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The significance of cardiac magnetic resonance imaging in detection and monitoring of the treatment efficacy of heart involvement in eosinophilic granulomatosis with polyangiitis patients

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Abstract. *Background:* Cardiac magnetic resonance (CMR) imaging has emerged as a sensitive and non-invasive technique in the evaluation of cardiac lesions in eosinophilic granulomatosis with polyangiitis (EGPA) patients. *Objectives:* To evaluate the ability of CMR imaging to detection and monitoring of the treatment efficacy in EGPA patients with cardiac involvement. *Methods:* To the retrospective-prospective study were enrolled 33 cardiac involvement EGPA patients. In 19 of them CMR imaging at the moment of diagnosis was performed, in 14 – CMR imaging after treatment was made, when this method was available - in this group the cardiac involvement was based on the clinical findings. All patients were treated with corticosteroids and/or cyclophosphamide. In the first group the control CMR imaging after one year of the treatment was performed, but in the second group the time from the end of the treatment to execution of CMR imaging was 2-5 years. *Results:* All patients had heart injury in CMR imaging. Myocardial edema was present in 87.8% cases, 54.5% of patients had perfusion defects and in all - late gadolinium enhancement was observed. Control CMR imaging was performed in 32 cases. Improvement was observed in 81% of patients – in 11% of them all lesions undergone completely remission and in 35% of them evolution to global fibrosis was found. In 7% of patients stabilization was achieved and in 12% - progression was observed. *Conclusions:* CMR imaging is a sensitive method detecting cardiac lesions in EGPA patients. It helps to detect patients, who need combined therapy and helps evaluate the therapeutic effect. *(Sarcoidosis Vasc Diffuse Lung Dis 2016; 33: 51-58)*

Key words: EGPA, heart involvement, magnetic resonance

Introduction

Eosinophilic granulomatosis with polyangiitis – EGPA (formerly called Churg-Strauss syndrome) is a rare necrotizing vasculitis characterized by asthma, eosinophilia and extrapulmonary manifestations (1-3). Cardiac involvement comprise pericarditis, restrictive or dilated cardiomyopathy, myocarditis, arrhythmias and sudden death. The frequency is described between 16%-92% (4-7). Symptomatic car-

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diomyopathy carries a poor prognosis, is responsible for nearly 50% of the deaths and requires combined therapy with corticosteroids and cytotoxic agents (8). Early detection of these lesions is very important. Unfortunately, cardiac pathology has often subclinical course and may be undiagnosed by clinicians. The electrocardiogram (ECG) and transthoracic echocardiography (TTE) are the most often used screening tools for heart evaluation.

Recently, cardiac magnetic resonance (CMR) imaging has emerged as a sensitive technique in the evaluation of myocardial function and structure (9-12).

This study analyzed the significance of CMR imaging in the cardiac involvement detection and monitoring effects of the treatment in EGPA patients.

Patients and method

Among the 54 patients (34 women, 20 men, aged 15-74 years, median 41) diagnosed as EGPA (one of them postmortem) based on the American College of Rheumatology 1990 criteria and Lanham's criteria (13,14) in the years 2003-2013 in the National Research Institute of Tuberculosis and Lung Diseases, in 36 patients (24 women, 12 men, aged 15-68, median 40) cardiac involvement was recognized. Three patients were excluded: one was treated and died because of cardiac infarct before CMR imaging was introduced, second died because cardiac infarct confirmed by autopsy before treatment and third didn't receive treatment because he had only post-inflammatory lesions in the papillary muscle of the heart in CMR imaging.

Thirty three patients were enrolled to the retrospective - prospective study. All gave written informed consent. For all these patients the following informations were collected: cardiovascular risk factors (cholesterol level, hypertension, tobacco use, diabetes, family history of coronary artery disease), history of cardiovascular manifestations and cardiovascular symptoms and clinical manifestations of EGPA.

In all patients basic laboratory tests (with levels of N-terminal brain natriuretic peptide NTpro-BNP and troponin I), TTE, ECG and antineutrophil cytoplasmic antibodies (ANCA) concentration were estimated. Cardiac involvement was considered, when the patient had or previously experienced cardiac insufficiency and/or the echocardiogram showed heart enlargement and/or cardiac dysfunction and/or abnormal ECG signs defined as complete right or left bundle branch block, biffascicular block, third-degree atrioventricular block, ventricular tachycardia or pathological Q or ST and/or elevated cardiac troponin I or N-terminal brain natriuretic peptide (NTpro-BNP).

