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Screening for Cardiac Sarcoidosis with the MRI under Immunosuppressive Therapy

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Abstract

The cardiac affection in systemic sarcoidosis often presents as functional impairment or rhythmic abnormalities and is of prognostic relevance. Due to the focal granulomatous changes, the detection of the sarcoid lesions can be challenging. Cardiac MRI allows for a unique non-invasive presentation of the cardiac structure, and detects the typical changes even in up to 30% of asymptomatic patients. Treatment options include immunosuppressive therapies such as systemic corticosteroids that suppress the inflammatory processes. In an unfiltered group of sarcoidosis patients, however, many of the patients will be or already had been on immunosuppressive therapy, often due to an extra-cardiac affection. The presented study examines the influence of the immunosuppressive therapy on the findings of the initial screening MRI.

All included patients have been seen at the University of Wuerzburg's Centre for Rare Diseases (ZESE). In the context of the diagnostic workup, a cardiac MRI (1.5 or 3.0 T) was performed including morphologic, functional, and contrast enhanced imaging as well as edema imaging. All data were analyzed retrospectively.

171 patients with systemic sarcoidosis proven through biopsy were included in the analysis. At the time of the MRI imaging procedure 58% of these patients had never had an immunosuppressive therapy, 22% had had already received an immunosuppressive therapy and 19% were currently under treatment. 21% of all patients showed positive MRI findings (11% without therapy, 9.4% with a prior or ongoing therapy). Between these groups, statistically no differences in the detection of late enhancement, edema and wall motion abnormalities were detected.

The data of the analyzed population showed that the MRI is a valuable screening tool for both acute and past myocardial affection in the management of patients with sarcoidosis regardless of their current or prior treatment.

Keywords: Sarcoidosis; Screening; MRI; Immunosuppressive therapy

Introduction

Systemic sarcoidosis is a challenging disease that presents with granulomatous lesions in the affected organs. Of unknown origin, the disease can affect multiple organs among which especially the cardiac affection is of prognostic relevance. The cardiac lesions represent as a focal or more extensive focal scarring and depending on the localization and the extent, the correlating clinical signs can be bundle branch blocks or ventricular arrhythmias. The cardiac left ventricular function is reduced as well, and the overall cardiac affection predisposes the patient to a sudden cardiac death [1,2]. A definitive prove of a cardiac affection can be obtained by a myocardial biopsy. However, due to the focal nature of the disease, the histological diagnostic rate of this invasive technique is not more than 20% even in patients with clinically highly suspected cardiac affection [3].

Cardiac Magnetic Resonance Imaging (cMRI) allows a unique non-invasive view on the characteristics of the myocardium. Recently published imaging studies using this technique display the sarcoid lesions in the heart, and managed to detect these lesions in even up to 30% of asymptomatic patients. In these studies, it was possible to establish the presence of scaring or necrosis on late enhancement images as an independent predictor of all-cause mortality, sustained VT or hospitalization due to heart failure [4,5]. Accordingly, the recommendations of the Cardiac Societies include non-invasive tissue characterization in the work up of known or suspected cardiac sarcoidosis [1].

The optimal medical care for patients with suspected cardiac involvement incorporates both a diagnostic workup including imaging procedures as well as treatment strategies [1]. The therapy for cardiac sarcoidosis includes the application of steroids or other immunosuppressive medication such as metotrexat and azathioprin, guided by the intention to suppress the inflammatory response that cause necrosis and, in the long term, scarring of the myocardium. Recent studies add antibody driven therapy concepts to the portfolio of treatment options [6,7]. Prior studies demonstrated a positive influence of corticosteroids on the healing process of patients with cardiac sarcoidosis [2,7,8]. Recently, a positive effect of an early start with corticosteroid treatment on the course of cardiac sarcoidosis was demonstrated [9].

Considering the fact that the identical immunosuppressive therapy elements can be used for the treatment of extra cardiac sarcoidosis as well, it appears obvious that a considerable amount of patients are already on immunosuppressive therapy when presenting for a cardiological work up. Thus, the question arises whether the prior or ongoing therapy might interfere with the detection of cardiac sarcoidosis. The presented work examines the influence of the immunosuppressive therapy on the findings of the initial screening MRI in a group of Caucasian patients with known extra cardiac sarcoidosis.

