SARCOIDOSIS VASCULITIS AND DIFFUSE LUNG DISEASES 2005; 22: 43-50

Association of small fiber neuropathy with cardiac sympathetic dysfunction in sarcoidosis

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Abstract. *Background and aim:* Recently we found that small fiber neuropathy (SFN) occurs frequently in sarcoidosis. Autonomic dysfunction may be a feature of SFN. Since cardiac autonomic dysfunction has been identified as a strong predictor of morbidity and mortality, recognition of cardiac autonomic involvement is of clinical relevance. It was hypothesised that SFN might be related to cardiac sympathetic denervation in sarcoidosis. *Methods:* In the present study 45 consecutive sarcoidosis patients (13 without SFN assessed by thermal threshold testing (TTT), 32 with SFN (abnormal TTT) were enrolled. To rule out bias due to myocardial ischemia, cases with abnormal Thallium (^{201}Tl) perfusion scintigraphy were excluded (n = 2). Cardiovascular autonomic function testing (Ewing tests) and ^{123}I-MIBG (metaiodobenzylguanidine) scintigraphy were used to assess cardiac autonomic function. Further cardiac diagnostic work-up included ECG, Holter recording and echo Doppler cardiography. *Results:* Mild to moderate heterogeneity of ^{123}I-MIBG uptake regional in the myocardium was demonstrated in a substantial number of the studied sarcoidosis population, especially in those with SFN (abnormal TTT). Mean inferior-anterior ratios were 0.85 ± 0.17 (SFN) and 1.0 ± 0.17 (no SFN; p = 0.003), respectively. Four out of the 14 cases with abnormal MIBG scintigraphy and SFN showed an abnormal Ewing test. *Conclusion:* Cardiac sympathetic dysfunction assessed by use of ^{123}I-MIBG myocardial scanning appeared to be heterogeneous in sarcoidosis patients and dependent on the presence or absence of SFN. MIBG scintigraphy may be of additional value in the management and follow-up of sarcoidosis patients. Future study is warranted to explore possible prognostic and therapeutic implications of these findings in sarcoidosis. ***(Sarcoidosis Vasc Diffuse Lung Dis 2005; 22: 43-50)***

Key Words. Autonomic dysfunction. Cardiac sympathetic denervation. MIBG scintigraphy. Sarcoidosis. Small fiber neuropathy.

Introduction

Sarcoidosis is a disseminated granulomatous disease of unknown origin. Estimates of prevalence range from 1-40 per 100,000 population, varying among ethnic and racial groups [1]. The clinical course of sarcoidosis is highly variable. Spontaneous recovery may occur, but the disease can also be chronic or progressive. Depending on the organs involved and the severity of granulomatous inflam-

Received: July 10, 2004
Accepted after Revision: November 8, 2004
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mation, patients suffer from a broad range of persistent physical symptoms. Besides respiratory symptoms such as coughing and dyspnoea on exertion, patients often suffer from apparently non-specific symptoms such as fatigue and pain, including atypical chest pain [2-6]. In most sarcoidosis patients suffering from recurring chest pain, palpitations and collapses, routine examination revealed no evidence of cardiac involvement.

Cardiac sarcoidosis is a challenging entity [7]. The extent to which the heart is involved in sarcoidosis has long been a matter of controversy [8]. Reports on incidence of clinically evident sarcoidosis involving the heart is rather uncommon, affecting 2 to 7% of patients with sarcoidosis. However, occult involvement is much higher (> 20%) [7]. In general, Japanese studies show more often cardiac involvement than those in other ethnic backgrounds [7, 8]. Moreover, the incidence is higher when specific cardiac tests are performed in unselected patents with sarcoidosis, e.g. echocardiography and radionuclide scans [7].