33 patients were treated by combined therapy corticosteroids (CSs) and cyclophosphamide (CY) or by alone CSs. The initial dose of CSs was 1 mg/kg/day (no more than 60 mg/day) and CY – 2 mg/kg/day. During one year treatment, the doses of CSs and CY were discontinuated. Addition of CY to CSs was performed according to recommendations (15). In addition to this therapy, patients with cardiac insufficiency, received angiotensin-converting enzyme inhibitors and/or beta – blockers and/or spironolacton. Patients with asthma additionally inhaled CSs and/or beta – 2 – agonist. Patients, in whom cardiac thrombosis was present, received anticoagulant treatment.

CMR imaging was performed in 33 patients: in 21 cases - at the moment of EGPA diagnosis – in these patients treatment was initiated and control CMR imaging twelve months after therapy was planed (prospective part of study), and in 12 cases – after treatment, when CMR imaging was available (in this group cardiac involvement was based on the clinical findings) – it was retrospective part of study. The time from the end of the treatment to perform CMR imaging was 2-5 years.

According to the guidelines (12,16,17) presence two tissue-based CMR imaging criteria: increased T2 - weighted images and increased late gadolinium enhancement (LGE) were the basis of acute myocardial involvement recognition, whereas presence of LGE alone indicated previous myocarditis. Additionally, the presence of the perfusion abnormalities, the left ventricular (LV) dysfunction and/or pericardial effusion were assessed. Left ventricular ejection fraction (LVEF) below 50% was considered as decreased.

The assessment of the therapy efficacy was based on the following findings in control CMR imaging: 1) decrease or resolution at least one of the following lesions: T2-weighted images and/or LGE lesions.

In response assessment was also taken decrease or resolution of the perfusion defect, LV volume and function improvement and reduction of the clinical symptoms. Evolution to LGE lesions alone, according to the data available in the literature, was interpreted as post inflammatory fibrosis and also was qualified as improvement (18). Expansion of the areas of T2-weighted images and/or of the LGE lesions was interpreted as a progressive disease. When lesions were similar to those before the treatment, a stable disease was diagnosed.

CMR imaging

CMR scans were performed with a clinical 1.5-T scanner (Avanto SQ-engine, T-class Tim [76x32], Siemens, Erlangen, Germany) using a 32-channel cardiac phased-array coil. ECG-gated, state-of-the-art, steady-state, free precession gradient echo cine sequences were obtained during breath holding in continuous short axis slices covering the whole left ventricle. For apical segment assessment additional horizontal and vertical long axes of the left ventricle were imaged. T2-weighted short axis images were obtained with a triple-inversion, black-blood, fast spin-echo sequence. Perfusion was performed at rest on 3 short axis slices with T1-weighted gradient echo sequence right after intravenous Gd-contrast administration (0,1 mmol/kg b.w. GD-DTPA) using a "first pass" method. Late enhancement images in short and long axis of the left ventricle were obtained 10-15 minutes after perfusion series with a state-of-the-art inversion recovery 2D gradient echo sequence. The inversion time was set to null normal myocardium.

Analysis of CMR images

The analysis was performed on a dedicated workstation (Syngo, Siemens). The endocardial borders were manually traced in systolic and diastolic frames of the short axis cine series. Left ventricular ejection fraction was calculated. Left Ventricular enlargement was defined as end-diastolic volume index > 92 ml/m^2 for male and > 81 ml/m^2 for female.

Valvular insufficiency was detected by the presence of a systolic jet back-flow across the valve. On T2-weighted images, the signal ratio of the myocardium relative to skeletal muscle was calculated based on manually drawn regions of interest covering the myocardium in short axis and a skeletal muscle present in the same image. A ratio of above 2 was considered abnormal (myocardial edema).

Perfusion was interpreted visually. Rest perfusion defect was defined as subendocardial or/and transmural hypointense region visible on 3-5 frames during first pass of contrast medium. Late gadolinium enhancement images were evaluated qualitatively for the presence of hyperintense lesions in contrast to hypointense normal myocardium (16,17,18).

Results

To the retrospective – prospective study were enrolled 33 EGPA patients with cardiac involvement. Twenty two patients were in the 0-I functional NYHA (New York Heart Assotiation) class, 10 – in the second class and 1 patient in the III.