Materials and Methods

All included patients have been seen at the University Hospital of Wuerzburg's Centre for Sarcoidosis as part of the ZESE (Centre for rare diseases). The patients were either sent to the ZESE due to a suspected systemic sarcoidosis or were referred to the Centre for further diagnostic steps and treatment of a confirmed systemic sarcoidosis. According to the Centre's standards, an extra-cardiac biopsy was obtained from all patients with suspected systemic sarcoidosis and any immunosuppressive therapy was withheld until the diagnostic steps, including a cardiac MRI scan, were completed. The patients with an already known systemic sarcoidosis did not receive another biopsy. If feasible, any immunosuppressive therapy that already had been started, e.g. due to pulmonary sarcoidosis, was stopped at least four weeks before the cardiac MRI was performed.

The imaging studies were performed either on a 1.5T or 3.0T clinical MRI scanner (Philips Healthcare, The Netherlands, ACHIEVA and ACHIEVA DS) between September 2012 and May 2017. The imaging protocol was conducted according to the recommendations of the SCMR [10]. The protocol included a morphologic study based on balanced turbo field echo sequences for cine long and short axis views (FOV 380 mm, Flip angle 60°, TE 2.6-3.0 ms, TR 130-158 ms). A T2-weighted multi echo gradient sequence was used for imaging myocardial edema in both long and short axis (FOV 370 mm, NSA 2, TE 90 ms, TR 2000-3600 ms). Late enhancement imaging was performed 9 to 12 min after antecubital intravenous administration of 0.15 mmol/kg of a gadolinium based contrast agent (Gadobutrol, Bayer HealthCare, Leverkusen, Germany). An inversion recovery T1 turbo field echo sequence was used and the inversion time was adjusted to completely nullify the myocardial signal. The imaging analysis was performed on a dedicated work station (Extended Workspace, Philips Healthcare, The Netherlands, release 2.63.5(2013)) by two experienced cardiac MRI specialists (TR and WR). The analysis included qualitative assessment of the late enhancement and edema imaging, and a quantitative evaluation of the heart function.

The statistical analysis was performed on the program SPSS 22 (IBM, SPSS Statistics). Quantitative values were expressed as mean ± standard deviation or median and range as appropriate. Comparisons of related metric measurements were performed using the Wilcoxon-signed rank test. The Chi square or Fisher exact test was conducted for comparison of frequency data between independent subgroups. For bi-variate correlation analysis Pearson correlation coefficients were calculated. All statistical tests were performed two-sided, and a p-value<0.05 was considered to indicate statistical significance. The patients' data were analyzed retrospectively. All patients gave written consent prior to the imaging procedure and the data analysis complies with the Declaration of Helsinki.

Results and Discussions

Patients' characteristics

A total of 171 consecutive patients were included in the series (105 males, 66 females, mean age 46.9 years (20-82 years, median 47 years)). 161 patients had histologically proven systemic sarcoidosis, for the remaining 10 patients no exact data with regards to the histological evidence existed. Among all affected organ systems, the lungs and lymph nodes were the most common ones (Table 1). At the time of the initial presentation at the ZESE, no patient had already been diagnosed with a cardiac sarcoidosis. 59 Patients presented with at least one symptom such as dyspnoe and fatigue. Among the symptoms arrhythmias and ECG changes were detected as well (Table 2). Besides the proven sarcoidosis, other relevant diseases included hypertension (16 patients, 9.4%), diabetes mellitus (7 patients, 4.1%), asthma (9 patients, 5.3%) and 14 patients had been treated for malignoma. Details are given in Table 3. Notably, two patients had had suffered from a myocardial ischemia. The resulting typical endocardial scarring matching the findings in the coronary angiograms were excluded from further analysis.

