CLINICAL RESEARCH STUDY

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Prevalence of Cardiac Sarcoidosis in Middle-Aged Adults Diagnosed with High-Grade Atrioventricular Block

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ABSTRACT

INTRODUCTION: Atrioventricular block may be idiopathic or a secondary manifestation of an underlying systemic disease. Cardiac sarcoidosis is a significant underlying cause of high-grade atrioventricular block, posing diagnostic challenges and significant clinical implications. This study aimed to assess the prevalence and clinical characteristics of cardiac sarcoidosis among younger patients presenting with unexplained high-grade atrioventricular block.

METHODS: We evaluated patients aged between 18 and 65 years presenting with unexplained high-grade atrioventricular block, who were systematically referred for cardiac magnetic resonance imaging, positron emission tomography-computed tomography, or both, prior to pacemaker implantation. Subjects with suspected cardiac sarcoidosis based on imaging findings were further referred for tissue biopsy. Cardiac sarcoidosis diagnosis was confirmed based on biopsy results.

RESULTS: Overall, 30 patients with high-grade atrioventricular block were included in the analysis. The median age was 56.5 years (interquartile range 53-61.75, years). In 37%, cardiac magnetic resonance imaging, positron emission tomography-computed tomography, or both, were suggestive of cardiac sarcoidosis, and in 33% cardiac sarcoidosis was confirmed by tissue biopsy. Compared with idiopathic high-grade atrioventricular block patients, all cardiac sarcoidosis patients were males (100% vs 60%, $P = .029$),

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were more likely to present with heart failure symptoms (50% vs 10%, $P = .047$), had thicker inter-ventricular septum on echocardiography (12.2 ± 2.7 mm vs 9.45 ± 1.6 mm, $P = .002$), and were more likely to present with right ventricular dysfunction (33% vs 10%, $P = .047$).

CONCLUSIONS: Cardiac sarcoidosis was confirmed in one-third of patients ≤ 65 years, who presented with unexplained high-grade atrioventricular block. Cardiac sarcoidosis should be highly suspected in such patients, particularly in males who present with heart failure symptoms or exhibit thicker inter-ventricular septum and right ventricular dysfunction on echocardiography.

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KEYWORDS: Cardiac Sarcoidosis; High-Grade Atrioventricular Block; Pacemaker; Middle-Aged Adults; Young Adults

INTRODUCTION

Atrioventricular block is a leading cause of pacemaker implantations worldwide. Its incidence is age-related, and etiology may differ between age groups. Idiopathic fibrosis and degeneration of the conduction system (Lenègre-Lev disease) is the most common cause of atrioventricular block in the older population.[1] In younger individuals, other underlying conditions leading to atrioventricular block are relatively more prevalent. Such conditions may include ischemia, infiltrative, inflammatory, or infectious processes, degenerative, metabolic, or neuromuscular disorders, and inherited syndromes. Although prognosis is usually favorable after pacing in patients with idiopathic or age-related conduction system disorders, the presence of some underlying conditions may significantly affect clinical outcomes. Of the infiltrative disorders, cardiac sarcoidosis requires particular attention, because it may pose decisive clinical implications, potentially necessitating immunosuppressive therapy. Furthermore, the primary implantation of an implantable cardioverter defibrillator (ICD) may be advocated for cardiac sarcoidosis patients requiring pacing.[2] Interestingly, literature concerning non-iatrogenic causes and the active screening for underlying disorders in young and middle-aged adults with atrioventricular block is scarce, especially when it comes to patients with no apparent history of cardiovascular conditions. A 2-decade nationwide Danish study[3] included 1088 patients implanted with a pacemaker before the age of 50. Atrioventricular block etiology remained unknown in 50% of the patients. The most common identified etiologies were complications of previous cardiac surgery (15%), followed by congenital atrioventricular block (9%) and cardioinhibitory reflex (4%). Cardiac sarcoidosis was identified in only 1.1% of this study population. Kandolin et al[4] reported cardiac sarcoidosis in 19% of 72 patients aged between 18 and 55 years who underwent pacemaker implantation for otherwise unexplained third-degree atrioventricular block. Another Japanese study found an 11.2% prevalence of clinically or histologically diagnosed cardiac sarcoidosis among 89 consecutive high-grade atrioventricular block patients with a mean age of 69.1 years.[5] Interestingly, cardiac sarcoidosis incidence is not well established, its presentation is variable and may include conduction abnormalities, arrhythmias, and heart failure.[6] There are no clear diagnostic criteria for cardiac sarcoidosis, and limited data are available on its prevalence and clinical characteristics in younger patients with high-grade atrioventricular block. In this report, we aimed to investigate the prevalence of cardiac sarcoidosis in young and middle-aged individuals (≤65 years) who were admitted with high-grade atrioventricular block (second-degree Mobitz II, third-degree, and other high-grade atrioventricular block), and describe their clinical presentation, manifestations, as well as their diagnostic and clinical outcomes.