Clinical cardiac symptoms (palpitations, mild exertion dyspnea, atypical chest pain), were found in 14/33 patients (42%). Among the 21 patients included to the prospective part of the study, 12 had cardiac symptoms, but among the 12 patients included to the retrospective part of the study, only 2 had cardiac symptoms, the rest was in clinical remission of the disease. Only 5 patients had life threatening symptoms: 2 - cardiac arrest, 1 – pulmonary edema, 1 – cardiogenic shock and 1 – cardiac infarct. Elevated cardiac enzymes (NTproBNP, troponin I) were observed in 25/33 cases (75.7%). TTE abnormalities were found in 21 (63.6%) patients, but ECG abnormalities - in 20 (60.6%). Elevated ANCA concentration was present in only two patients. CMR imaging was performed in 33 patients. All patients of both groups had evidence of myocardial injury on CMRI. Left ventricular ejection fraction (LVEF) was decreased in 22 patients (68%), left ventricular (LV) size was enlarged in 17 patients (51.5%). Valvular insufficiency was presented in 4 cases (12.1%), 13 patients (39.4%) had pericardial effusion (without clinical significance), in 4 (12.1%) thrombus in the LV was found . Myocardial edema in CMR imaging (increased T2-ratio imaging) was observed in 29 patients (87.8%), 18 patients (54.5%) had perfusion defect, LGE lesions were present in all patients (table 1). All patients including to the prospective part of the study had active myocarditis in CMR imaging

Table 1. Clinical characteristic and findings in the CMR imaging examination in 33 EGPA cardiac involvement patients

Parameter	Number of patients
women	22
men	11
all	33
age	15-68
median age	40
Functional class (NYHA)	
0-I	22
II	10
III	1
clinical symptoms	14 (42%)
exertion dyspnea	12
palpitations	7
chest pain	4
fainting	2
TTE findings	21 (63.6%)
active disease	13
non-active disease	8
ECG abnormalities	20 (60.6%)
active disease	11
non-active disease	9
cardiac enzymes elevated (NTpro-BNP or troponin I)	25 (75.7%)
ANCA present	2 (6%)
CMR imaging examination	33
LVEF > or = 50%	11 (33%)
LVEF < 50%	22 (66%)
LV size enlarged	17 (51.5%)
T-2weighted imaging	29 (87.8%)
perfusion abnormalities	18 (54.5%)
LGE	33 (100%)
valvular insufficiency	4 (12%)
mitral regurgitation	3
aortic regurgitation	1
pericardial effusion	13 (39.4%)
presence of thrombosis	4 (12%)

LGE – late gadolinium enhancement, LV – left ventricular, LVEF – left ventricular ejection fraction, ANCA – antineutrophil cytoplasmic antibodies, CMR imaging – cardiac magnetic resonance imaging, ECG – electrocardiography, NTpro-BNP – N-terminal brain natriuretic peptide, TTE – transthoracic echocardiography

(increased T-2 weighted images and LGE were present), but among the 12 patients including to the retrospective part of the study, 8 had active myocarditis, while in 4 - LGE areas alone were found. Subendocardial typical for EGPA distribution of the lesions was confirmed in 31/33 patients (94%) and in 2 (6%) – only subepicardial localization was found. Figures 1 a, b, c and 2 show typical for EGPA patients CMR lesions in our material.

