

Diagnostic and Therapeutic Management of Cardiac Sarcoidosis -Application of High Resolution Electrocardiography

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1. Introduction

Sarcoidosis is a common multisystem granulomatous disease of unknown etiology. Overall the prognosis is not necessarily deleterious because organ involvement is usually asymptomatic except for ocular or cutaneous involvements and the disease is often self-limiting. Cardiac Sarcoidosis is rare (5%) but once the heart is involved, the patient's prognosis is poor because of the development of fatal arrhythmias, atrioventricular conduction disturbance or refractory congestive heart failure (Newman et al., 1997). Despite advanced research, a clear cause and pathogenesis for sarcoidosis remains unknown. Sarcoidosis is thought to be caused by an abnormal, exaggerated response of the immune system. Infectious agents such as *Propionibacterium acnes*, *Mycobacteria* suspected of causing sarcoidosis (Nishiwaki et al., 2004; Hance, 1998), but The American Thoracic Society's wide-ranging *Statement on Sarcoidosis* suggested that there is no clear evidence of an infectious agent causing sarcoidosis. Genetic factors such as the human leucocyte antigens (specifically HLA-DRB1) may be a predisposition for sarcoidosis (Maliark et al., 1998), but not the only cause. Currently, sarcoidosis is considered to be caused by multiple factors.

2. Diagnostics

There are no specific symptoms or signs of CS. Clinical manifestations such as dyspnea, palpitations, syncope are often associated with arrhythmias or heart failure. There is no golden standard for diagnosis of CS. Since 1993, the Japanese Ministry of Health and Welfare (JMHW) guidelines (Hiraga et al., 1993) have been widely used as the reference standard (table 1).

Endomyocardial biopsy is specific but it shows noncaseating granulomas no more than 25% of CS (Uemura et al., 1999; Ardehali et al., 2005). Diagnosis of CS is often made by combination of cardiac abnormality and pathology of other organs.

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- 1 Histologic diagnosis group: endomyocardial biopsy demonstrates epithelioid granulomata without caseating granulomata.
 - 2 Clinical diagnosis group: in patients with histologic diagnosis of extracardiac sarcoidosis, cardiac sarcoidosis is suspected when "a" and at least one of criteria "b" to "d" is present, and other etiologies such as hypertension and coronary artery disease have been excluded:
 - a. Complete RBBB, left-axis deviation, AV block, VT, PVC, or pathological Q or ST-T change on resting or ambulatory electrocardiogram.
 - b. Abnormal wall motion, regional wall thinning, or dilation of the left ventricle.
 - c. Perfusion defect by ²⁰¹thallium-myocardial scintigraphy or abnormal accumulation by ⁶⁷Ga-citrate or ^{99m}Tc-PYP myocardial scintigraphy.
 - d. Abnormal intracardiac pressure, low cardiac output, or abnormal wall motion or depressed ejection fraction of the left ventricle.
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AV atrioventricular; LBBB left bundle branch block; PVC premature ventricular contraction; RBBB right bundle branch block; VT ventricular tachycardia.

Table 1. Modified Guidelines for the Diagnosis of Cardiac Sarcoidosis Based on the Study Report on Diffuse Pulmonary Diseases From the Japanese Ministry of Health and Welfare, 1993.

2.1 Electrocardiography

Electrocardiographic conduction abnormalities, atrioventricular block (AVB) or bundle branch block (BBB) are well known as the characteristic manifestation of CS. These manifestations have been detected in less than 5% of patients with sarcoidosis (Silverman et al., 1978). Nevertheless, in autopsy studies, cardiac involvements have been found in 20% to 58% of the cases, indicating latent CS does exist in a larger part of the sarcoidosis patients, even if routine electrocardiogram (ECG) shows no abnormal findings (Loncope et al., 1952; Iwai et al., 1994; Bargout et al. 2004). Previously, we reported the results of signal averaged electrocardiography (SAECG) in 10 cardiac sarcoidosis patients, 52 pulmonary sarcoidosis patients with normal ECG, and 52 normal controls (Yodogawa et al., 2007). We found that late potentials (LP) were positive in 80% of cardiac sarcoidosis patients, 46.2% in pulmonary sarcoidosis patients, and 5.8% in normal control ($P < 0.0001$). These results suggested that latent cardiac abnormality may exist in sarcoidosis patients even if ECG is normal. In a similar point of view, there is increasing concern about "subclinical" cardiac sarcoidosis. Soejima et al stated that many patients who have cardiac sarcoidosis are asymptomatic, and Positron Emission Tomography (PET) and Magnetic Resonance Imaging (MRI) are useful for early detection of cardiac abnormality (Soejima & Yada, 2009).