CLINICAL SIGNIFICANCE

- Middle-aged adults with high-grade atrioventricular block were referred for advanced cardiac imaging.
- Thirty-three were diagnosed with cardiac sarcoidosis, through biopsy. All had suggestive imaging. Ninety-one of patients with suggestive imaging had cardiac sarcoidosis.
- All cardiac sarcoidosis patients were males, had thicker inter-ventricular septum, and higher prevalence of heart failure symptoms and right ventricular dysfunction.
- Our study underscores the importance of active screening for cardiac sarcoidosis, and the role of imaging in guiding diagnosis and treatment.

METHODS

The study was conducted utilizing retrospective data retrieved from the medical record database of the Sheba Medical Center. We analyzed the records of all patients aged between 18 and 65 years who had been hospitalized in the Department of Cardiology between January 2015 and January 2023 due to Mobitz II second-degree atrioventricular block, third-degree atrioventricular block, or other high-grade atrioventricular block that was not considered iatrogenic or congenital and was otherwise unexplained. The study was conducted in accordance with the Declaration of Helsinki and was approved by the institutional ethics committee (8272-21-SMC).

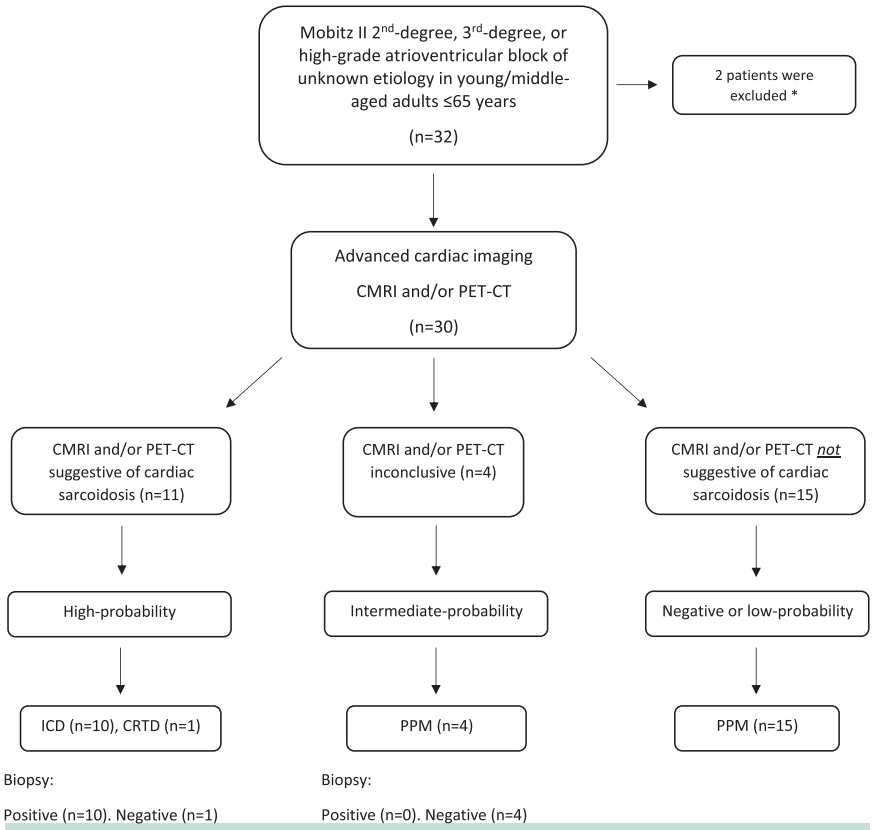

Figure 1 Screening and treatment algorithm for the investigation of cardiac sarcoidosis in subjects aged ≤ 65 years, presenting with Mobitz II second-degree, third-degree or other high-grade atrioventricular block of unknown ethicology.
CMRI = cardiac magnetic resonance imaging; CRTD = cardiac resynchronization therapy defibrillator; ICD = implantable cardioverter defibrillator; PET-CT = positron emission tomography-computed tomography; PPM = permanent pacemaker; n = number of patients.
* Two patients were not stable during initial work-up and did not undergo advanced imaging prior to PPM implantation. They were referred for further post-discharge imaging but were lost to follow-up, and hence were excluded from the final analysis.

Data regarding baseline characteristics including demographics, medical history, transthoracic 2-dimensional echocardiography, 12-lead electrocardiography (ECG), and chest X-ray, were all obtained during the index admission prior to permanent pacemaker (PPM) implantation and at the time point closest to presentation. All patients were assessed and managed by a senior cardiologist and a senior electrophysiologist. For the study purpose, ECGs and imaging data were retrospectively analyzed, and the results were adjudicated by an experienced electrophysiologist.

Advanced Cardiac Imaging and Cardiac Sarcoidosis Diagnosis