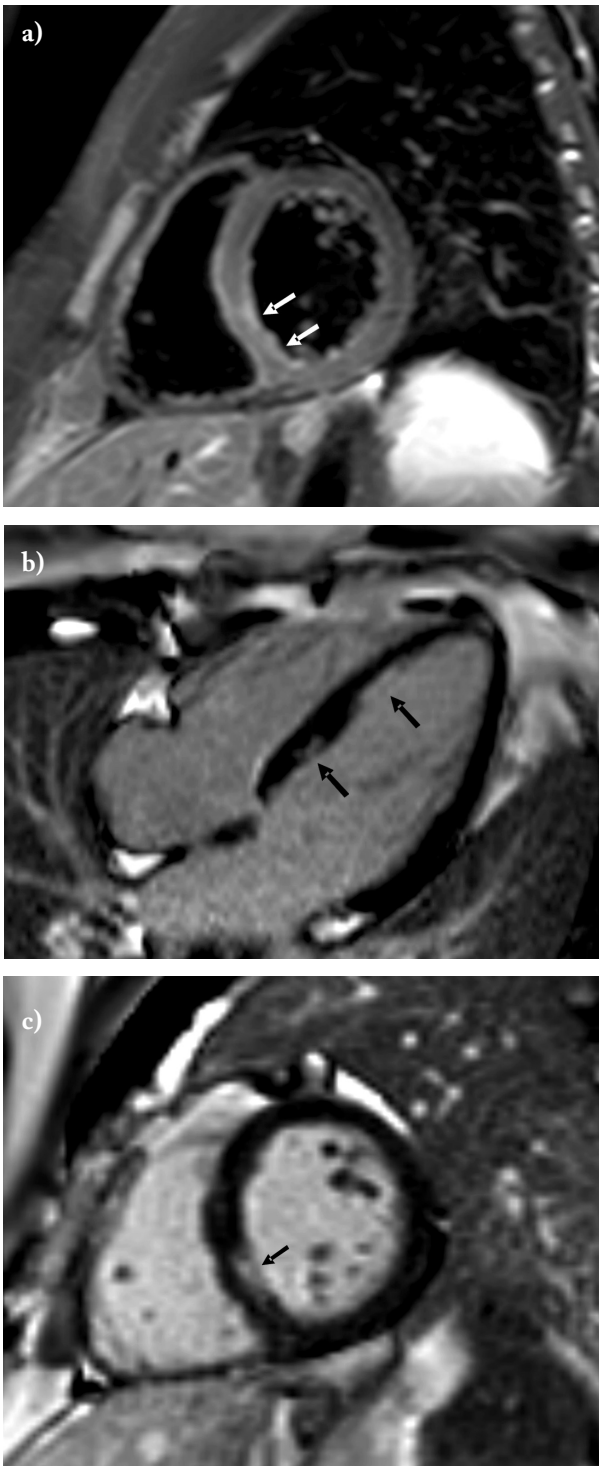

Fig. 1. 26 years old male; a – T2-weighted TSE image with fat saturation in short axis mid-cavity crossection, showing edema in infero-lateral segment (arrows). Delayed Gadolinium enhancement images in 4 chamber (b) and short axis mid-cavity (c) crossection showing subendocardial enhancement pattern (septal segments; arrows), typical for EGPA patient

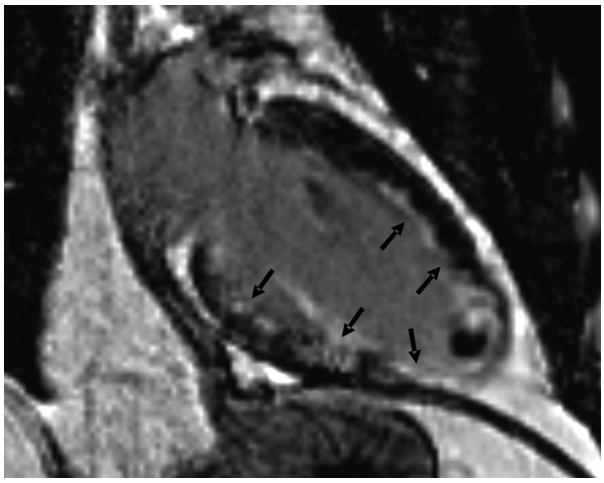

Fig. 2. 32 years old male; delayed Gadolinium enhancement image in vertical long axis crossection showing subendocardial enhancement of the anterior wall, subendocardial and transmural enhancement of the inferior wall, inferior papillary muscle and the LV apex (arrows). Thrombus seen as an unenhanced mass in the apical part of the LV cavity

Among 33 patients 17 received at the beginning combined therapy with CY (one patient died), in 4 patients initially treated by CSs - immunosuppressive agent (CY) was added based on the CMR imaging findings and 12 patients were treated only by CSs.

In the most patients (9/13), who had initially clinical symptoms and were treated, the clinical improvement after the therapy was observed. Two patients had still marked arrhythmias and were qualified to implantable cardioverter n- defibrillator implantation, one patient is waiting for heart implantation. One patient died after four months of the therapy probably because of the infection.

Control CMR imaging was performed in 32 cases - among them twenty patients had initial and follow-up CMR (one patient died). Improvement was observed in 26/32 patients (81%) – in 3 of them (11%) all lesions undergone completely remission and in 9 of them (35%) evolution to global fibrosis was found. Among the 20 patients treated by combined therapy (group I and II) improvement in CMR imaging was observed in 16/20 patients (80%), but among 12 patients treated only by CSs (group III) improvement in CMR imaging was found in 10 cases (83%). Comparison of the groups I and II together (including patients treated by CSs/CY) with the group treated only by CSs (group III) shows, that response for treatment in CMR imaging in all groups was similar (80% v 83%), but in the group III the evolution to global fibrosis was more frequently observed (42% v 25%). Six patients (19%) didn't achieve improvement in CMR imaging despite of the long term treatment: in 2 cases (7%) there was stabilization and in 4 cases (12%) there was progression (areas of the lesions were more widespread). It didn't correlate with the worsening of clinical status (table 2).

