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Cardiac sarcoidosis and ventricular arrhythmias. A rare association of a rare disease. A retrospective cohort study from the National Inpatient Sample and current evidence for management

Short title: Cardiac sarcoidosis and ventricular arrhythmias. A rare association of a rare disease

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Abstract

Background: Sarcoidosis is an increasingly recognized multi-systemic condition. Cardiac sarcoidosis is associated with ventricular arrhythmias and higher mortality rates. Little epidemiological data is available regarding the disease and associated ventricular arrhythmias.

Methods: Data from the National Inpatient Sample (NIS) database 2012–2014, were reviewed. Discharges associated with sarcoidosis were identified as the target population using relevant ICD-9-CM codes. Primary outcome was a diagnosis of ventricular tachycardia (VT) in the sarcoidosis population. Secondary outcomes include rate of ventricular fibrillation (VF) and cardiac arrest. Subgroup analyses were performed to examine the association of VT with multiple potential confounding clinical variables.

Results: Of 18,013,878 health encounters, 46,289 (0.26%) subjects had a diagnosis of sarcoidosis. VT and VF were more prevalent among patients with sarcoidosis compared to those without a diagnosis of sarcoidosis (2.29% vs. 1.22%; $p < 0.001$ and 0.25% vs. 0.21%; $p < 0.001$, respectively). Sarcoidosis was also associated with a higher prevalence of cardiac arrest (0.72% vs. 0.6%; $p < 0.001$). In unadjusted analyses, all examined comorbidities were significantly more common in those with sarcoidosis, including diabetes mellitus (31.6% vs. 21.25%; $p < 0.001$), hypertension (65.2% vs. 51.74%; $p < 0.001$), chronic kidney disease (21.09% vs. 14.02%; $p < 0.001$), heart failure (24.87% vs. 15%; $p < 0.001$) and acute coronary syndrome (ACS) (4.32% vs. 3.35%; $p < 0.001$).

Conclusion: The present study showed that sarcoidosis was associated with increased rates of ventricular tachyarrhythmia, which can affect the overall disease morbidity and mortality.

Key words: cardiac sarcoidosis, ventricular tachycardia, ventricular fibrillation, cardiac death

Introduction

Sarcoidosis is a multi-system granulomatous disease of unclear etiology with variable presentation. The prevalence ranges from 10.9 per 100,000 for whites to 35.5 per 100,000 for blacks [1]. The pathological hallmark of the disease is non-caseating granulomas. Cardiac sarcoidosis (CS) is increasingly recognized and associated with higher morbidity and mortality rates. Studies show a wide range (3.7–54.9%) of cardiac involvement in patients with systemic sarcoidosis [2].

Conduction abnormalities and arrhythmias are the most common clinical manifestations of CS, followed by congestive heart failure (HF) and sudden death [3]. The prevalence of specific arrhythmias is as follows: 26–62% atrioventricular block, 0–15% supraventricular tachycardia, 2–42% ventricular tachycardia (VT), and 12–65% sudden cardiac death [4]. Given the very rare nature of CS, electrophysiologists rely on small observational studies. It is hypothesized herein, that CS could be a significant independent predictor for development of VT. The National Inpatient Sample (NIS) was analyzed to test this possibility.

Methods

Study design and data source

Data from the NIS database, part of the Healthcare Cost and Utilization Project (HCUP), an Agency for Healthcare Research and Quality (AHRQ) was used. This is the largest inpatient healthcare database available to the public in the United States of America. The study utilized data for the years from 2012 to 2014. The NIS includes a 20-percent stratified sample of all discharges from U.S. hospitals participating in the HCUP, approximately 7–8 million discharges per year, excluding rehabilitation and long-term acute care hospitals. It contains variables extracted from hospital discharge records, including demographic characteristics, principal diagnosis, secondary diagnoses or comorbidities, insurance, cost and the procedures performed. The database allows for calculating national estimates by providing a "weight" variable [5]. When the data expands to estimate nation-wide discharges, it provides estimates corresponding to about 38 million annual hospitalizations or 97% of discharges nationwide [6]. Estimates from the NIS have been validated against the Centers for Medicare and Medicaid Services registry [5, 7]. Each discharge record was treated as an individual database entry. The databases used International Classification of Diseases-9th Edition (ICD-9) codes to identify diagnoses and procedures.

Subjects and variables

The study population was derived from 18,013,878 hospital discharges available in the NIS. Patients with VT and sarcoidosis were identified using ICD-9 codes, 427.1 and 135,

respectively. Primary outcome was a diagnosis of VT in the sarcoidosis population. Secondary outcomes include rate of ventricular fibrillation (VF) and cardiac arrest. Analyses of clinical variables were performed to examine the association of VT with multiple confounding factors.