Following assessment and prior to PPM implantation, all patients underwent cardiac magnetic resonance imaging (CMRI), positron emission tomography-computed tomography (PET-CT), or both, for suspected cardiac sarcoidosis, based on the availability of these imaging modalities. If initial imaging was not suggestive of cardiac sarcoidosis or any other specific cardiomyopathy, patients were diagnosed with idiopathic high-grade atrioventricular block and subsequently underwent PPM implantation. However, if imaging results were suggestive (high-probability) of cardiac sarcoidosis, or were inconclusive (intermediate probability [eg, basal septal, insertion point, or right ventricular late-gadolinium enhancement]), patients were further referred for tissue biopsy (Figure 1).

In most of the patients with suggestive imaging findings, both CMRI and PET-CT were performed to evaluate for extra-cardiac sarcoidosis and to identify an accessible extra-cardiac target for tissue biopsy. If such extra-cardiac site was not identified with PET-CT, an endomyocardial biopsy was performed and processed following the accepted standard of care and in accordance with the consensus statement from the American Heart Association, American College of Cardiology, and European Society of Cardiology.[7]

Patients with suggestive imaging underwent an ICD implantation, while awaiting biopsy results in most cases. Patients with inconclusive imaging underwent PPM

implantation, prior to final biopsy results in half the cases. The final cardiac sarcoidosis diagnosis was established based on suggestive clinical and imaging findings, confirmed by a positive tissue biopsy. Cardiac sarcoidosis patients were subsequently followed in the Cardiology and Rheumatology outpatient clinics.

Statistical Analysis

Patient characteristics were summarized and compared according to the status of cardiac sarcoidosis diagnosis (cardiac sarcoidosis vs. idiopathic high-grade atrioventricular block). Categorical variables were presented as proportions, and continuous variables were presented as means and standard deviations (SDs) or medians and interquartile range (IQR) for continuous variables, depending on their distribution. In detail, the normality of the continuous variables was evaluated using the Kolmogorov-Smirnov test, QQ-plot visualization, and by examining the distribution and variation of residuals. Continuous variables with a normal distribution were represented as mean and SD values and were compared between the groups using the Student t-test. Continuous variables with non normal distribution were presented as the median and IQR and were compared with the Mann-Whitney U test to determine their significance. The chi-square or Fisher's exact test was employed to compare categorical variables between groups.

All P values are 2-tailed, and $P < .05$ was considered significant for all analyses. Statistical analysis was performed using R version 4.1.0 (R Foundation for Statistical Computing, Vienna, Austria) software.