Clinical parameters in the analyzed population	
Staging on chest radiograph	
0 9 (5%)	IV 8 (5%)
I 11 (6%)	Heerfordt's Syndrome 1 (<1%)
II 117 (68%)	Löfgren Syndrome 9 (5%)
III 4 (2%)	Not Known 12 (7%)
Affected Organs	
Lymphnodes 156 (91%)	Brain 7 (4%)
Lungs 156 (91%)	Bones 6 (4%)
Heart 36 (21%)	Liver 5 (3%)
Skin 24 (14%)	Larynx 3 (2%)
Joints 18 (11%)	Parotid gland 2 (1%)
Eyes 17 (10%)	Kidney 2 (1%)
Spleen 8 (5%)	Stomach 1 (<1%)

Table 1: Clinical parameters in the analyzed population. The radiographic staging and affected organs at the time of initial diagnosis are given in absolute numbers and as percentage.

Symptoms at the presentation suspicious of cardiac involvement	
None 111 (65%)	Bundle Branch Block 11 (6%)
Shortness of breath 25 (15%)	Fatigue 5 (3%)
Angina pectoris 10 (6%)	Heart failure 9 (5%)

Arrhythmias 18 (11%)	ICD/life vest required 3 (2%)

Table 2: Suspicious symptoms pointing towards a cardiac affection are given in absolute numbers and as percentage.

Inflammatory diseases	Malignant diseases	Others
		16 hypertension
		7 diabetes
	5 melanoma	9 asthma
	1 basaliom	2 hypercholesteremia
	1 b-NHL	3 COPD
1 ileitis	1 colon cancer	4 thrombembolic event
2 Hashimoto Thyreoditis	1 testicular cancer	1 Liver Transplant
1 hepatitis C	1 breast cancer	2 heart failure
3 Psoriasis	1 kidney cell cancer	4 atrial fibrillation
1 periarthritis	1 pheochromocytoma	3 cerebral ischemia
1 Raynauld Syndrome	1 retinoblastoma	1 Guillan Barré Sydrome
1 suspected polymyositis	1 meningeoma	1 neurofibromatosis

Table 3: Relevant comorbidities.

Of all patients, 100 patients (58%) had not received any immunosuppressive medication prior to the imaging procedure. 37 (22%) had had a prior immunosuppressive therapy but had none at the time of the imaging procedure and 33 patients (19%) were on immunosuppressive therapy by the time of the MRI scan. In the group of patients with immunosuppressive therapy, 10 patients (7%) were on low dose steroids (10 mg prednisolone or less), 7 patients (4%) had a maximum dosage of 50 mgs, 6 patients (3.5%) had a high dosage prednisolone therapy (60 mg up to 100 mg per day), and 8 patients (4.6%) were on a combination of prednisolone and azathioprim or metotrexat. Only three patients had an immunosuppressive medication without prednisolone. A total of 168 patients completed the protocol including the LGE imaging; three patients did not receive an LGE scan.

Imaging characteristics

The values for the established left ventricular functional parameters are given in Table 4. A total of 36 imaging studies (21%) showed positive findings in the late enhancement imaging in a non-ischemic distribution pattern. The amount of scarring ranged from focal intramyocardial or epicardial fibrosis to severe transmural scarring. The latter was detected in the anterior, anteroseptal and septal basal and midbasal segments, whereas minor focal scarring showed no preference in localization (Figure 1). The majority showed singular epicardial focal or nodular lesions (20 patients, 12%), however 14 patients (8.2%) presented with multiple focal or more extensive lesions, covering at least one segment, and 2 presented with severe, transmural scarring that was not of ischemic origin (1.2%). 12 MRI scans (7%) with positive LGE scans additionally had positive findings in the T2 weighted images. 17 (10%) showed wall motion abnormalities. In comparison between the group with positive LGE findings and the group with negative LGE findings, the LVEDD, LV-EF and the LV-ESV showed significant differences (Table 2). The presence of cardiac symptoms significantly correlated with wall motion abnormalities (p=0.06) and late enhancement (p=0.003). The presence of cardiac symptoms showed a non-significant correlation with the presence of myocardial edema (p=0.07).