Confounding variables were identified using the ICD-9 diagnosis codes including both patient and hospital level variables, in addition to data year. Patient characteristics included age, gender, diabetes mellitus, HF, hypertension, ACS (during the same hospitalization) and chronic kidney disease.

Statistical analysis

Normally distributed continuous variables were expressed as means ± standard deviation and compared using the Student t-test. Continuous variables that were not normally distributed were expressed as medians with interquartile ranges and compared using Mann-Whitney test. Categorical variables were compared using the χ^2 test. In order to adjust for potential confounders, multivariable logistic regression was performed.

A median Charlson-Deyo Index (CDI) was calculated for both sarcoidosis and non-sarcoidosis groups. CDI is a validated measure of comorbidities for administrative data [8]. All analyses were performed using STATA 2015 TX: Stata Corp LP. Two-tailed p-value < 0.05 was considered statistically significant.

Results

18,013,878 health encounters were identified from the NIS that represent hospitalizations from 2012 to 2014. Of these, 46,289 (0.26%) subjects had a diagnosis of sarcoidosis, and the remaining 17,967,589 (99.7%) do not have sarcoidosis among their discharge diagnoses. Baseline characteristics of patients with and without sarcoidosis diagnosis are shown in Table 1.

In unadjusted analyses, patients with sarcoidosis were middle-aged (mean 58.2 ± 13.6 years) and predominantly female (64.2%). All examined comorbidities were significantly more common in those with sarcoidosis, including diabetes mellitus (31.6% vs. 21.25%; $p < 0.001$),

hypertension (65.2% vs. 51.74%; p < 0.001), chronic kidney disease (21.09% vs. 14.02%; p < 0.001), HF (24.87% vs. 15%; p < 0.001) and ACS (4.32% vs. 3.35%; p < 0.001).

The CDI was 2.3 in the sarcoidosis group vs. 1.7 in the control group. 2.29% (1,059) of patients in the sarcoidosis group had a diagnosis of VT vs. 1.22% (218,330) of the control group, p < 0.001 (Fig. 1).

The adjusted odds ratio (OR) of VT in the sarcoidosis group was 1.83 (95% CI 1.72–1.95; p < 0.001). Table 2 shows independent predictors of VT among CS patients in a multivariable analysis. HF (OR 5.24; 95% CI 5.19–5.29; p < 0.001) and ACS (OR 2.84; 95% CI 2.81–2.87; p < 0.001) were associated with higher OR for VT.

Ventricular fibrillation was also more common in the sarcoidosis group (0.25% vs. 0.21%; p < 0.001). The OR of VF in the sarcoidosis group after multivariable logistic regression analysis was 1.24 (95% CI 1.03–1.49; p < 0.019; Table 3). Rates of VF was higher with ACS (OR 10.45; 95% CI 10.22–10.68; p < 0.001) and HF (OR 3.58; 95% CI 3.50–3.67; p < 0.001).

Finally, sarcoidosis carries a higher prevalence of cardiac arrest (0.72% vs. 0.6%; p < 0.001). Cardiac arrest remained more prevalent in sarcoidosis patients (OR 1.21; 95% CI 1.08–1.35; p < 0.001) as well as ACS 4.91 (95% CI 4.84–4.98; p < 0.001) and HF (OR 2.14; 95% CI 2.11–2.17; p < 0.001) in multivariable logistic regression analysis as shown in Table 4.

Discussion

Cardiac involvement in sarcoidosis is associated with increased morbidity and mortality. Isolated CS is much more common than suspected; in a retrospective study, 66% of patients with CS had disease isolated to the heart [9]. To date, CS has been extremely difficult to diagnose due to non-specific clinical manifestations, and the limited sensitivity and specificity of various diagnostic modalities [10]. There is also a lack of consensus regarding the diagnostic criteria for CS. Ventricular arrhythmias (VT, multifocal or frequent PVCs) are one of the minor criteria of the Japanese Ministry of Health and Welfare Criteria for diagnosis of CS, while the HRS consensus statement did not include ventricular arrhythmias as a criteria for diagnosing CS [11].

The present study analyzed a large database and revealed an increased rate of VT in patients with sarcoidosis (2.29%) compared to patients without sarcoidosis (1.22%); $p < 0.001$. HF, hypertension, chronic kidney disease and diabetes mellitus were more common in the sarcoidosis group. Even after adjustment for possible biological confounders, the odds for having VT was still higher (1.82; 95% CI 1.72–1.95; $p < 0.001$) in sarcoidosis patients, which suggest that CS may be an independent risk factor for VT.