RESULTS

Patient screening and subsequent work-up are summarized in Figure 1. Overall, we identified 32 patients who were hospitalized with high-grade atrioventricular block during the study period. Of these, 2 patients were not clinically stable during initial work-up and thus did not undergo advanced imaging prior to PPM implantation. They were referred for further post-discharge imaging but were lost to follow-up, and hence were excluded from the final analysis, which included 30 patients. Eleven patients (37%) had imaging suggestive of cardiac sarcoidosis (7 patients underwent both CMRI and PET-CT, 3 patients had MRI only, and 1 had PET-CT only). All 11 patients with imaging findings suggestive of cardiac sarcoidosis were referred for biopsy (7 patients had endomyocardial biopsy, and 4 patients had extra-cardiac biopsies) and an ICD implantation. In 10 of these patients, cardiac sarcoidosis diagnosis was confirmed based on biopsy results. In 1 patient, an ICD was implanted based on a highly suggestive PET-CT, however subsequent pathology from an endomyocardial biopsy returned negative for sarcoidosis. Hence, 10/30 (33%) of the cohort were ultimately diagnosed with cardiac sarcoidosis, and in 10/11 (91%) patients with suggestive imaging findings, cardiac sarcoidosis was subsequently confirmed pathologically.

Four patients (13% of the overall cohort) had inconclusive imaging findings (2 had both CMRI and PET-CT, and 2 had PET-CT only). All these patients were implanted with a standard PPM, and subsequent biopsies were negative for sarcoidosis in all. In the remaining 15 patients (50% of the overall cohort), CMRI and PET-CT findings were not suggestive of cardiac sarcoidosis and they were all implanted with a standard PPM.

Patient baseline characteristics are presented in Table 1. Overall, patients were relatively young with a median age of 56.5 years (IQR 53.00, 61.75 years). Compared with idiopathic high-grade atrioventricular block patients, cardiac sarcoidosis patients were all males (100% vs 60%, $P = .029$), and were more likely to have concomitant heart failure symptoms (50% vs 10%, $P = .047$). The prevalence of syncope at presentation was comparable between the groups, and none of the patients in our cohort presented with aborted sudden cardiac death. Cardiac sarcoidosis patients had slightly higher creatinine levels and lower white blood cell counts (Table 1), whereas no additional significant differences were noted between the groups with regard to comorbidities, presentation, laboratory work-up (including serum Ca^{2+} levels), or baseline medical therapy.

Electrocardiographic Analysis

Twelve-lead ECG was analyzed in all patients (Table 2). Of them, 17 (56.7%) had complete atrioventricular block and 13 (43.3%) had Mobitz II second-degree atrioventricular block. ECG parameters did not differ significantly between the two groups, including left or right bundle branch block prevalence. Tachyarrhythmias were not common (~7% of the overall cohort) and consisted of non-sustained ventricular tachycardia episodes. No patients presented with ventricular fibrillation in our cohort.

Echocardiographic Analysis

Detailed echocardiographic findings are summarized in Table 3. The mean left ventricular ejection fraction (LVEF) was 53.7 (±11.84%) with no significant differences between the study groups. Left ventricular end-systolic and end-diastolic dimensions were also similar between the groups. Interestingly, compared with idiopathic high-grade atrioventricular block patients, cardiac sarcoidosis patients had thicker inter-ventricular septum (12.2 ± 2.7 mm vs 9.45 ± 1.6 mm, $P = .002$) and higher prevalence of right ventricular dysfunction (33% vs 10%, $P = .047$).

Distinctive Clinical and Radiological Characteristics of Patients with Confirmed Cardiac Sarcoidosis

The characteristics of the 10 patients with confirmed cardiac sarcoidosis are summarized in Table 4. Five patients (50%) were diagnosed with concomitant extra-cardiac disease based on PET-CT, and 4 of these patients had a biopsy obtained from an extra-cardiac site (1 lung biopsy and 3

Table 1 Baseline Patient Characteristics According to Cardiac Sarcoidosis Diagnosis