MRI parameters			
LA Area [cm²]	21 (11-32; 21)	SV [ml]	82 (50-138; 79)
RA Area [cm²]	22 (11-35; 22)	EF [%]	61 (30-79; 61)
LVEDD [mm]	52 (40-68; 52)	SI [ml/beat/m²]	41 (22-69, 41)
LV-EDV [ml]	136 (73-245; 134)	CO [l/min]	5.9 (3-10.7; 5.8)
LV-ESV [ml]	54 (19-116; 51)	CI [l/min/m²]	3.2 (1.4-5.1; 2.9)
Septal Wall [mm]	10 (5-18; 9)	Lateral Wall [mm]	7 (4-14;7)
	positive LGE	**negative LGE**	**p-values**
LVEDD [mm]	53.4 (42-65; 55)	51.7 (40-68; 52)	0.004
LV-EDV [ml]	140.8 (73-245; 136)	134.8 (84, 215; 134)	0.16
LV-ESV [ml]	60.5 (23-116; 56)	52.3 (19-144; 50)	0.018
SV [ml]	81.3 (50-138;77)	82.9 (52-138; 81)	0.54
EF [%]	58.3 (30-75; 58)	62.1 (47-79; 63)	0.002
SI [ml/beat/m²]	40.4 (22-69; 39)	42.0 (27-61; 42)	0.31
CO [l/min]	5.9 (3.0-10.7; 5.7)	6.0 (3.2-9.5; 5.8)	0.7
CI [l/min/m²]	2.9 (1.4-4.9; 2.8)	3.0 (1.8-5.1; 3)	0.37

Table 4: MRI findings in patients with positive findings in the LGE imaging sequence and with negative findings in the LGE imaging sequence. Values given as mean value [minimum-maximum; median]. P-values were considered significant, when <0.05. LA: left atrium. RA: right atrium. LVEDD: left ventricular enddiastolic diameter; LV-EDV: left ventricular enddiastolic volume. LV-ESV: left ventricular endsystolic volume. SV: stroke volume; EF: ejection fraction, SI: stroke index, CO: cardiac output, CI: cardiac index.

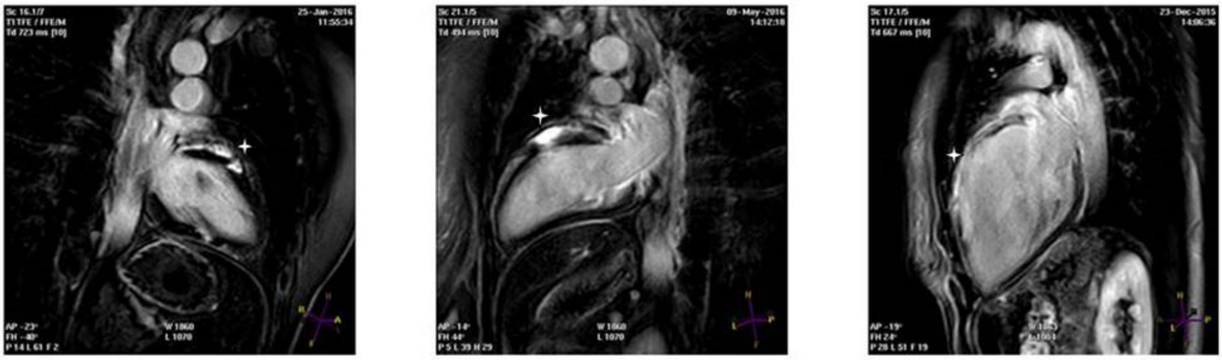

Figure 1: Examples for positive LGE findings in the two chamber view from three different patients. The white asterices marks the area of scarring.

Immunosuppressive therapy prior to the imaging procedure

The majority of patients were referred to the MRI department without a prior or current immunosuppressive therapy (57%). The findings with regards to morphology and function did not differ significantly between patients on or after immunosuppressive therapy and patients without therapy. In the group with no prior or present immunosuppressive medication, 19 patients (11%) had positive findings in the LGE, and among these, 8 patients (4.8%) additionally had positive findings in the T2 weighted images. 10 patients (5.8%) presented with wall motion abnormalities.

