SARCOIDOSIS VASCULITIS AND DIFFUSE LUNG DISEASES 2019; 36 (1); 11-17 DOI: 10.36141/svdld.v36i1.7132

Diagnostic approach for cardiac involvement in sarcoidosis

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Abstract. *Aims:* Cardiac sarcoidosis (CS) is a potentially life-threatening condition. Early detection of CS is therefore important. The aim of this study was to eludicate the usefulness of different investigations in a subgroup of patients with sarcoidosis regarded as having an increased risk for cardiac involvement. *Methods:* 42 sarcoidosis patients, who had an abnormal resting electrocardiogram (ECG) and/or symptoms indicating possible cardiac involvement (i.e. palpitations, pre-syncope or syncope), were included in the study. They were identified in a consecutive manner among patients followed-up at outpatient clinics for respiratory disorders. Holter monitoring, exercise test, transthoracic echocardiogram (TTE), cardiovascular magnetic resonance (CMR) and analysis of N-terminal pro B-type natriuretic peptide (NT-pro-BNP) in serum were performed. Note, that the role of FDG-PET was not investigated in this study. *Results:* In the group with a pathologic ECG 11/25 (44%) were ultimately diagnosed with CS (all with pathologic CMR). However, in the group with only symptoms but a normal ECG just 1/17 got the diagnosis CS ($p<0.05$). This patient had a pathologic Holter monitoring. The risk for CS was increased if serum NT-pro-BNP was elevated (i.e. NT-pro-BNP>125 ng/L), sensitivity 78% ($p<0.05$), specificity 67%. By adding a pathologic ECG to an elevated NT-pro-BNP increased specificity to 93% and sensitivity remained at 78%. *Conclusion:* Our findings indicate that CMR should be performed at an early stage in sarcoidosis patients with an abnormal resting ECG. Holter monitoring and elevated levels of NT-pro-BNP may enhance the diagnostic accuracy whereas exercise testing and TTE in this study had less impact on the identification of CS. *(Sarcoidosis Vasc Diffuse Lung Dis 2019; 36: 11-17)*

Key words: sarcoidosis, extra-pulmonary involvement, cardiovascular magnetic resonance, sarcoidosis

Introduction

Sarcoidosis is an inflammatory disease with unknown origin that in at least 90% of cases affects the lungs and/or intrathoracic lymph nodes. It is characterized by the formation of non-necrotizing granulomas and almost any organ can be affected leading to a high variability in the clinical presentation (1, 2). Engagement of the heart, cardiac sarcoidosis (CS), may manifest itself as benign arrhythmias or give rise to severe conduction blocks and in worst case life threatening arrhythmias and/or heart failure secondary to infiltration of the cardiac conduction system or the myocardium (3). Early detection of cardiac involvement and evaluation of the need of glucocorticoids and/or antiarrhythmic drugs, pacemaker and/or implantable cardioverter defibrillator (ICD) is therefore of great importance

Received: 12 March 2018
Accepted after revision: 19 September 2018
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(4). Some studies reported that approximately 5% of the patients with sarcoidosis will have symptomatic cardiac involvement and another 20-25% may have asymptomatic disease. There seems to be a variation pending on ethnic origin (5, 6) and the access to new techniques to detect cardiac disease has contributed to an enhanced detection of CS (7). There are today scarce data to compare the specificity and sensitivity of screening tests for cardiac involvement in patients with extra-cardiac sarcoidosis (6). Since there is a possibility to prevent severe events of CS, the need for good screening methods for early detection is urgent. The today commonly used methods are resting ECG, 24-hrs Holter monitoring, transthoracic echocardiogram TTE, cardiovascular magnetic resonance (CMR) and positron emission tomography with 2-deoxy-2-[fluorine-18] fluoro- D-glucose integrated with computed tomography (FDG PET/CT) (4).

The overall objective of this study was to compare the accuracy of and usefulness of various techniques to diagnose cardiac involvement in a co-hort of well-characterized Swedish sarcoidosis patients with abnormal resting ECG pattern and/or symptoms generally regarded as compatible with CS (i.e. palpitations, pre-syncope or syncope). Note, that the role of FDG-PET was not investigated in this study. The reason was that it at the time for the study not was a routine investigation but rather used as a complement when there were contraindications to perform CMR.