	Overall (n = 30)	Idiopathic Atrioventricular Block (n = 20)	Cardiac Sarcoidosis (n = 10)	*P* Value
Demographics				
Age at diagnosis, median [IQR]	56.50 [53.00, 61.75]	56.00 [52.75, 58.75]	58.50 [54.50, 62.00]	.415
Male sex, n (%)	22 (73.3)	12 (60.0)	10 (100)	.029
Medical history				
Hypertension, n (%)	15 (50.0)	9 (45.0)	6 (60.0)	.699
Dyslipidemia, n (%)	12 (40.0)	8 (40.0)	4 (40.0)	>.99
Atrial fibrillation, n (%)	3 (10.0)	2 (10.0)	1 (10.0)	>.99
Diabetes mellitus, n (%)	6 (20.0)	5 (25.0)	1 (10.0)	.628
Chronic kidney disease, n (%)	3 (10.0)	2 (10.0)	1 (10.0)	1
Smoker, n (%)	6 (20.0)	5 (25.0)	1 (10.0)	.628
Chronic obstructive pulmonary disease, n (%)	1 (3.3)	0 (0.0)	1 (10.0)	.719
Peripheral vascular disease, n (%)	2 (6.7)	1 (5.0)	1 (10.0)	1
Clinical and laboratory characteristics				
Heart failure symptoms upon admission,* n (%)	7 (23.3)	2 (10.0)	5 (50.0)	.047
Syncope, n (%)	9 (30.0)	6 (30.0)	3 (30.0)	1
HgB, mg/dL, mean (SD)	13.73 (1.78)	13.65 (2.12)	13.88 (0.81)	.749
WBC, K/microL, mean (SD)	8.80 (2.78)	9.54 (3.02)	7.31 (1.44)	.036
Platelets, K/microL, mean (SD)	227.27 (64.02)	229.55 (51.35)	222.70 (87.20)	.788
Creatinine, mg/dL, mean (SD)	0.98 (0.28)	0.91 (0.28)	1.13 (0.23)	.046
Albumin, mg/dL, mean (SD)	3.97 (0.36)	4.03 (0.30)	3.86 (0.46)	.244
ALT, U/L, mean (SD)	36.97 (46.39)	41.40 (56.43)	28.10 (9.07)	.469
CRP, mg/L, mean (SD)	11.69 (17.25)	11.20 (18.25)	12.62 (16.06)	.838
Serum Ca^{2+} mg/dL, mean (SD)	9.44 (0.63)	9.54 (0.48)	9.25 (0.85)	.248
Baseline medications				
Beta blockers, n (%)	4 (13.3)	3 (15.0)	1 (10.0)	1
ACEI /ARB, n (%)	11 (36.7)	6 (30.0)	5 (50.0)	.503
Spironolactone, n (%)	4 (13.3)	3 (15.0)	1 (10.0)	1

ACEI = angiotensin-converting enzyme inhibitors; ALT = alanine transaminase; ARB = angiotensin receptor blocker; CRP = C-reactive protein; HgB = hemoglobin; IQR = interquartile range; WBC = white blood cells; n = number of patients.

*Symptoms such as exercise intolerance, dyspnea, orthopnea, paroxysmal nocturnal dyspnea, peripheral edema, weakness, and fatigue were regarded as heart failure symptoms.

lymph-node biopsies). In 6 of the 10 patients, an endomyocardial biopsy was required to confirm cardiac sarcoidosis.

Patient ages ranged from 41 to 65 years, and 5 of the 10 patients (50%) were above the age of 60. Interestingly, heart failure symptoms did not directly correlate with echo LVEF measurements, with several patients having normal LVEF despite heart failure symptoms, and others presented with reduced LVEF but without classic symptoms.