Optimal strategies to diagnose cardiac involvement have not yet been clarified. Thallium^{201} scintigraphy has been most extensively studied. Echocardiography may have a complementary role but it is less sensitive. Clinical features of cardiac involvement include supra-ventricular arrhythmias and conduction disturbances [9, 10]. It has been suggested that these cardiac manifestations reflect granulomatous infiltration within the conduction system or ventricular wall [7]. Sudden death without a premonitory sign seems to be relatively frequent and selecting patients at risk is one of the major obstacles facing clinicians [11]. Therefore, given the often life-threatening nature of cardiac involvement an appropriate diagnostic approach is warranted [1, 2]. Making the diagnosis early and promptly initiating appropriate treatment can be life-saving [7].

Recently, we demonstrated the presence of small fibre neuropathy (SFN) in sarcoidosis patients [12, 13]. Small nerve fibres carry sensory functions (pain and temperature sensation) and autonomic functions. As a result, SFN may cause peripheral pain, paraesthesias, intolerance of bedclothes, hyperhidrosis, hypohidrosis, sicca syndrome, facial flushing, diarrhoea, constipation, micturation disturbances, sexual dysfunction and/or orthostatic intolerance. It is important to recognize that pain can be due to impairment of small sensory fibres as well as autonomic C-fibres [14].

Autonomic dysfunction has been identified as a strong predictor of cardiovascular morbidity and mortality [15-18]. Therefore, recognition and evaluation of autonomic dysfunction is very important. Different methods have been proposed to study the myocardial sympathetic nervous system, including measurement of plasma noradrenaline concentration, baroreflex-sensitivity, heart rate variability and noradrenaline spillover [19]. Iodine-123 meta-iodobenzylguanidine (^{123}I-MIBG), an analogue of norepinephrine, is a tracer for the functioning of sympathetic neurons. Cardiac sympathetic nerves take up ^{123}I-MIBG, which radiolabels the vesicles in the terminals. This allows visualisation of the sympathetic innervation of the heart by scintigraphy after injection of ^{123}I-MIBG. MIBG imaging seems an interesting tool for the quantitative assessment of presynaptic sympathetic nerve terminal disturbances. Moreover, an imbalance of the sympathetic tone is considered to increase the propensity to develop ventricular arrhythmias in various cardiac diseases and conditions [20].

The aim of the present study was to test the hypothesis that myocardial sympathetic innervation might be impaired and variable according to the presence or absence of small fiber neuropathy. Therefore, we examined 32 sarcoidosis patients with and 13 patients without SFN by use of ^{123}I-MIBG single photon emission computed tomography as a non-invasive screening test of cardiac sympathetic function. Myocardial perfusion scintigrams (Thallium^{201}) were used to rule out deficiencies of MIBG uptake due to myocardial ischemia.

Patients and Methods

Patients

Forty-seven consecutive sarcoidosis patients (18 female, 29 male; mean age 45 ± 11 years) from the Maastricht Sarcoidosis Management Center, which serves as a tertiary referral centre for sarcoidosis patients in the Netherlands, were included in the present study. Diagnosis of sarcoidosis was based on the international criteria [2]. None of the patients included had a history of alcohol abuse, renal insufficiency, diabetes or involvement of the central nervous system and none of them were receiving medication that could affect ^{123}I-MIBG uptake and metabolism. Sensory symptoms such as peripheral pain, paraesthesias, hypoesthesia, hyperesthesia, and/or intolerance for bedclothes and autonomic symptoms such as hyperhidrosis, hypohidrosis, sicca syndrome,

facial flushing, diarrhoea, constipation, micturation disturbances, sexual dysfunction and/or orthostatic intolerance were regarded as SFN symptoms. Palpitations were regarded as cardiac symptoms. To rule out deficiencies of MIBG uptake due to myocardial ischemia, cases with abnormal myocardial perfusion scintigrams were excluded from further analyses.

MIBG scintigraphy

All subjects received an oral dose of potassium perchlorate to block the thyroid uptake. After an intravenous injection of 185 MBq ^{123}I-MIBG, an early (30 minutes) and a late (240 minutes) planar image was obtained of the thorax and upper abdominal region using a dual detector gamma camera (Siemens Multispect-2). Immediately after image collecting sessions a SPECT study was performed, with data collection of 30 frames per camera head for 60 seconds per frame. Reconstruction was performed to produce short axis, vertical and horizontal long axis tomograms.