Among the patients who already had a prior therapy with prednisolone or were presently on the medication, 16 patients (9.4%) had positive findings in the LGE. 4 (2.3%) of the patients who had been treated with corticosteroids showed intramyocardial edema and 7 (4.1%) had wall motion abnormalities. Notably, between these groups, statistically no differences in the detection of late enhancement, edema and wall motion abnormalities were detectable ($p=0.68$ for LGE, $p=0.64$ for edema, $p=0.66$ for wall motion abnormalities). In the combination of presence of positive findings in the late enhancement imaging and presence of edema as well as positive late enhancement and wall motion abnormalities, no significant differences between the groups (no immunosuppressive therapy, prior immunosuppressive therapy and immunosuppressive therapy) were detected ($p=0.59$ and $p=0.78$).

Effect of the MRI results on the further medication

In those patients who initially had not been on immunosuppressive therapy, the suspicion of a cardiac sarcoid affection significantly more often led to changes in the medication ($p<0.001$). The findings on the MRI scans lead to changes in the immunosuppressive medication. In 20 (12% of all) patients an immunosuppressive medication was started or escalated due to findings in the MRI, and in 24 (14% of all) patients the medication was maintained. In 9 (5%) patients the immunosuppressive therapy was stopped or reduced due to the lack of MRI signs of cardiac affection. In patients with negative MRI scans, no immunosuppressive therapy was started, except in those who had an extra-cardiac indication (39 patients, 23%).

Discussion

Extensive data substantiate the diagnostic value of non-invasive myocardial imaging. Recent data advocate this concept for the diagnostic proceedings in suspected cardiac sarcoidosis as the LGE proves to be an independent predictor of a worse outcome and even predicts the annual risk for death or sustained ventricular tachycardias [11,12]. Overall, our data of the morphological and functional findings within the analyzed population comply with the prior published data. When comparing the group without signs of a myocardial sarcoid affection and those who present with a positive finding in the LGE, significant differences in the LV functional parameters can be detected. The MRI findings showed significantly more positive LGE findings in the presence of cardiac symptoms than in those without symptoms.

However, in a setup that includes the MRI as a valuable screening tool, a substantial part of the population will already be or had been on an immunosuppressive medication due to other organ affections at the time of the MRI scan. Shimada et al. showed that the MRI is able to monitor the effect of the immunosuppressive therapy by analyzing pre and post contrast MRI scans for edema detection and its changes during immunosuppressive medication [13]. While being a desirable effect in the therapy monitoring, this leads to the question whether a general screening for all patients might be influenced by the medication at the time of the MRI scan. The presented data show that the detection of fibrotic myocardial changes due to a sarcoid affection is not necessarily influenced by an ongoing or prior immunosuppressive therapy. Having originated from a focal granulomatous inflammation and subsequent scarring, these fibrotic changes remain present under therapy. Consequently, the patients' outcome has been correlated to the findings in the LGE scans, but necessarily to the existence of an acute ongoing inflammation.

However, myocardial edema as tell-tale sign of an ongoing inflammation can be used for the monitoring of therapy effects [13]. Most likely, the start of immunosuppressive therapy does not immediately suppress all myocardial edema, thus the detection of an acute myocardial sarcoid affection is possible, even after the start of medication. Recently presented data suggest that a recurrence of disease activity under immunosuppressive therapy occurs in up to 13% [14]. Comparably, our data showed findings in the T2 weighted and LGE images, pointing towards an acute inflammation in a small portion of patients who had had been already treated with corticosteroids.

Limitations

In this study, both 1.5T and 3.0T MRI scanner were used, however, the data of each scanner was not matched to each other, so in our opinion, this is not a serious inconsistency in the choice of methods. We did not use any advanced mapping techniques such as T1 or T2 mapping because we focused on established standard imaging sequences.

Conclusion

In summary, our data of the analyzed population demonstrated that an ongoing or prior immunosuppressive therapy does not interfere with the usefulness of a MRI screening for imaging signs of a cardiac sarcoidosis, and even with ongoing or prior immunosuppressive therapy, signs of an acute inflammation can be detected.

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