Late gadolinium enhancement was demonstrated on CMRI in all cases, with a predilection to the interventricular septum and the basal inferior segments of the left ventricular wall. All cardiac sarcoidosis patients were implanted with an ICD, in accordance with current guidelines,[2,8] and the common practice in our center. Two (20%) of the cardiac sarcoidosis patients presented with markedly reduced LVEF upon admission. Left ventricular ejection fraction

Table 2 Electrocardiographic Analysis

	Overall (n = 30)	Idiopathic atrioventricular block (n = 20)	Cardiac sarcoidosis (n = 10)	*P* Value
Complete atrioventricular block, n (%)	17 (56.7)	13 (65.0)	4 (40.0)	.362
Mobitz II 2^{nd}-degree atrioventricular block, n (%)	13 (43.3)	7 (35.0)	6 (60.0)	.155
Complete left bundle-branch block, n (%)	7 (24.1)	5 (26.3)	2 (20.0)	1
Complete right bundle-branch block, n (%)	12 (41.4)	8 (42.1)	4 (40.0)	1
QRS duration, msec, mean (SD)	122.86 (29.74)	121.05 (31.45)	126.30 (27.46)	.66
Left anterior hemiblock, n (%)	2 (6.9)	2 (10.5)	0 (0.0)	.77

SD = standard deviation; n = number of patients.

Table 3 Admission Echocardiographic Findings

	Overall (n = 30)	Idiopathic atrioventricular block (n = 20)	Cardiac sarcoidosis (n = 10)	*P* Value
LVEF %, mean (SD)	53.69 (11.84)	54.45 (10.74)	52.00 (14.57)	0.615
LVESD, mm, mean (SD)	33.45 (7.37)	32.95 (8.05)	34.56 (5.85)	0.597
LVEDD, mm, mean (SD)	48.90 (5.95)	48.40 (6.89)	50.00 (3.08)	0.513
Interventricular septum, mm, mean (SD)	10.31 (2.36)	9.45 (1.64)	12.22 (2.68)	0.002
Right-ventricular function				0.047
Normal, n (%)	24 (82.8)	18 (90.0)	6 (66.7)	
Mild dysfunction, n (%)	2 (6.9)	2 (10.0)	0 (0.0)	
Moderate dysfunction, n (%)	1 (3.4)	0 (0.0)	1 (11.1)	
Severe dysfunction, n (%)	2 (6.9)	0 (0.0)	2 (22.2)	
Left atrial diameter, mm, mean (SD)	36.81 (10.68)	35.88 (11.29)	39.21 (9.26)	0.495
Pulmonary pressure				0.297
Normal, n (%)	16 (69.6)	12 (66.7)	4 (80.0)	
Mild pulmonary hypertension, n (%)	5 (21.7)	5 (27.8)	0 (0.0)	
Moderate pulmonary hypertension, n (%)	2 (8.7)	1 (5.6)	1 (20.0)	
Severe pulmonary hypertension, n (%)	0(0.0)	0(0.0)	0(0.0)	

LVEF = left ventricular ejection fraction; LVEDD = left ventricular end-diastolic diameter; LVESD = left ventricular end-systolic diameter; SD = standard deviation; n = number of patients.

improved during hospitalization in one of them, and he was implanted with an ICD. The second patient was implanted with a cardiac resynchronization therapy defibrillator, owing to persistent left ventricular dysfunction.

After discharge there were 2 cases of all-cause mortality recorded, both in patients with cardiac sarcoidosis ($P = .1$, compared with idiopathic high-grade atrioventricular block).

DISCUSSION

In the current study we aimed to characterize a population of young to middle-aged patients presenting with otherwise unexplained high-grade atrioventricular block and assess the prevalence of cardiac sarcoidosis within this population. A third of our cohort (10/30 patients) were ultimately diagnosed with cardiac sarcoidosis. All had suggestive (high probability) CMRI and/or PET-CT findings, and positive pathology. Moreover, 10 out of 11 patients (91%) with suggestive imaging were ultimately confirmed to have cardiac sarcoidosis based on biopsy results. In 4 patients, imaging findings were inconclusive, and all these patients had negative biopsy results. Hence, the diagnostic yield of CMRI and PET-CT in our cohort was high, stressing the importance of incorporating advanced imaging strategies in the work-up of unexplained high-grade atrioventricular block in younger individuals. We specifically focused on patients with no apparent history of cardiac abnormalities, such as ischemic heart disease, prior cardiac surgery, or structural intervention. Additionally, we excluded individuals with congenital heart diseases that may predispose them to high-grade atrioventricular block.