Other reports suggested VT is the most frequent arrhythmia noted in CS with a reported incidence of 23% [12]. ACS and HF are traditional risk factors for development of VT, a fact that was confirmed after multivariable logistic regression analyses that showed higher odds of VT in ACS and HF population (2.84; 95% CI 2.81–5.87; $p < 0.001$) and (5.24; 95% CI 5.19–5.29; $p < 0.001$), respectively.

Secondary outcomes of VF and cardiac arrest were both higher in the sarcoidosis group (0.25% vs. 0.21%; $p < 0.001$) and (0.72% vs. 0.6%; $p < 0.001$), respectively. Moreover, ACS and HF were associated with higher cardiac arrest rates (Table 4). This is consistent with a high mortality rate in CS seen by Roberts et al. [13], where sudden death was the most common manifestation of CS. The present analysis shows increased rates for VF in sarcoidosis patients (OR 1.24; 95% CI 1.03–1.49; $p < 0.019$; Table 3).

The causality between VT and sarcoidosis cannot be assessed in a retrospective database study such as this one. Postulated mechanisms include active inflammation [11], enhanced automaticity [12], and ventricular activation and recovery process, which explains the reentry mechanism that leads to VT, the most frequent arrhythmia noted in CS [14]. A multicenter registry of patents with CS who underwent an EP study showed that the mechanism of VT was reentry in virtually all patients [15].

Management of arrhythmias in CS is difficult, and effective control of VT is often not achievable with a single method therapy. Steroids remain central in the management of CS as it can ameliorate cardiac dysfunction [16]. However, recurrent VT may increase with steroid therapy as active granulomas are replaced by fibrosis, a substrate for reentrant arrhythmias [17]. Corticosteroids have been associated with ventricular aneurysm formation [13], so immunosuppressive therapies are recommended in cases of resistant arrhythmias or as a steroid-sparing strategy [18].

Amiodarone and sotalol are widely used to treat VT in patients with CS, although adverse reactions may limit their practicality [15]. Amiodarone use may be limited by the incidence of pulmonary complications which are often difficult to distinguish from pulmonary sarcoidosis. beta-blockers have been shown to increase the incidence of heart block in patients with CS, thus limiting the utility of sotalol [14].

Prophylactic implantable cardioverter-defibrillator (ICD) placement is recommended for patients with sarcoidosis who develop sustained VT or left ventricular systolic dysfunction with left ventricular ejection fraction ≤ 35% despite optimal medical therapy and immunosuppression. It may also be a reasonable treatment for patients with cardiac sarcoidosis, regardless of their left ventricular function, after syncope, near syncope, or inducible VT [11]. ICD placement will prevent VT progression but will not prevent recurrence. Therefore, concurrent treatment with anti-arrhythmic therapy is necessary in refractory VT [19]. Some experts recommend ICD placement in patients with sarcoidosis and non-sustained VT given the high rate of recurrent VT despite antiarrhythmic and corticosteroid treatment [10].

Radiofrequency ablation is very effective in decreasing or eliminating VT in patients with CS according to data from a multicenter registry that showed a 98% reduction in VT burden in the first 3 months after ablation [15]. Resistant ventricular tachyarrhythmia and severe intractable HF, especially in younger patients, are indications for cardiac transplantation in patient with CS [14].

Study power

According to available research, this is the largest epidemiological study to assess the role of sarcoidosis in VT. Primary analysis confirms an increased rate of VT in sarcoidosis, even after adjustment for possible biological confounders. The strength of these findings lies in the fact that HCUP is a well-validated database that has been previously utilized in similar research studies.

Limitation of the study

ICD-9 codes were used to identify patient comorbidities. However, prior studies have demonstrated that ICD-9 codes exhibit high (> 90%) sensitivity, specificity and positive predictive value for cardiovascular disorders such as HF, myocardial infarction and arrhythmias, when compared to full medical chart review [7]. Also, due to the nature of the NIS database analysis, functional outcomes and long-term data were not available. Moreover, specific information regarding medications, electrophysiological studies, or echocardiographic parameters were not available. Lastly, due to the observational nature of the study, and unmeasured confounding factors may have affected interpretation and causality cannot be demonstrated.

Conclusions

Sarcoidosis carries a risk of various cardiac complications. The present analysis shows that hospitalized patients with sarcoidosis have elevated risk of VT, VF, and cardiac arrest.