Completely remission of LGE lesions was observed only in 3 patients, in the rest they persisted on follow-up images. Completely remission of edema was found in 5 patients and completely remission of perfusion defect was detected in 7 patients. In 3 patients all three lesions regressed (table 3).

Decrease of the LVEF was observed in 22/33 patients (68%). Increase after treatment achieved 12/22

Table 2. CMR imaging improvement in 32* treated EGPA patients depends on the kind of the treatment

The type of the treatment	Number of patients	Progression Number of patients	Stabilization number of patients	Good response number of patients/(%)	Fibrosis number of patients/(%)
Initially combined therapy (CSs and CY) group I	16	2	2	16/20 (80%)	5/20 (25%)
CY added based on the CMR findings group II	4	-	-		
Only CSs therapy group III	12	2	-	10/12 (83%)	4/12 (42%)
Overall	32	4/32 (12%)	2/32 (7%)	26/32 (81%)	9/32 (28%)

CMR – cardiac magnetic resonance, PR – partial regression, CSs – corticosteroids, CY-cyclophosphamide *one patient, who received combined therapy, died after 4 months

Table 3. Comparison of CMR imaging data at baseline and after treatment

Parameter	Baseline data n=21	Post-treatment data n=32*	Completely remission n=32*
T2-weighted images	21/21	19/32	5
Perfusion abnormalities	13/21	9/32	7
LGE	21/21	17/32	3
Three lesions presence	13/21	8/32	3

LGE – late gadolinium enhancement *one patient died during therapy

patients (54%), but in 10 patients (45%) LVEF was still reduced. The relationship between LVEF and the presence of intensity of fibrosis in CMR imaging was observed. Among 22 patients with cardiac insufficiency and LVEF < 50% global myocardial fibrosis was found in 13 cases (59%), while in the group with normal LVEF, only in 4 patients fibrosis was observed (36%). Similarly, in patients without LVEF improvement after therapy. In this group significant fibrosis was found in 7 among 10 cases (70%), while in the group with LVEF improvement after therapy – only in 6/12 patients (50%). We didn't observe LV size or valvular abnormalities normalization, but mild pericardial effusion resolved in all cases.

Discussion

In recent years CMR imaging has been successfully used to identify myocarditis patients (9,12,19). The most prominent findings are: 1) focal and global myocardial edema appears as an area of high signal intensity in T2-weighted images, 2) increased LGE specifically reflects irreversible myocardial injury (necrosis or fibrosis) and 3) early gadolinium enhancement interpreted as hyperaemia (9). The presence of at least 2 positive criteria is diagnostic accuracy for myocarditis CMR imaging features (positive predictive value 91%) (9,16,17). In our study we evaluated two required features (T2 – weighted images and LGE) and presence of both at the same time was the basis of myocarditis recognition. CMR imaging reveals as a more sensitive method to detect of cardiac involvement in EGPA patients compare with other usually used methods, like ECG or TTE, especially in asymptomatic myocarditis with normal LV systolic function. In this cases heart abnormalities can be overlook and CMR imaging is helpful (20, 21). In our study normal ECG had 39.4% of patients and normal echocardiography – 36.4% of patients – in all CMRI showed cardiac lesions. It supports, the normal ECG and/or TTE does not exclude cardiac involvement in EGPA patients.

The ability of CMR imaging to diagnose myocardial inflammation in EGPA patients was previously reported by others (11,22,23,25), but usually there were single studies with the small number of patients. Especially important and marked problem are cardiac lesions discovered in asymptomatic patients in clinical remission of the disease. Marmursztejn at all CMR imaging abnormalities found in 13/20 EGPA patients, including all 9 patients with clinical manifestation of EGPA, and 4 of the 11 asymptomatic patients (25). In our material, in 21 patients changes in CMR imaging were found at the moment of diagnosis during active disease (only 12 had cardiac symptoms), in 12 cases changes in CMR imaging after treatment were found – 10 of these patients were in clinical remission of the EGPA. It is not clear, what should be done in this situation. Some authors (19) have decided to give immunosuppressive agents patients, in whom cardiac lesions after therapy were present and it resulted decreased of edema and early enhancement lesions in control CMR imaging, but without impact on the LVEF and late enhancement lesions. We decided to increase the CSs dose in 4 patients and to introduce immunosuppressive drug – CY – in 4 patients, who earlier were treated only by CSs. Four patients didn't receive new treatment, because during 6 years observation the LV function was not worse and in CMR imaging postinflammatory fibrosis dominated. The long-term follow-up of asymptomatic and in clinical remission patients, in whom lesions in CMR imaging were detected is, at present, unknown. Careful monitoring of cardiac manifestations is recommended, because some EGPA patients have had late heart failure and succumbed to sudden death, even months or years after vasculitis recovery. Further investigations are needed to determine the meaning and evaluate the prognosis of CMR imaging abnormalities and to decide whether such imaging findings should induce therapeutic intervention.