Our collaborative interdisciplinary approach emphasizes the diagnostic difficulties encountered in patients with high-grade atrioventricular block. It also addresses the optimal timing for device implantation in relation to the probability of cardiac sarcoidosis based on CMR/PET-CT findings, all while ensuring an accurate diagnosis of the underlying cause for high-grade atrioventricular block. This aspect was effectively demonstrated in our study by the 91% accuracy of imaging in identifying patients with cardiac sarcoidosis, and by deferring this diagnosis in patients with inconclusive imaging findings, who underwent a standard PPM implantation, with subsequent biopsy results excluding cardiac sarcoidosis. This observation may suggest that cardiac sarcoidosis can safely be excluded in patients with inconclusive, intermediate-probability, imaging findings. Although the negative predictive value of advanced cardiac imaging is beyond the scope of our study, we can reasonably hypothesize that deferral of cardiac sarcoidosis is also safe in patients with negative, low-probability, imaging findings. This assumption is supported by previous reports indicating CMRI sensitivity of 75%-100% for diagnosing cardiac sarcoidosis.[9]

Cardiac sarcoidosis patient ages ranged from 41 to 65 years. Five of the ten cardiac sarcoidosis patients were above the age of 60, which may suggest not limiting additional diagnostic work-up for otherwise unexplained high-grade atrioventricular block to 60 years of age. Several previous reports found male predominance of cardiac involvement in sarcoidosis, including from patient cohorts with approximately even male to female distribution at baseline.[10] Nevertheless, female predominance was noted in other studies.[6] In our cohort, all cardiac sarcoidosis patients were males, compared with 60% males in the idiopathic atrioventricular block group. These findings further support that male sex may be a specific risk factor for cardiac sarcoidosis in some populations, which warrants further investigation.

Clinical heart failure was reported in up to 30% of cardiac sarcoidosis patients. However, asymptomatic left ventricular dysfunction may be more common. We found that cardiac sarcoidosis patients were significantly more likely to present with heart failure symptoms when compared with idiopathic high-grade atrioventricular block patients

Table 4 Distinctive Clinical and Radiological Characteristics of Patients with Confirmed Cardiac Sarcoidosis

Subject	Age	Sex	Presenting rhythm	Heart failure symptoms	Syncope	Admission LVEF (%)	CMRI LGE findings	Biopsy source	Extracardiac organ involvement on PET-CT	Device type
1	41	M	Mobitz II	Y	N	28%	Subendocardial - basal inferoseptal	EMB	N	ICD*
2	51	M	CAVB	Y	N	60%	Subepicardial -basal inferoseptal	lung	Y (lung, liver, spleen)	ICD
3	62	M	Mobitz II	N	Y	60%	Subepicardial -basal inferior	EMB	N	ICD
4	57	M	CAVB	Y	Y	55%	Subendocardial - anterior + inferior right ventricle + septal	lymph node	Y (lymph nodes)	ICD
5	54	M	Mobitz II	Y	N	60%	Inferobasal right ventricle	lymph node	Y (lymph nodes)	ICD
6	65	M	CAVB	N	N	30%	Subepicardial -inferoseptal	EMB	Y (liver, spleen, lymph nodes)	CRTD
7	60	M	Mobitz II	N	Y	45%	Midmyocardial inferoseptal	EMB	N	ICD
8	56	M	Mobitz II	Y	N	60%	Midmyocardial septobasal + subepicardial anteroseptal	EMB	N	ICD
9	63	M	Mobitz II	N	N	70%	Midmyocardial septum	lymph node	Y (lymph nodes)	ICD
10	61	M	CAVB	N	N	60%	Subendocardial - basal inferior	EMB	N	ICD

CAVB = complete atrioventricular block; CMRI = cardiac magnetic resonance imaging; CRTD = cardiac resynchronization therapy defibrillator; EMB = endomyocardial biopsy; ICD = implantable cardioverter defibrillator; LGE = late gadolinium enhancement; LVEF = left ventricular ejection fraction; M = male; N = no; Y = yes.

*LVEF improved during hospitalization in this patient, and he was subsequently implanted with an ICD.