Materials and Methods

Study subjects

The study included 42 sarcoidosis patients of Caucasian origin (Table 1) residing in Stockholm, Sweden and attending two different University Centers for respiratory disorders. The patients were included (from 2008 - 2014) in a consecutive order from the out-patient clinics if they had an abnormal resting ECG (n=22), were investigated because of a newly detected arrhythmia (n=3) or complained of palpitations, pre-syncope or syncope (n=17). In the majority, the investigations were conducted within a time frame of 2 months. The patients were followed until 2017 with a median time of follow-up of 6 years (min 3 years, – max 9 years). The patients were diagnosed with sarcoidosis by typical clinical and chest radiographic manifestations, findings at bronchoscopy with bronchoalveolar lavage (BAL) including an elevated CD4+/CD8+ cell ratio (>3.5), and/or granulomatous biopsies, using the criteria outlined by WASOG/ATS and ERS (8). Patients were diagnosed with CS according to HRS the diagnostic methodology established "clinical diagnosis of probable cardiac sarcoidosis" except in cases that underwent direct myocardial biopsy where a "histological diagnosis was also established", i.e. when there were no positive cardiac biopsy but CMR showed pattern compatible with sarcoidosis, the patient were judged in consensus as having CS (none of the patients had LVEF<40%, sustained ventricular tachycardia or atrioventricular block (AV-block) II, Mobitz II or AV-block III without findings on CMR compatible with CS) (4). In line with expert consensus statements from the World Association of Sarcoidosis and Other Granulomatous Disorders (WASOG) all patients with CS had "probable CS" (9). Löfgren´s syndrome (LS) was found in 4/42 patients and was defined as bilateral hilar lymphadenopathy with or without parenchymal infiltration, erythema nodosum and/or ankle arthritis, and an elevated CD4+/CD8+ ratio in BAL fluid. Patients were defined as ever smokers if they had previously smoked or were current smokers. Chest radiographs were evaluated, and findings staged by one of the authors (chest radiologist K.C.) according to the following system: Stage 0 – normal; Stage I – bilateral hilar lymphad-

Table 1. Clinical characteristics of patients and medication

	All patients	Patients with CS
Subjects	42	12
Gender M/F	20/22	5/7
Age, years^	50 (28-78)	51 (42-78)
Years with sarcoidosis	7 (0-45)	1 (0-29)
Smoker (never/ever)	22/20	8/4
Radiographic stage 0/I/II/III/IV	3/10/18/2/9	2/2/5/1/2
Löfgren/non-Löfgren	4/38	0/12
Oral glucocorticoids	14	1
Cardiovasular treatment	16	7
No treatment	16	5

CS = cardiac sarcoidosis. ^Age, years at time CMR was performed: values are medians (min – max). Cardiovascular treatment, all patients: angiotensin converting enzyme (ACE) inhibitors or angiotensin II receptor blockers [(n=9), 5 with CS], beta-blockers [(n=13), 6 with CS], diuretics [(n=6), 3 with CS], calcium channel blockers (n=1).

enopathy; Stage II – bilateral lymphadenopathy with parenchymal infiltrates; Stage III – parenchymal infiltrates alone; Stage IV – fibrotic bands and volume reduction (10). Ongoing medications at the time of inclusion are described in Table 1. An evaluation of patients was performed in December 2017. Data was missing for those who were no longer residents in Sweden (n=2). All patients with suspected CS were evaluated by two of the authors (AG and PS, both cardiologists and certified CMR specialists). Written informed consent was obtained from all subjects, and the study was approved by the Regional Ethical Review Board in the Stockholm county.

The investigation methods reflecting possible cardiac involvement and used in this study in addition to routinely performed 12-leads resting ECG were: 1 – 24-hrs Holter monitoring, 2 – exercise test, 3 – (TTE), 4 – CMR, and N-terminal pro B-type natriuretic peptide (NT-pro-BNP) in serum. Patients were only included if there were no contraindications according to current guidelines regarding investigation with CMR.