Thallium scintigraphy

A dose of 110 MBq of ^{201}thallium chloride was administered intravenously. Both rest and stress studies were performed. The stress study was performed following dynamic exercise on a treadmill with a ^{201}Tl injection at the peak of exercise. A triple-detector gamma camera (Siemens, Multispect-3) was used for the SPECT imaging. A non-circular body contour tracking 360° acquisition was performed to obtain 60 projection images of 45 seconds each. Short-axis, vertical and horizontal long axis tomograms were produced.

MIBG and thallium scintigraphy were performed with a minimum delay of two days between the two studies. Visual assessment was based on regional heterogeneity in ^{123}I-MIBG and ^{201}Tl uptake. Scans were considered abnormal if obvious heterogeneity was present. The images were examined independently and blindly by two experienced nuclear physicians (G.H. and M.v.K.). Both observers scored all images twice for assessment of intra- and inter-observer variability.

Quantitative ^{123}I-MIBG uptake assessment was based on the count ratio of the heart and mediastinum (H/M), of the inferior and anterior wall of the left ventricle (I/A) and the cardiac wash-out rate (percentage of [early counts – delayed counts]/early counts).

Temperature threshold testing (TTT)

TTT was used to assess small sensory fibre functioning by measuring temperature sensation thresholds using a Medoc TSA-2001 device (®Medoc, Ramat Yishai, Israel). Thresholds for warm and cold sensation were determined on the hand and on the dorsum of the foot on both sides using the method of levels (MLE) and the method of limits (MLI) as described previously [13, 21]. Normative data according to Yarnitsky and Sprecher were used [22]. Temperature sensation was considered abnormal if at least on one side both MLE and MLI testing resulted in Z values exceeding 2.5 (above the 99th percentile) [13].

Cardiovascular autonomic function test (CAFT)

Cardiovascular autonomic function was assessed using 5 tests (Ewing tests) recommended by the San Antonio Consensus Meeting [23]. Heart rate variability and blood pressure were measured while the patient rested in a supine position for about 10 minutes, while the patient remained standing for about 5 minutes, during deep respiration (respiratory sinus arrhythmia) with a frequency of 0.1 Hz, during a Valsalva manoeuvre (forced expiration against 40 mm Hg during 15 seconds) and while rapidly changing posture from supine to upright. Various time and frequency domain measures of heart rate variability (HRV) and manually measured sphygmomanometric systolic and diastolic blood pressure were determined. CAFT was classified abnormal if at least two of the five tests were abnormal.

Cardiac assessment

Standard 12 lead electrocardiograms (ECGs) were obtained by the MAC VU electrocardiograph (GE Medical Systems, Milwaukee, USA), using a frequency range of 0.01-150 Hz.

Twenty-four hours of continuous electrocardiograms were recorded using analogue 3-channel Holter recordings with amplitude modulation and a speed of 1 mm per second (GE Medical Systems). Tapes were analysed on a digital system (Marquette 8000).

Echocardiograms were recorded using a Hewlett-Packard (Sonos 2500 with a 2.5 MHz transducer) echocardiograph. Parasternal long and short axis and apical views were obtained. LV end-diastolic and end-systolic volumes were computed using the disc summation method (modified Simpson's rule), according to the recommendations of the American Society of Echocardiography (cutoff values for left ventricular mass index of 110 g/m2 or greater for women and 134 g/m2 or greater for men) [24].

Statistical analysis

The Mann Whitney-U test and χ^2-test (or Fisher exact test if appropriate) were used for comparisons between groups. Probability values of less than 0.05 were considered significant. To assess intraobserver agreement and for interobserver agreement kappa statistics were used. A κ-value less than 0.20 indicates poor agreement, between 0.21 and 0.40 moderate, between 0.41 and 0.60 fair, between 0.61 and 0.80 good and between 0.81 and 1.00 excellent agreement.