2.2 Echocardiography

In the early stage, regional wall thickness caused by granulomatous infiltration may be noted (Yazaki et al., 1998; Matsumori et al., 2000). Later, myocardial scar occurred as the result of healed sarcoid granulomas. In the progressed stage, thinning of myocardium, wall motion abnormality, and sometimes aneurysms (Sato et al., 2010) are seen. Valantine et al. reported that thinning at the base of the intra-ventricular septum is pathognomonic for CS (Valantine et al., 1987). However, the sensitivity is reported to be relatively low (20%) (Uemura et al., 2005).

2.3 Gallium-67 scintigraphy

Gallium-67 scintigraphy has been widely used in diagnosis and management of CS. Gallium uptake in the heart indicates active inflammation, which is a useful finding in predicting the response to corticosteroid therapy (Okayama et al. 1995). Futamatsu et al. recently reported that gallium-67 scintigraphy is useful for evaluation of CS with ventricular tachycardia (VT) (Futamatsu et al., 2006). According to the study, accumulation of gallium-67 in the heart at the time of diagnosis was detected more frequently in the VT group than in the non-VT group (14.3 vs 71.4%, $P < 0.05$). Thus, Gallium-67 uptake is highly specific to inflammatory disease and a useful for detection of disease activity of cardiac sarcoidosis. Meanwhile, the main disadvantage is lack of sensitivity (20%, 36%) (Okayama et al., 1995; Kiuchi et al., 2007).

2.4 Positron Emission Tomography (PET)

PET is noninvasive imaging technique using small amounts of radioactive positrons for measuring the metabolic activity of cells in the human body. Fluorine-18 fluorodeoxyglucose (18F-FDG) is accumulated by inflammatory cells, and widely used radiotracer for PET imaging studies. Yamagishi *et al.* reported a significantly higher sensitivity of 18F-FDG uptake for detection of CS compared with that of Gallium-67 uptake (Yamagishi et al., 2003). They also showed improvement of 18F-FDG uptake after corticosteroid therapy. Hence, FDG-PET is considered to be useful not only for detection but therapeutic monitoring of cardiac involvement. The biggest advantage of PET is its high sensitivity (87.5%, 100%, and 100%), but the specificity is obscure (38.5%, 81.5%, and 90.9%) (Ohira et al., 2008; Ishimaru et al., 2005; Okumura et al., 2004). This may be due to the possibility of detecting subclinical CS or natural accumulation with interindividual variability.

2.5 Magnetic Resonance Imaging (MRI)

Cardiac MRI is a noninvasive diagnostic testing to detect structural abnormalities. Increased signal intensity of T2-weighted images is considered to indicate active inflammation area, and Gadolinium-DTPA enhanced the detection of the region. Cardiac MRI has been reported to be useful for detecting areas of inflammation associated with sarcoid granulomas (Shimada et al., 2001). Several reports have shown high sensitivity (100%) and specificity (78% and 100%) for diagnosis of CS (Smedema et al., 2005; Tadamura et al., 2005). However, one of the main disadvantages is that MRI is not recommended for patients with implantable cardiac devices, such as pacemaker, or implantable cardioverter-defibrillator (ICD).

3. Treatment

In patients with definite diagnosis of CS, corticosteroid therapy should be considered. In general, the initial dosage is 30 mg/day of prednisone or its equivalent on alternate days, which was tapered over a period of 6 months to a maintenance dosage of 5-10 mg/day. Initiation of corticosteroid therapy is reported to preserve LV function and improve outcomes (Yazaki et al., 2001; Chiu et al., 2005). Concerning arrhythmias, Kato et al. described that AVB resolved in 4 of the 7 CS patients by corticosteroid therapy, but did not resolve or improve in any of the patients without corticosteroid therapy (Kato et al., 2003). Recently, Banba et al evaluated the effect of corticosteroids in CS patients presenting VT or CAVB. In their cohort, atrioventricular conduction improved in 5 of 9 CAVB patients after corticosteroid therapy albeit the fact that ventricular arrhythmias were not improved after corticosteroid therapy (Banba et al., 2007). In regard to ventricular arrhythmias, we evaluated the effect of corticosteroids in CS patients presenting VT (Yodogawa et al., 2008). After corticosteroid therapy, VT was suppressed in 6 of 15 patients (Responder group). Accumulation of gallium-