Methods used for detecting CS

Standard methods were used for evaluation with 12- leads ECG, 24-hours Holter monitoring, exercise test and TTE (11-15). For definition of pathologic findings, see Table 2. We chose VES >100/24 hour as a cut-off level, which is a widely accepted risk marker for malignant arrhythmias (16). NT-pro-BNP >125 ng/L was considered as pathologic as outlined by European Society for Cardiology (ESC) guidelines for the diagnosis and treatment of acute and chronic heart failure (17). CMR was performed using a 1.5 T Philips Intera CV (Best, The Netherlands) and Siemens Aera, (Erlangen, Germany) with a phased-array five to eigtheen-channel body maitrix coil. All patients were examined in the supine position. All CMR examinations were evaluated by an experienced cardiologist after a standardized protocol which evaluates specifically right and left ventricles, edema and structural changes in the myocardium (18). Late gadolinium enhancement (LGE) images were initiated 8-12 min after the administration of 0.2 mmol/kg extracellular gadolinium-based contrast agent (gadoteric acid, Gd-DOTA; Guerbet, Gothia Medical AB, Billdal, Sweden). Patients were typically considered to have cardiac sarcoidosis if there were an increased signal intensity in water sensitive images (edema) in short- or long-axis images or a typical non-ischemic LGE pattern (infiltration with or without fibrosis) not corresponding to an ischemic lesion (an example figure is shown in online supplement) (19).

Table 2. Definitions of pathologic findings

ECG	Any degree of AV-block Bundle branch block Left axis deviation Pathologic Q waves ST-T changes Supra- and ventricular arrhythmias VES
Holter monitoring	VES >100 / 24 hour Supra- and ventricular arrhythmias
Exercise test	Supra- and ventricular arrhythmias Occurrence of VES in bigamy Development of pathologic ST-changes Poor pulse rise Pathologic blood pressure reaction
NT-pro-BNP	NT-pro-BNP>125 ng/L
TTE	Regional wall motion abnormalities Wall thickening LV systolic dysfunction (LVEF <50%)
CMR	Edema/inflammation Typical non-ischemic LGE pattern

AV-block=atrioventricular block, CMR=cardiovascular magnetic resonance, ECG=electrocardiogram, NT-pro-BNP=N-terminal pro B-type natriuretic peptide, LGE=Late gadolinium enhancement, LV=left ventricular, LVEF=left ventricular ejection fraction, VES=ventricular extrasystole and TTE=transthoracic echocardiogram

Statistical analysis

Data were analyzed by Chi-square test or in the case of small numbers by Fisher's Exact Test. Sensitivity, specificity, positive predictive value and negative predictive values were also calculated. Statistical analyses and graphs were performed with Graph Pad Prism 6 (GraphPad Software Inc., San Diego, CA, USA). P-value <0.05 was regarded as significant.

Result

All patients (n=42) in the study underwent examination with 12-leads ECG and CMR. However, not all patients were investigated with all of the other

techniques. Thus, Holter monitoring was done in 37 patients, exercise test in 29, serum analyses of NT-pro-BNP in 24 and TTE in 41 (see online supplement for detailed information). Sixteen patients out of seventeen with symptoms but a normal 12-leads ECG underwent Holter monitoring. Sensitivity, specificity, positive predictive value and negative predictive value for ECG, Holter monitoring, exercise test, TTE and NT-pro-BNP are presented in Table 3.

Among patients with a pathologic ECG (n=25), 44% were diagnosed with CS compared to one out of 17 patients with a normal ECG but with symptoms indicative of CS, p<0.05, Figure 1. The patient with a normal ECG and CS had a history of palpitations and a pathologic Holter monitoring with a high number of ventricular extra-systoles (VES). Pathologic findings on Holter monitoring were seen in 82% with CS and 50% without CS investigated with this test. Exercise test had a sensitivity of 67%, p<0.01. In common for all the patients with increase of VES from single to bigamy, was that it occurred at end of work and at rest after work. Among patients diagnosed with CS, TTE indicating cardiac involvement showed a high specificity (93%) but a low sensitivity (58%) p<0.01. Elevated NT-pro-BNP were a risk marker for cardiac involvement and was seen in 7/9 patients with CS resulting in a sensitivity of 78%, but was also seen in 5/15 without CS where NT-pro-BNP was measured so therefore the specificity was 67%. When combined with a pathologic ECG the specificity increased to 93% since only one of the patients without CS (a patient with arterial flutter) had the combination of pathologic tests (p<0.001). None of the three patients with a normal ECG, normal Holter monitoring and normal NT-pro-BNP was diagnosed as having CS.