Results

Cardiac assessment

In only two patients a perfusion defect was found using a Thallium scintigraphy. Those two cases both had abnormal MIBG scintigraphy and abnormal TTT results. However, to rule out that the deficiencies of MIBG uptake might be due to myocardial ischemia these two cases were excluded from further analyses. Therefore, 45 cases were included in this study.

Table I
Summary of characteristics of the studied sarcoidosis patients without (Group 1) and with (Group 2) small fiber neuropathy

	Group 1 (n = 13)	*Group 2 (n = 32)*	*Total population (n = 45)*
Age (years)	40.9 ± 8.7 (30-56)	45.9 ± 10.7 (32-70)	44.5 ± 10.3 (30-70)
Sex (male/female)	11/2	17/15	28/17
Smoking (yes/no)	3/10	4/28	7/28
Time since diagnosis (years)	4 (1-7)	4 (1-6)	4 (1-7)
Prednisone (yes/no)	6/7	19/13	25/20
SFN symptoms (yes/no)			
Sensory symptoms	4/9	31/1***	35/10
Autonomic symptoms	4/9	25/7**	29/11
Cardiac symptoms (yes/no)	8/5	25/7	33/12
CXR (0/I/II/III/IV)	3/1/3/3/3	2/5/8/13/4	5/6/11/16/7
ACE (U/l)	24.4± 14.3	22.3±10.7	23.0±11.7

Data are expressed as absolute number and mean ± standard deviation with range in parentheses if appropriate. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.0001$; CXR = Chest radiographs graded according to DeRemee (0 to III), adding stage IV, the end stage of lung fibrosis; ACE = Angiotensin converting enzyme (normal range: 9-25 U/l); SFN = small fiber neuropathy

Thermal threshold testing

TTT was abnormal in 32 of 45 (71.1%) cases *(Table I)*. Symptoms of SFN were significantly more frequent in patients with abnormal TTT than in patients with normal TTT ($p < 0.0001$). Cardiac symptoms, age, sex, or the use of prednisone did not differ significantly between the two groups.

Cardiovascular autonomic function tests

CAFT were performed in 45 patients and were abnormal in 4 (8.9%) of them. The 4 cases (2 males) with abnormal CAFT all had cardiac and SFN symptoms, abnormal TTT results and abnormal MIBG-scintigraphy.

MIBG scintigraphy

As a measure of internal consistency and reliability, we assessed intra- and inter-observer variability. κ-values for intra-observer variability were excellent for observer 1 and good for observer 2 (0.87 and 0.71, respectively). Inter-observer variability κ-values (calculated for all possible matches) varied from fair (0.56) to good (0.62, 0.67 and 0.71). The MIBG results of both scores of observer 1 and 2 are presented in *Table II*. A significant reduction of ^{123}I-MIBG uptake regional in the myocardium was demonstrated in a substantial number of the studied sarcoidosis population (varying from 24.5 to 37.8 percent depending on which score was used) with various distribution patterns of myocardial ^{123}I-MIBG accumulation *(Fig. 1)*. Observer 1, the observer with the most optimal intra-observer variability, scored 35.6% and 37.8% of MIBGs as abnormal. Both scores achieved statistically significant differences between sarcoidosis patients with or without SFN, respectively. The first scores of observer 1 were used for further analysis because of optimal intra-observer variability.

In 7 cases an apical defect was found, in 2 cases an anterior defect, in 12 cases an inferior defect, in 6 cases a lateral defect and in 1 case a septal defect.