Conflict of interest: None declared

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Variables	Sarcoidosis (n= 46,289)	No sarcoidosis (n= 17,967,589)	P value
Age in years, means (SD)	58.2 (+/-13.6)	57.3 (+/-20.6)	< 0.001
Male, % (n)	35.8 (16,556)	40.9 (7,352,675)	< 0.001
Diabetes Mellitus, % (n)	31.60 (14,626)	21.25 (3,818,578)	< 0.001
Hypertension, % (n)	65.20 (30,179)	51.74 (9,297,154)	< 0.001
Chronic kidney disease % (n)	21.09 (9,763)	14.02 (2,519,784)	< 0.001
Acute coronary syndrome, % (n)	3.35 (1,551)	4.32 (777,054)	< 0.001
Heart failure, % (n)	24.87 (11,510)	15.01 (2,696,906)	< 0.001
Charlson-Deyo Index, mean (SD)	2.3 (+/- 2.07)	1.7 (+/- 2.15)	< 0.001
Ventricular tachycardia % (n)	2.29 (1,059)	1.22 (218,330)	< 0.001
Ventricular Fibrillation, % (n)	0.25 (118)	0.21 (38, 012)	< 0.001
Cardiac arrest, % (n)	0.72 (331)	0.60 (108,312)	< 0.001

Table 1: Baseline variables between the target group (Sarcoidosis patients) and the control group

Variables	Odds ratio	95% Confidence Interval	P value
Age	1.01	1.013-1.014	< 0.001
Female	0.44	0.43-0.44	< 0.001
Sarcoidosis	1.83	1.72-1.95	< 0.001
Acute coronary syndrome	2.84	2.81-2.87	< 0.001
Heart failure	5.24	5.19-5.29	< 0.001

Table 2: Independent predictors of Ventricular Tachycardia

Variables	Odds ratio	95% Confidence Interval	P value
Age	0.998	0.997-0.999	< 0.001
Female	0.44	0.43-0.45	< 0.001
Sarcoidosis	1.24	1.03-1.49	0.019
Acute coronary syndrome	10.45	10.22-10.68	< 0.001
Heart failure	3.58	3.50-3.67	< 0.001

Table 3: Independent predictors of Ventricular Fibrillation

Variables	Odds ratio	95% Confidence Interval	P value
Age	1.01	1.013-1.014	< 0.001
Female	0.65	0.65-0.67	< 0.001
Sarcoidosis	1.21	1.08-1.35	< 0.001
Acute coronary syndrome	4.91	4.84-4.98	< 0.001
Heart failure	2.14	2.11-2.17	< 0.001

Table 4: Independent predictors of Cardiac Arrest

Chart Title

< 0.001

< 0.001

< 0.001

- Sarcoidosis
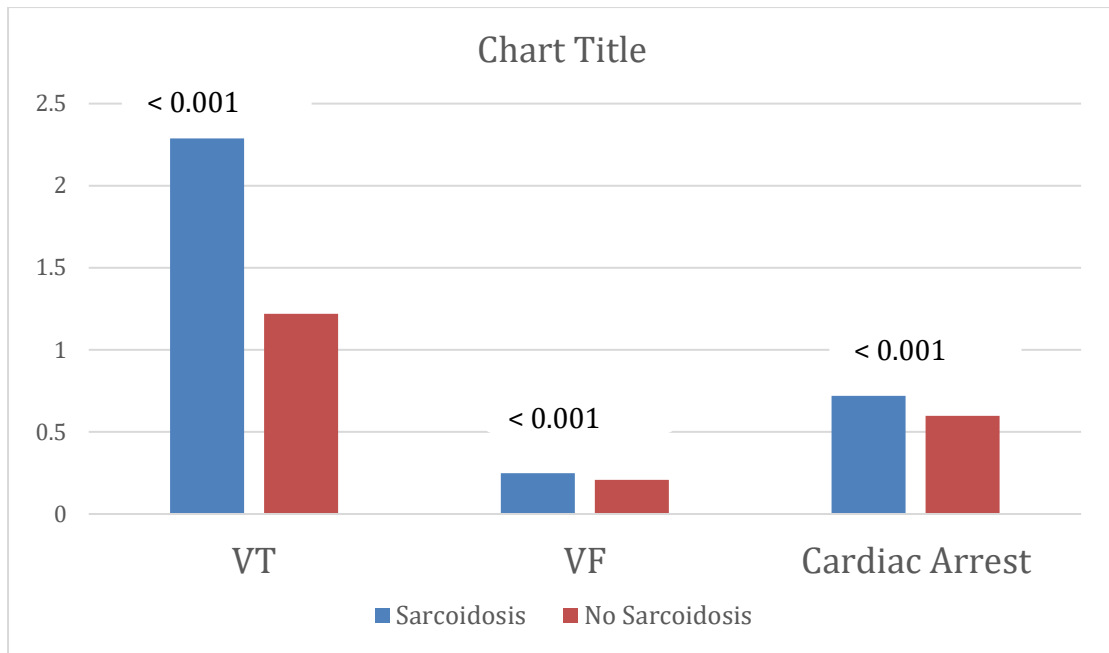- No Sarcoidosis

VT   VF   Cardiac Arrest

Figure 1 summarises the outcomes in patient with and without Sarcoidosis