(50% vs 10% of the patients, respectively). Interestingly, mean LVEF values did not differ significantly between the groups, and only 20% of cardiac sarcoidosis patients had markedly reduced LVEF at presentation. Hence, heart failure symptoms in cardiac sarcoidosis may have been multifactorial, stemming from right ventricular dysfunction (noted in 33% of cardiac sarcoidosis patients, compared with 10% of idiopathic atrioventricular block), and potential extra-cardiac sarcoidosis, which may manifest with a variety of non-specific symptoms.

The most commonly reported cardiac sarcoidosis electrocardiographic manifestations are right bundle branch block and the different forms of atrioventricular block, followed by ventricular arrhythmias.[11-15] Conduction abnormalities occur presumably due to infiltrative involvement of the inter-ventricular septum, and ventricular arrhythmias of re-entrant and non-re-entrant mechanisms may be secondary to granulomatous involvement and fibrosis.[5,16,17] Although malignant ventricular arrhythmia and sudden cardiac death were previously reported in the context of cardiac sarcoidosis, none of the patients in our cohort presented with these conditions. Syncope was equally prevalent in 30% of cardiac sarcoidosis and idiopathic atrioventricular block patients.

Interestingly, cardiac sarcoidosis patients had significantly thicker inter-ventricular septum per echocardiography. Indeed, a correlation between inter-ventricular septum thickness and cardiac sarcoidosis has been previously reported.[18,19] Cardiac sarcoidosis patients were more likely to present with right ventricular dysfunction, which was moderate or severe, compared with the only mild right ventricular dysfunction documented in idiopathic atrioventricular block patients. Because the definitive diagnosis was obtained only later during hospitalization and echocardiography results were obtained upon admission, it is reasonable to assume that measurements were unbiased.

The CMRI late gadolinium enhancement pattern in cardiac sarcoidosis is patchy, multi-segmental, not related to coronary artery territories, and predominantly involves the mid-myocardial and subepicardial layers. In line with previous reports, we found that the inter-ventricular septum and the basal left ventricular segments were most frequently involved based on CMRI.[20]

Altogether, our data suggest that among the young and middle-aged patients presenting with otherwise unexplained high-grade atrioventricular block, a significant proportion may be diagnosed with cardiac sarcoidosis. Cardiac magnetic resonance imaging, positron emission tomography-computed tomography, or both, are important for establishing the diagnosis and may be followed by tissue biopsy from an affected organ for further confirmation. Possibly, such work-up should not be restricted to patients aged 60 years or less, but further investigation is required to set the correct age threshold for underlying cause screening in patients presenting with atrioventricular block. Male gender, presentation with concomitant heart failure symptoms, inter-ventricular septum $\geq$ 12 mm, and $\geq$ moderate

right ventricular dysfunction per echocardiography, should all increase the clinical suspicion of cardiac sarcoidosis based on our findings, although requiring additional study in larger patient cohorts for further confirmation.

Importantly, the patients in our study were actively screened for possible cardiac sarcoidosis using advanced imaging, and cardiac sarcoidosis diagnosis was confirmed with biopsy. Cardiac sarcoidosis prevalence was 33% in our cohort, whereas 50% of cardiac sarcoidosis patients had concomitant extra-cardiac involvement. Cardiac magnetic resonance imaging and positron emission tomography-computed tomography were highly accurate in directing further work-up.

Our study is not without limitations. It is a retrospective, single tertiary-center study, and hence some bias in patient referral and selection could have been present. Our work included 30 young and middle-aged patients admitted with high-grade atrioventricular block, and hence the ability to generalize or extrapolate our findings may be limited and further larger-scale studies are required. Nevertheless, because high-grade atrioventricular block in the younger population is relatively rare, and cardiac sarcoidosis even more so, most of the previous reports assessing for cardiac sarcoidosis in the context of high-grade atrioventricular block similarly did not include large patient populations.[3,21,22]

In conclusion, cardiac sarcoidosis is an important cause of high-grade atrioventricular block in young and middle-aged patients, bearing significant clinical implications. cardiac sarcoidosis should be suspected and sought for in such patients, especially in males, presenting with concomitant heart failure symptoms, having thicker inter-ventricular septum, or presenting right ventricular dysfunction on echocardiography.

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