Outcomes in Patients With High-Degree Atrioventricular Block as the Initial Manifestation of Cardiac Sarcoidosis

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Although high-degree atrioventricular block (AVB) is a common initial manifestation of cardiac sarcoidosis, little is known about the outcomes. The aim of this study was to assess outcomes in patients with AVB as an initial manifestation of cardiac sarcoidosis compared with those in patients with ventricular tachyarrhythmia (VT) and/or heart failure (HF). Fifty-three consecutive patients with cardiac sarcoidosis, who had high-degree AVB (n = 22) or VT and/or HF (n = 31), were enrolled. The end point was defined as major adverse cardiac events, including cardiac death, ventricular fibrillation, sustained VT, and hospitalization for HF. Over a median follow-up period of 34 months, the outcomes of major adverse cardiac events were better in patients with high-degree AVB than in those with VT and/or HF (log-rank test, p = 0.046). However, this difference was due mainly to HF hospitalization. The outcomes of fatal cardiac events, including cardiac death, ventricular fibrillation, and sustained VT, were comparable between the 2 groups (log-rank test, p = 0.877). The fatal cardiac events in patients with high-degree AVB were not associated with the initiation of steroid treatment or left ventricular dysfunction. In conclusion, the outcomes of major adverse cardiac events are better in patients with high-degree AVB than in those with VT and/or HF. However, patients with high-degree AVB have a high rate of fatal cardiac events, similar to those with VT and/or HF. An indication for an implantable cardioverter-defibrillator, but not a pacemaker system, can be considered in patients with cardiac sarcoidosis manifested by high-degree AVB. **(Am J Cardiol 2015;115:505−509)**

Sarcoidosis is a systemic granulomatous disease of unknown origin.[1] Cardiac involvement is increasingly recognized because of adverse outcomes.[2−5] The principal initial manifestation of cardiac sarcoidosis is high-degree atrioventricular block (AVB), ventricular tachyarrhythmia (VT), or heart failure (HF).[5] Patients with VT have a high rate of recurrence of fatal VT or sudden cardiac death.[6−10] HF caused by left ventricular dysfunction is one of the most common causes of cardiac death.[11] Therefore, patients with VT and/or HF as the initial manifestation of cardiac sarcoidosis are regarded as at high risk for cardiac events, whereas outcomes in patients with high-degree AVB have not been well investigated. One study showed that patients with AVB caused by cardiac sarcoidosis had an increase in the risk for cardiac events compared with those with idiopathic AVB.[12] However, whether the outcomes are different according to the initial manifestation, such as high-degree AVB or VT and/or HF, remains unknown. Understanding the incidence of cardiac events in patients with high-degree AVB may be important for selecting the appropriate device (i.e., pacemaker system vs implantable cardioverter-defibrillator [ICD]). The aim of this study was to assess outcomes in patients with high-degree AVB as the initial manifestation of cardiac sarcoidosis compared with those in patients with VT and/or HF.

Methods

The study population consisted of 53 consecutive patients diagnosed with cardiac sarcoidosis in our institution from July 1998 to November 2013, who had high-degree AVB (n = 22) or VT and/or HF (n = 31) as the initial manifestation. Cardiac sarcoidosis was diagnosed according to Japanese Ministry of Health and Welfare guidelines, revised in 2006 by the Japanese Society of Sarcoidosis and Other Granulomatous Disorders.[13,14] In brief, cardiac sarcoidosis is diagnosed on the basis of histologic findings or clinical findings. Histologic diagnosis is confirmed when endomyocardial biopsy specimens demonstrate non-caseating epithelioid cell granulomas. Clinical diagnosis is confirmed in the absence of endomyocardial biopsy when extracardiac sarcoidosis is diagnosed and the following clinical cardiac criteria (>2 of 4 major criteria, or 1 of 4 major criteria and >2 of 5 minor criteria) is satisfied. Major criteria consist of advanced AVB, basal thinning of the interventricular septum, positive myocardial uptake of gallium-67 citrate (^{67}Ga) scintigraphy or ^{18}F-fluoro-2-deoxyglucose (^{18}F-FDG) positron emission tomography (PET), and a left ventricular ejection fraction <50%. Minor criteria consist of abnormal electrocardiographic results, abnormal echocardiographic results, perfusion defect on thallium-201 or technetium-99m myocardial scintigraphy, delay enhancement of myocardium on gadolinium-enhanced

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See page 509 for disclosure information.