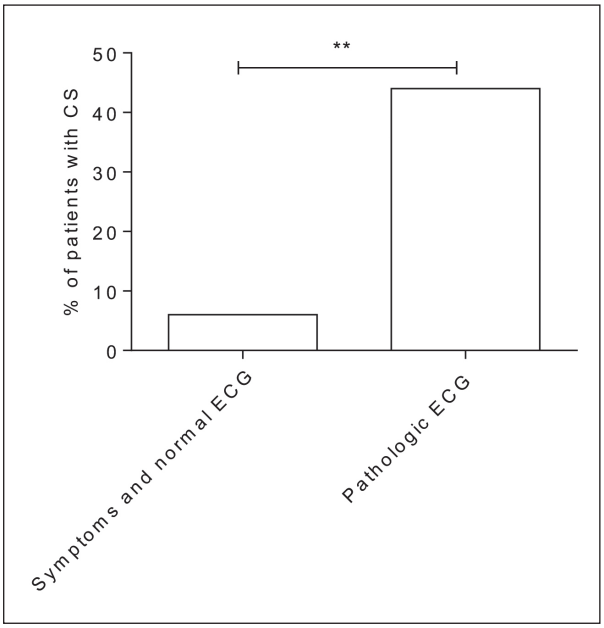

Fig. 1. Frequency of cardiac sarcoidosis (CS) in patients divided into patients with symptoms but a normal electrocardiogram (ECG) (n=one out of 17) and patients with a pathologic ECG (n=11 out of 25). Symptoms are palpitations, pre-syncope and syncope. ** <0.05

An evaluation of deceased patients was possible since patient records do simultaneously operate with the tax authority system registrating all Swedish citizens. Four patients died during the median time of follow-up of 6 years from time of inclusion in the study (min 3 years, – max 9 years). Three of the patients had advanced pulmonary fibrosis and the fourth had CS. Two patients with cardiac sarcoidosis underwent heart transplantation. Among the five patients with increased serum NT-pro-BNP levels without findings of CS, one patient had artrial flutter and pulmonary fibrosis and two presented later with artrial flutter. The two others had pulmonary fibrosis.

Table 3. Usability of diagnostic tests for cardiac sarcoidosis

	Sensitivity%	Specificity%	PPV%	NPV%	p-value
ECG	92	53	44	94	<0.05
Exercise test	67	90	75	86	<0.01
Holter monitoring	82	50	41	87	0.14
NT-pro-BNP	78	67	58	83	<0.05
TTE	58	93	78	84	<0.01
CMR	100	100	100	100	<0.0001
NT-pro-BNP and ECG (both pathologic)	78	93	87	87	<0.001

ECG=electrocardiogram, CMR=cardiovascular magnetic resonance, TTE=transthoracic echocardiogram,
NT-pro-BNP=N-terminal pro B-type natriuretic peptide, PPV=positive predictive value, NPV=negative predictive value.

Discussion

The overall objective of this study in a well-characterized co-hort of Scandinavian sarcoidosis patients was to evaluate a standardized approach of diagnostic testing for early detection of CS. We found that the risk for CS was significantly higher in sarcoidosis patients presenting with a pathologic ECG compared to patients with a normal ECG but with symptoms indicating possible cardiac involvement. This is in line what we previously have shown in a retrospective study where we found that patients who later were diagnosed with CS in most cases had an abnormal ECG at disease onset (20). In the current study, we also measured NT-pro-BNP and found that an elevated level was common in patients with CS. Measurement of NT-pro-BNP has not yet been added to diagnostic routines or guidelines for diagnosis of cardiac sarcoidosis.