A frequent outcome of the myocarditis is fibrosis, which has been visualized with CMR imaging. Late gadolinium enhancement lesions has been

correlated with histologically proven fibrosis and/or active myocarditis and LGE alone assessment did not help distinguish between fibrosis and inflammation (18). Other CMR imaging features, like T-2 weighted images detecting myocardial edema, may help make this distinction. Indeed, the signal – to noise ratio of T-2 weighted images strongly depends on sequence parameters. Particularly in patients with arrhythmia and other motion artifacts, image quality may not allow for reliable visualization or quantification of edema, but a high diagnostic accuracy has been shown for this approach in acute inflammatory (26,27). In our patients all doubtful T-2 weighted images were repeated and those without artifact were chosen. When at least two lesions were found (T-2 weighted images, LGE), it corresponds to inflammation, while presence of the LGE lesions alone is connected with fibrosis (18). It is important, that the group of patients with dominated fibrosis is heterogeneous and the prognosis in this group is unclear. In part of them fibrosis is global and due to cardiac insufficiency with LFEV decreased and LV enlargement, what showed our study too. It is interesting, that in our material, fibrosis was more frequently found in patients treated only by CSs. Perhaps insufficient treatment is cause of this phenomenon. Patients, in whom predominates fibrosis, in our opinion, don't need immunosuppressive treatment, but the further studies are needed to confirm this view.

Not entirely clear is the significance of the rest perfusion abnormalities in EGPA. They seem to be caused by small-vessel obstruction secondary to local subendocardial inflammation. This is compatible with the known histological abnormalities of EGPA, i.e., fibrinoid necrosis of the small subendocardial vessels accompanied by eosinophilic infiltration of the endocardium and adjacent myocardium with myocytolysis. Due to the rarity of EGPA, further studies are necessary to evaluate the impact of this technique (28).

EGPA patients' survival rate is good, when treatment is stratified to the baseline FFS (Five-Factor Score). Relapses are frequent, especially in patients with anti-myeloperoxidase antibodies and baseline eosinophilia < 3000/mm3 (4, 5). Optimal therapy is therefore important, since Cohen et al (29)reported that long-term treatment with adjunctive immunosuppressive agents in patients with poor prognosis, including cardiac involvement, improved event- and disease-free survival rates. There are very few reports demonstrated the ability of CMR imaging to monitoring effects of the treatment in EGPA patients with cardiac involvement and there are usually single case reports (230,10). The largest prospective study of its kind date comprised 8 EGPA patients with myocarditis treated with CY, showed a clinical or radiological improvement demonstrated on CMR imaging in 6 of them (31). In our knowledge, our study included 33 patients, is the first large study presented effects of treatment with CMR imaging control in EGPA cardiac involvement patients.

Conclusions

We would advocate the use of CMR imaging in all EGPA patients at the beginning of diagnosis. It is a sensitive, non-invasive method detecting cardiac lesions in patients also without evidence of cardiac disease in conventional investigations and in patients in clinical remission of the disease. CMR imaging could be helpful to decide, whether immunosuppressants are indicated in addition to CSs in agreement to guidelines. Our study showed, that efficacy of the alone CSs is comparable to combined treatment, however it can be more often complicated by cardiac fibrosis. In our opinion, CMR imaging is a helpful method of the therapy efficacy, but there are need further prospective studies to determine the value of this technique in improving the management and control outcome of patients with this disease.

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Authors' contribution

EW and KRS conceived the idea for the study and contributed to the design of the research. DPK made and interpreted cardiac magnetic resonance imaging and JK made and interpreted echocardiography. UN, DG, MMB were involved in data collection. All authors edited and approved the final version of the manuscript.

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