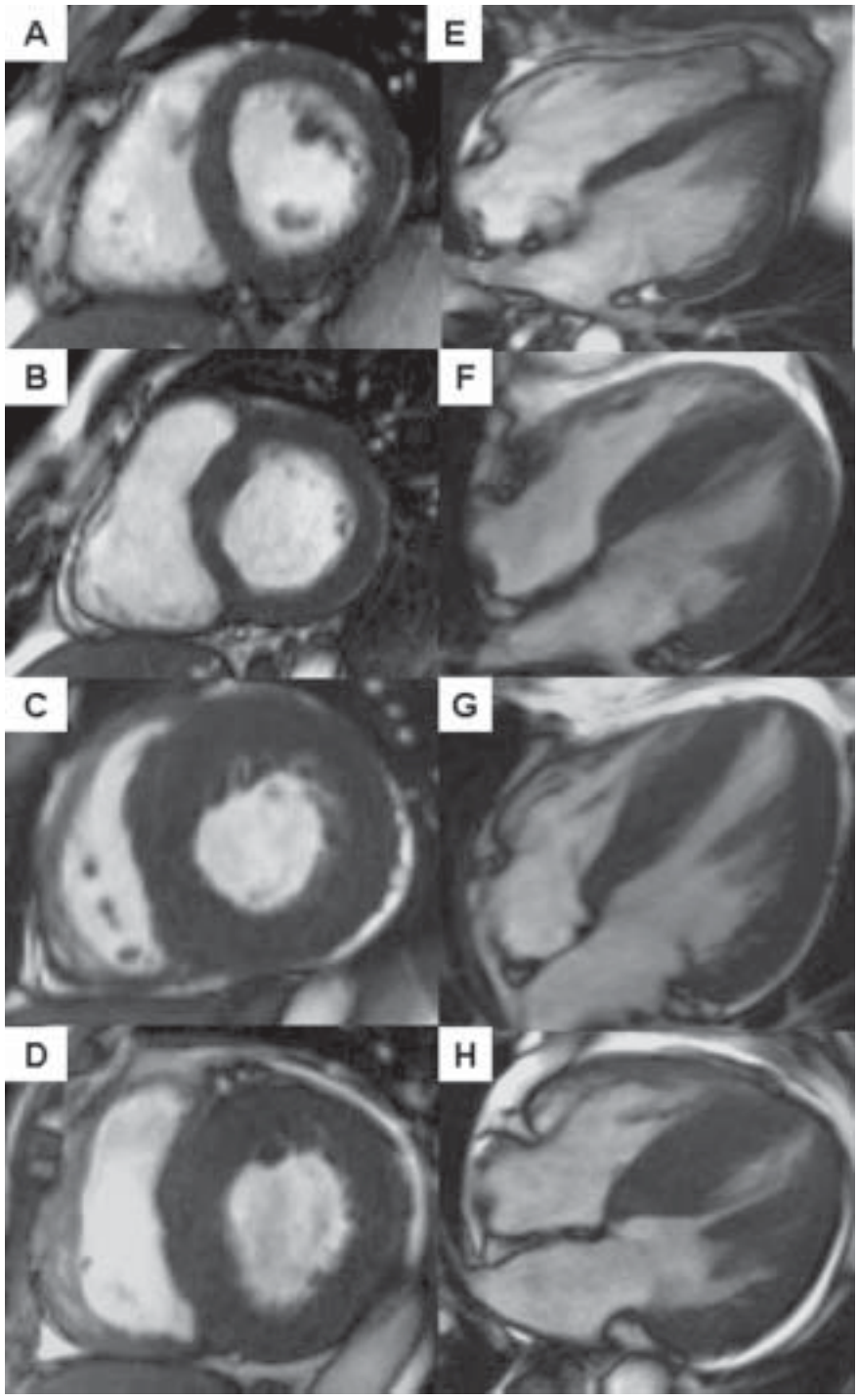

Figure 1. Steady-state free precession cine cardiovascular magnetic resonance images in end-diastole in short axis (**A–D**) and in 4-chamber view (**E–H**) in 4 of the presented patients with Fabry's disease aligned according to the growing LVH/RVH (from top to bottom)

quently accompanied by the symmetric and diffused RV hypertrophy which seems to increase with increasing LVH. Systolic function and dimensions of both ventricles are generally not affected.

To our knowledge this is the first CMR study in patients with FD focusing on RVH. Our results show that CMR enables an accurate and detailed analysis of the RV and is free from the limitations attributed to acoustic window, two-dimensional plane and relatively low spatial resolution of transthoracic echocardiography.