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Table 1
Patient characteristics

	All (n = 53)	High-degree atrioventricular block (n = 22)	Ventricular tachyarrhythmia and/or heart failure (n = 31)	p
Age (years)	60 ± 13	60 ± 9	60 ± 15	0.948
Female	33 (62%)	16 (73%)	17 (55%)	0.193
Extracardiac organ involvements	43 (81%)	17 (77%)	26 (84%)	0.554
Lung	34 (64%)	13 (59%)	21 (68%)	0.527
Skin	11 (21%)	5 (27%)	6 (19%)	0.771
Eye	19 (36%)	9 (41%)	10 (32%)	0.527
Others	10 (19%)	4 (18%)	10 (32%)	0.475
New York Heart Association functional class III or IV	27 (51%)	6 (27%)	21 (68%)	0.003
Left ventricular end-diastolic diameter (mm)	55 ± 9	51 ± 7	57 ± 9	0.013
Left ventricular end-systolic diameter (mm)	43 ± 11	38 ± 10	46 ± 11	0.005
Left ventricular ejection fraction (%)	42 ± 16	48 ± 15	38 ± 15	0.012
Angiotensin-converting enzyme (IU/L)	15.1 ± 7.0	16.0 ± 6.8	14.4 ± 7.2	0.438
Log plasma B-type natriuretic peptide (pg/ml)	2.34 ± 0.50	2.16 ± 0.43	2.46 ± 0.52	0.035
Positive myocardial uptake of gallium-67 citrate or ^{18}F-fluoro-2-deoxyglucose	40 (75%)	19 (86%)	21 (68%)	0.125
Diagnosis at the time of initial manifestation	48 (91%)	17 (77%)	31 (100%)	0.005
Initiation of 30 or 40 mg prednisone daily	42 (79%)	17 (77%)	25 (81%)	0.771
Medications after initial manifestation				
Beta-blockers	33 (62%)	7 (32%)	26 (84%)	<0.001
angiotensin-converting enzyme inhibitors/ angiotensin receptor blockers	31 (58%)	11 (50%)	20 (65%)	0.300
Diuretics	25 (47%)	2 (9%)	23 (74%)	<0.001
Anti-arrhythmic drugs	14 (26%)	2 (9%)	12 (39%)	0.015
Implantable cardioverter defibrillator	12 (23%)	1 (5%)	11 (35%)	0.007
Cardiac resynchronization therapy with defibrillator	9 (17%)	1 (5%)	8 (26%)	0.043
Median follow-up period (months)	35	45	33	0.605

Data are presented as mean ± standard deviation or number (%).

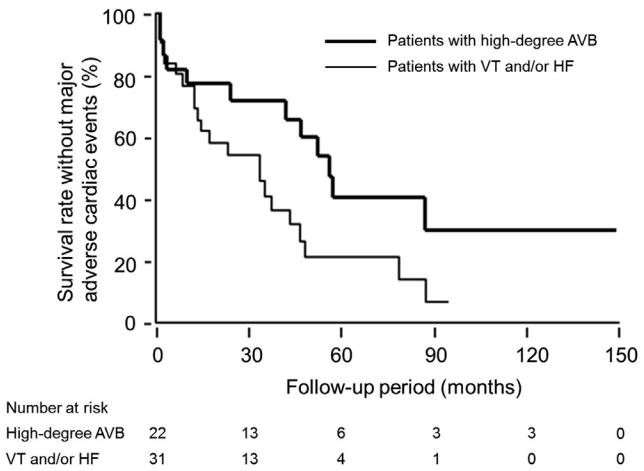

Figure 1. Survival rate without major adverse cardiac events in patients with high-degree AVB and in those with VT and/or HF.

cardiac magnetic resonance imaging, and interstitial fibrosis or monocyte infiltration on endomyocardial biopsy. This study was performed according to the principles of the Declaration of Helsinki and was approved by the institutional ethics committee.

This was a retrospective observational study. Patients with high-degree AVB were defined as having complete AVB or Mobitz II block at the time of initial manifestation of cardiac sarcoidosis. Patients with VT and/or HF were defined as having ventricular fibrillation or sustained VT and/or as being hospitalized for HF caused by left ventricular dysfunction without high-degree AVB, at the time of initial manifestation. Sustained VT was defined as spontaneous ventricular tachycardia at a rate of ≥120 beats/min that lasted ≥30 seconds. Steroid treatment was initiated at a dose of 30 or 40 mg/day of prednisone. Doses of prednisone were tapered over a period of 6 to 12 months to maintenance doses of 5 to 10 mg daily.

The end point was defined as major adverse cardiac events, including cardiac death, ventricular fibrillation, sustained VT, and hospitalization for HF. Patients were followed from the date of initial manifestation of cardiac sarcoidosis, such as high-degree AVB or VT and/or HF hospitalization, until the date of first documentation of cardiac events or the end of follow-up, whichever occurred first. The first documentation of cardiac events was assessed after the initial manifestation had been recovered. Follow-up information was obtained by medical records, contact with the patient's physicians, or telephone interview with the patient or, if deceased, with family members.

Gallium-67 citrate scintigraphy was performed in all patients. Fluorine-18-FDG PET was performed in 6 patients who were diagnosed after September 2010 and had no positive myocardial uptake of ^{67}Ga at baseline. On ^{18}F-FDG PET, patients were instructed to fast for ≥12 hours, blood glucose levels were determined to ensure a level of