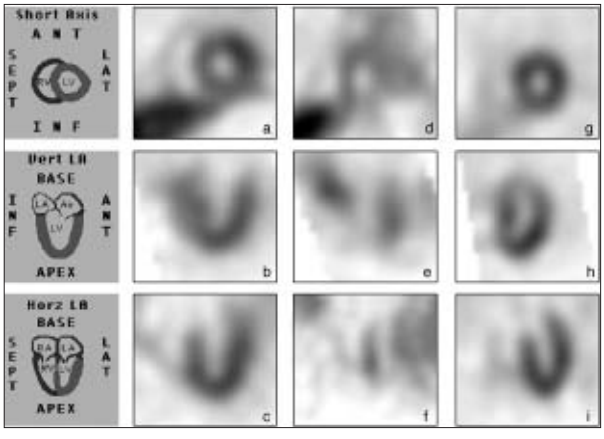

Fig. 1. a, b, c: Tomographic images of the heart performed in a sarcoidosis patient (male; 50 years) with normal ^{123}I-MIBG uptake. d, e, f, g, h, i: Tomographic images of the heart in a sarcoidosis patient (male; 44 years) with infero-apical defects of ^{123}I-MIBG uptake, with extension to the lateral wall (d, e, f), but with normal ^{201}Thallium uptake (g, h, i).

Table II
Cardiac and scintigraphy characteristics of sarcoidosis patients without (Group 1) and with (Group 2) small fiber neuropathy

	Group 1 (n = 13)	*Group 2 (n = 32)*	*Total population (n = 45)*
^{123}I-MIBG (normal/abnormal)			
observer 1, first score	12/1	16/16**	28/17
observer 1, second score	11/2	18/14*	29/16
observer 2, first score	12/1	21/11	33/12
observer 2, second score	12/1	22/10	34/11
CAFT (normal/abnormal/missing)	13/0/0	27/4/1	40/4/1
TTE (no/yes/missing)			
Left ventricular hypertrophy	11/1/1	22/7/3	33/8/4
Right ventricular hypertrophy	12/0/1	27/2/3	29/2/4
Holter (normal/abnormal)	13/0	32/0	45/0
ECG (normal/non-specific[1]/abnormal[2])	11/1/1	24/5/3	25/6/4
H/M	2.90±0.60	3.10 ± 0.56	3.01 ± 0.58
IAR	1.03±0.17	0.85 ± 0.17**	0.91 ± 0.19
Washout percentage	24.9 ± 6.9	20.6 ± 9.2*	21.8 ± 9.3

Data are expressed in absolute number or as mean ± standard deviation if appropriate.
* $p < 0.05$; ** $p = 0.003$; [1] Including low voltage ECG and non-specific ST-segment abnormalities;
[2] Including conduction disturbances and right ventricular hypertrophy; ^{123}I-MIBG = Iodine-123 meta-iodobenzylguanidine;
CAFT = cardiovascular autonomic function testing; H/M = heart-mediastinum ratio; IAR = inferior-anterior ratio;
TTE = trans thoracic echocardiography

Eleven patients showed more than one defect. There was a significant difference between MIBG results in patients with abnormal TTT and normal TTT ($p = 0.007$) *(Table II)*.

MIBG scintigraphy, quantitative assessment (Table II)

The inferior-anterior ratios (IAR) were significantly decreased in patients with SFN ($p = 0.003$). No significant gender difference was found. IAR was significantly lower in patients with abnormal CAFT and abnormal MIBG scans than in patients with normal results ($p = 0.02$ and $p = 0.001$, respectively).

H/M was significantly lower in patients with abnormal CAFT than in patients with normal CAFT ($p = 0.007$).

Myocardial MIBG wash-out was significantly higher in patients with abnormal MIBG scans and abnormal CAFT compared with patients with normal MIBG scans and CAFT ($p = 0.01$ and $p = 0.03$, respectively).

Echocardiography was performed in 40 patients. Left ventricular hypertrophy was found in 1 out of 14 patients with an abnormal MIBG scan and in 1 out of 26 with a normal MIBG scan. Right ventricular hypertrophy was found in 1 out of 14 patients with an abnormal MIBG scan. There were no signs of cardiac granulomas, fibrosis or valve abnormalities. All Holter recordings were normal. ECG findings revealed non-specific abnormalities including low voltage and non-specific ST segment abnormalities in 5 out of 17 with MIBG abnormalities and in 8 of the 28 cases with normal MIBG scans, respectively (not significant). Abnormalities that could be related to sarcoidosis, including conduction disturbances and right ventricular hypertrophy, were found in 3 out of 17 cases with MIBG abnormalities and 2 out of 28 patients with normal MIBG scans, respectively (not significant).