The increased risk for CS in patients with a pathologic ECG, which in our study most commonly showed atrioventricular block and/or bundle branch block, matches well the findings in autopsy cases of sarcoidosis patients, where the septum most frequently was engaged thereby causing damage to the conduction system (21). In our study, CS was diagnosed in about half of the patients with a pathologic ECG. An increased incidence of CS was also seen in a study by Metha et al. where they investigated patients with symptoms indicative of CS or an abnormal ECG more carefully (22). A complement to ECG is Holter monitoring, where a high frequency of VES was reported by Suzuki et al. to be more common in patients with CS than in those without (23). We found that Holter monitoring is a good complement in symptomatic patients with a normal ECG. Further, the additive value of exercise test for the diagnosis of sarcoidosis seems less convincing. TTE is a commonly used investigation method for detection of CS. However, several of the patients in our study with findings of CS on CMR had a normal TTE. This is consistent with findings reported by Metha et al. and Kouranos et al., where TTE had low sensitivity as a single screening method for CS (22, 24). NT-pro-BNP, which is increased in patients with cardiac failure, has previously been shown by Handa et al. and Martusewicz-Boros et al. to commonly be elevated in patients with cardiac sarcoidosisis (25, 26). In our study we found that NT-pro-BNP has a higher sensitivity but lower specificity in comparison to TTE. However, if NT-pro-BNP was combined with ECG (both pathologic) the sensitivity was higher than for TTE but with the same specificity. CMR is a well-established diagnostic tool for CS and has emerged as gold standard (27). Fluorodeoxyglucose (FDG) positron emission tomographic (PET) – computed tomography (CT) is an alternative to CMR that visualizes pathologic changes due to CS. In a previous study where FDG PET-CT was compared with CMR in sarcoidosis patients, both investigation methods provided high sensitivity (28) and may complement one another (29-31). FDG PET-CT, however, uses ionizing radiation which makes it less attractive for follow-up investigations. It is also a more expensive examination method than CMR and therefore not cost-beneficial. We chose in this study not to include FDG PET-CT since we do not use it as it as the time for the study not was a routine investigation but rather used as a complement when there are were contraindications to perform CMR.

There were only a few patients with Löfgren's syndrome who met the inclusion criteria which are in line with that extra-pulmonary manifestations (erythema nodosum and ankle arthritis excluded) are rarely seen in this subgroup (32). On the other hand, three patients with more advanced disease with pulmonary fibrosis had increased NT-pro-BNP serum level without signs of CS. This may indicate that an increased NT-pro-BNP is hazardous to interpret in patients with radiologic stadium IV as it may be secondary to pulmonary hypertension.

Limitations with the study are the relatively few numbers of patients included and that not all patients had all the investigations done, e.g. NT-pro-BNP was only measured in about half of the patients. However, cardiac sarcoidosis is a relatively rare condition among Scandinavian sarcoidosis patients and during the time the patients were included NT-pro-BNP were not an established test for this patient group. Further, many of the patients were on medication, which may lead to lower levels of NT-pro-BNP and less inflammation on CMR. However, we believe that our findings clearly show the importance of following-up patients with sarcoidosis and a pathologic ECG by doing a CMR. The value of measuring NT-pro-BNP need to be investigated in larger studies, but the observation of increased values merits further investigations. Furthermore, a poten-

tial weakness is that patients were not examined with FDG PET-CT and the role of FDG PET-CT as an alternative investigation method to CMR was therefore not analyzed.

In conclusion, our results show that the risk for CS is significantly higher in sarcoidosis patients presenting with a pathologic ECG in comparison to patients with symptoms indicative of CS but with a normal ECG. The risk seems to be even higher if NT-pro-BNP in serum is elevated. In line with our findings we recommend that all sarcoidosis patients who have a pathologic ECG and/or elevated NT-pro-BNP should be further investigated with CMR. If a patient has no symptoms indicative of CS and both ECG and NT-pro-BNP are normal, the risk for clinically significant CS seems to be low.

Acknowledgements

This work was supported by the Swedish Heart-Lung Foundation, the King Oscar II Jubilee Foundation, the Swedish Research Council, the King Gustaf V's and Queen Victoria's Freemasons' Foundation, Torsten and Ragnar Söderberg´s Foundation and Karolinska Institutet. Support was also given through the regional agreement on medical training and clinical research (ALF) between Stockholm County Council and Karolinska Institutet. None of the funding sources had any influence on the production of this manuscript.

Authors contribution

PD designed and coordinated the study, wrote the application to the Ethics Committee, characterized patients, summarized data and drafted the manuscript. AG co-designed the study and characterized patients, evaluated CMRs, interpreted data and helped writing the manuscript. KC classified radiographs. SK and JG characterized patients, interpreted data and helped writing the manuscript. AE co-designed the study and characterized patients, interpreted data and helped writing the manuscript. PS co-designed the study and characterized patients, evaluated CMRs, interpreted data and helped writing the manuscript. All authors read and approved the final manuscript.

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