Late gadolinium enhancement (significant of myocardial fibrosis) in patients with FD is characterised by the in-

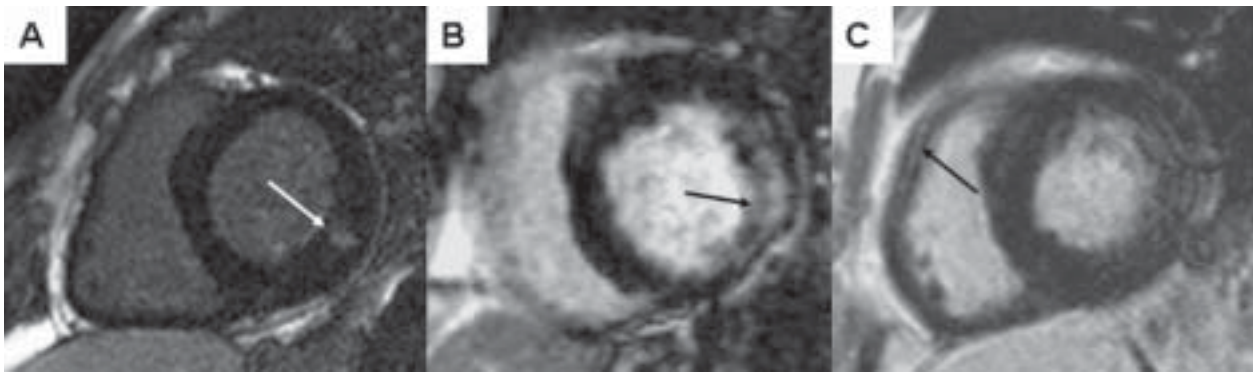

Figure 2. Short axis cardiovascular magnetic resonance images. Intramyocardial late gadolinium enhancement (arrows) in studied patients with Fabry's disease in the infero-lateral segments of the LV (**A, B**) and in the RV free wall (**C**)

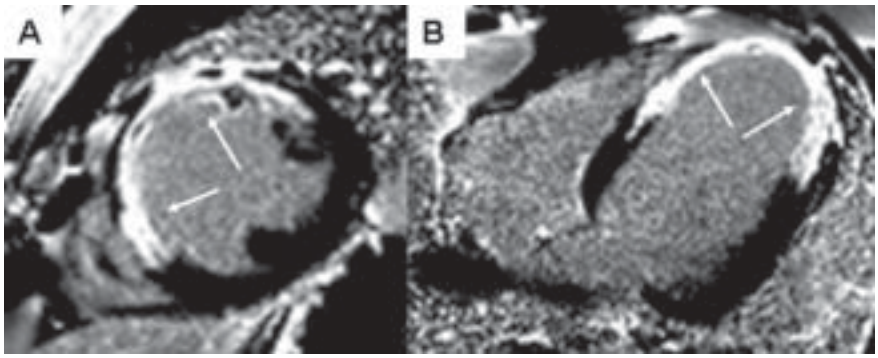

Figure 3. Subendocardial late gadolinium enhancement (arrows) in a patient after antero-septal myocardial infarction with coexisting Fabry's disease: **A.** Short axis view; **B.** Four-chamber view

tramyocardial localisation and is typically found in the mid-ventricular infero-lateral segments. The finding of focal intramyocardial fibrosis in infero-lateral segment of LV led to the suspicion of an early stage of FD in one of the studied patients (C.J.), before the onset of the advanced hypertrophy or failure of other organs. Subsequent genetic confirmation of the presence of disease in this patient supports the value of the CMR testing in subjects with symmetric and diffused pattern of LVH. This is in line with previous report showing the utility of CMR in the diagnosis of FD [15]. In one case of FD we were able to demonstrate that fibrosis may also affect the hypertrophied RV wall which to our knowledge has not been shown before. It is important to note that patients with FD may suffer from other heart diseases such as for example coronary artery disease (Table 1). Therefore, the presence of symptomatic coronary artery disease does not exclude the diagnosis of FD. Myocardial injury of ischemic origin leads to the distinct subendocardial or transmural pattern of fibrosis as demonstrated in one of our patients (Fig. 3).

Unfortunately, not all patients with FD may undergo CMR study, because of the known contraindications such as pacemaker implantation which diminishes the value of CMR as a screening method. Additional safety measures have to be implemented in patients with prior renal transplantation or with end-stage chronic kidney disease. In this situation gadolinium contrast agents should not be administered.

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