Discussion

This is the first study assessing myocardial sympathetic integrity by use of qualitative and quantitative ^{123}I-MIBG-scintigraphy in sarcoidosis patients with and without SFN. A significant reduction of ^{123}I-MIBG uptake regional in the myocardium was demonstrated in a substantial number of the studied sarcoidosis population (varying from 24.5 to 37.8 percent depending on which score was used). In our study, the inferior/anterior ratio and myocardial washout ratio of MIBG were significantly decreased

in patients with SFN compared to sarcoidosis patients without signs of SFN assessed by TTT. Moreover, patients with SFN demonstrated striking differences in the visual qualitative scintigraphic scores of both observers. Sarcoidosis patients with SFN exhibit prominent myocardial adrenergic denervation with normal or impaired sympathetic neural function of the heart.

In contrast to ^{123}I-MIBG scintigraphy and frequently presented symptoms of autonomic dysfunction, the frequency of CAFT (Ewing tests) abnormalities was relatively low in our patients. This is in line with previous results in sarcoidosis, diabetes and idiopathic SFN [13, 25, 26]. CAFT provides indirect measures of sympathetic nervous system effects on the heart and seems inherently less sensitive than MIBG. The only direct and precise method is the determination of heart norepinephrine spillover [27, 28], which is however an invasive procedure requiring heart catheterisation. An advantage of MIBG myocardial scintigraphy is that it can be performed safely and does not require special equipment.

Potential mechanisms of MIBG heterogeneity in sarcoidosis

Defects on MIBG scans in sarcoidosis have been reported before [29-31], but so far the underlying mechanism has remained unclear. One possible explanation postulated was that local ischemia or myocardial inflammation may play an important role. In the present study, myocardial MIBG abnormalities due to myocardial hypoperfusion were excluded as a mechanism as cases with an abnormal myocardial perfusion (^{201}Tl-scintigraphy, n = 2) were excluded. Moreover, none of the studied cardiac parameters appeared to be related to the cardiac denervation. Furthermore, there were no signs of granulomatous cardiac involvement or fibrotic lesions related to sarcoidosis in the studied sarcoidosis population. Sympathetic neuronal damage measured by MIBG scintigraphy may be related to the area of inflammation, since neuronal damage is highly sensitive to inflammation compared with myocardial cells [30].

Experimental studies have shown that cytokine production by the heart may be regulated by sympathetic nervous system stimulation of cardiac beta-adrenergic receptors. Moreover, neuronal damage may be induced by the involvement of cytokines including tumor necrosis factor-alpha or interleukin-10 which are involved in the inflammatory process in sarcoidosis as well [32, 33]. Parthenakis *et al* demonstrated that reduced cardiac sympathetic innervation in heart failure is associated with elevated levels of inflammatory cytokines, suggesting that it has a potential inflammatory effect via modulation of the cardiac production of these cytokines [34]. It is tempting to speculate that the observed autonomic dysfunction and SFN is related to the ongoing inflammatory process and cytokine production in sarcoidosis.

Implications/relevance

In general, the assessment of cardiac involvement is focussing on the presence of cardiac granulomatous lesions. So far, search for abnormal sympathetic innervation is less common in sarcoidosis. The results of this study stress the importance of including search for cardiac neuronal dysfunction in the management of sarcoidosis patients even in asymptomatic cases. Autonomic dysregulation might contribute to fatal arrhythmias and unexplained sudden death in diabetes mellitus, amyloidosis, epilepsy and Guillain Barré syndrome. It is known from patients with neuropathy that the involvement of small autonomic nerve fibres is a predictor of cardiovascular mortality [35, 36]. Sudden death is a rare but dramatic complication. In the case of sarcoidosis it is thought to be due mostly to cardiac involvement. Active granulomatous infiltration and resulting myocardial fibrosis are considered to be the substrate. Because of the potential danger of malignant arrhythmias, intensive screening is indicated when cardiac sarcoidosis is suspected. Another explanation could be autonomic involvement due to SFN. Until now, sympathetic innervation has not been evaluated systematically. Moreover, adequate and sensitive techniques to assess patients at risk for life threatening arrhythmias are lacking and better diagnostic tools are needed.