67 was detected more frequently in the responder group than in the non-responder group (66.7% vs. 11.1%, $p < 0.05$). All patients underwent SAECG in which the filtered QRS duration (f-QRS), the root mean square voltage of the terminal 40 ms (RMS_{40}) in the filtered QRS complex and the duration of low-amplitude signals $< 40\mu V$ (LAS_{40}) in the terminal filtered QRS complex were measured. In the responder group, f-QRS and LAS_{40} were significantly decreased and RMS_{40} was significantly increased compared with those before corticosteroid therapy (f-QRS: 136.3 ± 30.6 msec vs 116.8 ± 25.4 msec, $p < 0.05$ LAS_{40} : 68.2 ± 24.0 msec vs 47.8 ± 22.9 msec, $p < 0.05$ RMS_{40} : 7.2 ± 3.3 msec vs 13.3 ± 7.6 msec, $p < 0.05$). However, SAECG parameters did not change significantly in non-responder group. In addition, we recently reported the effect of corticosteroid therapy in CS patients presenting ventricular arrhythmias (Yodogawa et al., 2010). The less advanced LV dysfunction patients ($EF \geq 35\%$) showed improvement of ventricular arrhythmias after corticosteroid therapy, and had a significantly higher prevalence of Gallium-67 uptake compared with the advanced LV dysfunction patients ($EF < 35\%$). Remission of Gallium-67 uptake was observed in 5 of 6 CS patients after corticosteroid therapy. These results suggested that active and reversible inflammation might play an important role for the occurrence of ventricular arrhythmias in CS. Thus, CS patients with gallium-67 uptake and relatively preserved LV function are thought to be good candidates for treatment of the steroid therapy. On the contrary, CS patients with advanced LV dysfunction and no gallium-67 uptake are considered to be non-responders to corticosteroid therapy, and require earlier initiation of additional therapy such as catheter ablation, permanent pacemaker or ICD implantation. In patients with no response to corticosteroid therapy or intolerant to steroid side effects, alternative therapy such as methotrexate, cyclosporine is the treatment of choice. Although rare, cardiac transplantation may be needed for severe CS patients unresponsive to these therapies.

4. Prognosis

The prognosis of symptomatic CS is not well elucidated. Although it has been considered poor, recent studies have shown better prognosis in patients treated with corticosteroids. Yazaki et al. showed 5-year survival rates of 75% in the steroid-treated patients and of 89% in patients with a left ventricular ejection fraction $\geq 50\%$ (Yazaki et al., 2001). According to a report by Chiu et al., survival rate of CS patients was relatively good, at 98% after 1 year, 93% after 3 years, 90% after 5 years, and 84% after 10 years. Especially, there were no cardiac deaths in preserved EF patients (initial LV ejection fractions $> 55\%$), during the follow-up period of 10 years (Chiu et al., 2005). Therefore earlier initiation of corticosteroid therapy is mandatory for CS patients before the deterioration of cardiac function.

5. Conclusion

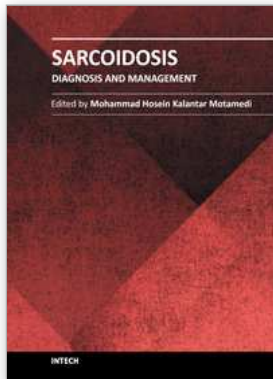
The early detection of CS is critical for successful treatment and improved prognosis. Although MRI and PET scan have renewed the awareness of CS, the early detection still remains difficult. Currently, no single test has proven consistently reliable in detecting CS. A combination of multiple testing methodologies is considered to be the most reliable approach for the early identification. Refinements in noninvasive electrocardiographic studies may help in the early detection and management for CS.

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Sarcoidosis Diagnosis and Management

Edited by Prof. Mohammad Hosein Kalantar Motamedi

ISBN 978-953-307-414-6

Hard cover, 280 pages

Publisher InTech

Published online 17, October, 2011

Published in print edition October, 2011

Sarcoidosis is a type of inflammation that occurs in various locations of the body for no known reason. Normally, when foreign substances or organisms enter the body, the immune system will fight back by activating an immune response. Inflammation is a normal part of this immune response, but it should subside once the foreign antigen is gone. In sarcoidosis, the inflammation persists, and some of the immune cells form abnormal clumps of tissue called granulomas. The disease can affect any organ in the body, but it is most likely to occur in the lungs. It can also affect the skin, eyes, liver, or lymph nodes. Although the cause of sarcoidosis is not known, research suggests that it may be due to an extreme immune response or extreme sensitivity to certain substances. It also seems to have a genetic component as well, and tends to run in families. Sarcoidosis most commonly develops in people between 20 and 50 years of age. African Americans are somewhat more likely to develop sarcoidosis than Caucasians, and females are somewhat more likely to develop sarcoidosis than males. The symptoms of sarcoidosis depend on the organ involved. This book deals with the diagnosis and treatment of this mysterious disease of unknown etiology.

How to reference

In order to correctly reference this scholarly work, feel free to copy and paste the following:

Kenji Yodogawa (2011). Diagnostic and Therapeutic Management of Cardiac Sarcoidosis -Application of High Resolution Electrocardiography, Sarcoidosis Diagnosis and Management, Prof. Mohammad Hosein Kalantar Motamedi (Ed.), ISBN: 978-953-307-414-6, InTech, Available from:

<http://www.intechopen.com/books/sarcoidosis-diagnosis-and-management/diagnostic-and-therapeutic-management-of-cardiac-sarcoidosis-application-of-high-resolution-electroc>

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