In line with our observations, it is recommended that the possibility of autonomic cardiac dysfunction should be considered in the management of sarcoidosis patients. Moreover, careful follow-up is mandatory to evaluate the prognostic implications. Whether there might be a relation with conduction distur-

bances and implantation of an intracardial defibrillator (ICD) should be recommended needs for future study. The proper and adequate treatment of SFN is currently unknown. Although there is common consensus that corticosteroids are beneficial in granulomatous cardiac involvement in sarcoidosis, this is not known for SFN related to sarcoidosis. Whether other therapeutics such as anti-TNFα or lipoic acid are beneficial also deserves further study [37, 38].

Limitations of the study

In normal subjects, regional MIBG uptake may be non-homogeneous and apparently lower in the inferior and septal wall than in the anterior wall, especially in older males [39-41]. However, in our study MIBG results and IAR did not differ significantly between males and females. Furthermore, our population was of relatively young age. Finally, cardiac ^{123}I-MIBG markers that have been used include not only regional uptake heterogeneity but also global myocardial uptake (H/M ratio) and wash-out kinetics. However, H/M ratios and wash-out measurements are highly influenced by the placement of the regions of interest (ROI), by varying background ^{123}I-MIBG uptake in the mediastinum, over projecting breasts and subcutaneous fat [42]. Therefore, in line with others [20, 43], we rely on quantifying regional rather than global uptake and ratios.

Although we did not have the opportunity to include healthy subjects in our study, the difference between both studied patients subgroups was obvious. The myocardial uptake and turnover of MIBG in patients with sarcoidosis are heterogeneous and dependent on the presence or absence of SFN.

Conclusion

The results of our study provide evidence of the presence of abnormal sympathetic myocardial innervation in sarcoidosis patients, more prominent in those with SFN. ^{123}I-MIBG SPECT seems a feasible relatively non-invasive approach investigating cardiac adrenergic innervation and localizes the territories of reduced sympathetic innervation. Moreover, ^{123}I-MIBG scintigraphy is more sensitive in detecting inflammatory induced myocardial sympathetic neuronal damage in sarcoidosis than myocardial perfusion Thallium^{201} scintigraphy and therefore of additional value in the workup of cardiac involvement related to sarcoidosis. The intriguing hypothesis that small fibre neuropathy might explain – at least in part – the hitherto unexplained but frequently presented symptoms of myocardial autonomic dysfunction in sarcoidosis needs prospective studies. The results of such studies may not only provide new insight in the pathophysiology of arrythmogenesis in sarcoidosis but also have future therapeutic implications, because pharmacological interventions resulting in a normalization of autonomic imbalance may reduce arrhythmias in sarcoidosis. Future studies are needed to evaluate its clinical implications and therapeutic options. Moreover, the important question of whether SFN with or without cardiac innervation impairment is reversible or not should be explored.

Acknowledgements

We thank Professor J. Troost, who proposed the idea for this study, and Professor F. Spaans, for advice and for critically reading the manuscript. We also want to acknowledge Petal Wijnen for taking care of the data base.

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Pioneers of Sarcoidosis
Jorgen Schaumann (1879-1953)

Jorgen Schaumann was born in Soustad, Malmohus, Sweden on June 3, 1879 and studied medicine at nearby Lund. He became a dermatologist at St Goran's Hospital and at the Finsen Institute in Stockholm. He provided a common pathological basis for diverse clinical aspects so he was the first to provide a clinico-pathological synthesis of multisystem sarcoidosis. He called it lymphogranulomatosis benigna to distinguish it from Hodgkin's malignant granuloma. This was an admirable Zambaco prize essay written in 1914 but not published until 1936. He is buried in Ekebyholm near his birthplace and the inscription on his tomb is:

Jorgen Schaumann
3.6.1879 - 9.8.1953
Medicus Arte Insignio
Professor Illustrissimi
Investigator Morbi
Lymphogranulomatosis Benigna

D. Geraint James

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