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Increased risk of ventricular tachycardia in patients with sarcoidosis during the very long term follow-up

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ABSTRACT

Background: Sarcoidosis is an important diagnostic consideration in patients with ventricular tachycardia (VT) of unknown origin. The clinical course of VT as the primary presentation in patients with sarcoidosis is mostly unknown. This study aimed to investigate the incidence of life-threatening VT and mortality during long term follow-up in patients with sarcoidosis.

Methods: We analyzed the epidemiological features of sarcoidosis in Taiwan using the National Health Insurance Research Database from 2000 to 2004. Patients with sarcoidosis were identified, and healthy controls without prior histories of structural heart disease were matched with a 1:1 propensity-score to the sarcoidosis group. The risk of life-threatening VT and mortality with sarcoidosis was analyzed.

Results: A total of 2237 sarcoidosis cases were enrolled with a matching number of healthy controls, and the baseline characteristics between the two groups were similar. After a mean follow-up of 11.4 ± 2.15 years (IQR: 12, 11.3–12), the VT incidence in the sarcoidosis group was higher than in healthy controls (0.94% [85 per 100,000 person-year] in the sarcoidosis group, and 0.09% [8 per 100,000 person-year] in healthy controls). After a multivariate adjustment including the sex, age, and other comorbidities, the VT risk was still higher in the sarcoidosis group (hazard ratio: 12.7, 95% confidence interval: 2.82–56.9; $P < 0.001$). The risk of defibrillator implantations for secondary prevention, cardiovascular death, and total mortality between the groups was equivalent.

Conclusions: Sarcoidosis may increase the predisposition to ventricular arrhythmias with a cumulative incidence of 0.94% during a very long term follow-up of nearly 10 years from initially diagnosing sarcoidosis.

1. Introduction

Sarcoidosis is a multisystem chronic granulomatous disease of unknown etiology with noncaseating granulomas as its pathological hallmark [1]. The annual incidence of sarcoidosis in the United States is estimated at 10.9 per 100,000 in whites and 35.5 per 100,000 in African Americans [2]. In Europe, the Scandinavians have the highest incidence rates of 50 to 60 cases per 100,000 [3]. Most diseases (70%) occur in patients aged 25 to 45 years, however, in Europe and Japan, there is a bimodal distribution and a second peak occurs in women older than 50 years old [3,4]. Myocardial involvement of sarcoidosis was described as early as 1929 by Bernstein and Sidlick [4]. Cardiac sarcoidosis was reported to be involved in only 2% to 5% of patients with systemic sarcoidosis [5]. It is more common in Japan than in Europe or the United States, and involves as many as 85% of sarcoidosis-related deaths in Japan [6,7]. Although it was first described more than 80 years ago [8], its diagnosis, the assessment of its prognosis and planning its treatment remain a challenge for many clinicians due to its protean manifestation ranging from silent myocardial granulomas, that may lead to sudden cardiac death (SCD) [9,10], to symptomatic conduction disturbances, ventricular arrhythmias [11], and progressive heart failure [5,12]. Sarcoidosis is also an important diagnostic consideration in patients with ventricular tachycardia (VT) of unknown origin. The clinical course of patients with ventricular tachyarrhythmias as a primary presentation during the long-term follow-up in patients with sarcoidosis is mostly unknown.

The aim of this study was first to investigate the cardiovascular outcomes of patients with sarcoidosis who primarily presented with ventricular tachyarrhythmias during a very long-term follow-up. Secondly, this study assessed the outcomes of patients with sarcoidosis who had VT compared to those who did not have VT, and attempted to identify the independent predictors of life-threatening VT in these patients.

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2. Methods

2.1. Database

This study used the Taiwan National Health Insurance Research Database (NHIRD) to determine the risk of ventricular tachycardia (VT) and cardiovascular (CV) death in patients with sarcoidosis during long-term follow-up (from 2000 to 2011). The Taiwan Collaboration Centre of Health Information Application, Ministry of Health and Welfare, provided the entire datasets used in this study. The Taiwan's National Health Insurance (NHI) program enrolled 23 million people, which covered 99% of the country's population and contained data on utilization of all NHI resources, including outpatient visits, hospital care, prescribed medications, and the National Death Registry. The protocol was reviewed and approved by the Research Ethics Committee of National Taiwan University Hospital (NTUH-Rec Number: 201,305,044 W [Institutional Review Board reference, IRB]). Additionally, we obtained permission of the rights from the National Research Institute for the Department of Health, and the Health Promotion Administration, Ministry of Health and Welfare.

2.2. Study design and participants

This study was a population-based retrospective cohort study. From January 1, 2000 to December 31, 2004, a total of 2237 patients aged 18 years old and above, who were diagnosed with sarcoidosis were identified from the NHIRD according to the International Classification of Diseases, 9th Revision - Clinical Modification (ICD9-CM) codes (135). The diagnosis of sarcoidosis must be recorded twice in the outpatient records or at least once in the inpatient records. Life-threatening ventricular tachycardia was defined as sustained ventricular tachycardia with near-syncope/syncope and/or hemodynamic instability (systolic blood pressure < 80 mmHg) which may lead to ventricular fibrillation, asystole, and sudden death. These were identified from the NHIRD according to the ICD9-CM codes 427.4 to 427.5. On the same index date, the same number of healthy patients without prior structural heart disease with a matched age, gender, prevalence of a history of non-structural heart disease, hypertension (HTN), chronic obstructive pulmonary disease (COPD), and diabetes mellitus (DM) were selected to be the control group for each study patient. Patients who were diagnosed with coronary artery disease, ischemic heart disease, heart failure, valvular heart disease, congenital heart disease, cardiomyopathy, any type of ventricular arrhythmia, those who had previously received an implantable cardioverter defibrillator (ICD), and those with other systemic inflammatory diseases/connective tissue disease known to be associated with myocardial involvement prior to the enrollment date were excluded from the study. The co-morbidities of each individual were retrieved from the medical claims database based on the ICD-9-CM codes.

2.3. Study endpoints during follow-up

The follow-up period ended when the subjects either died during the course of follow-up or lived beyond 31 December 2011. The outcome measures studied were the time to the development of new-onset VT, cardiovascular death, all-cause mortality and implantable cardioverter defibrillator (ICD) implantations during the follow-up. Death was confirmed by referencing the Taiwan's National Death Registry.

2.4. Statistical methods

The normally distributed continuous variables were compared using a Student's t-test, whereas the non-normally distributed variables were compared using the Mann–Whitney U test. Frequencies were compared using a chi-square test. The incidence rates of cardiovascular events were calculated as the number of cases per 100,000 person-years of follow-up. This study also employed a 1:1 propensity-score matching technique to minimize the confounders. We matched pairs 1:1 under identical propensity scores with a 0.01 caliper for the age, sex, DM, HTN, hyperlipidemia, COPD, and thyroid disease.

The event-free survival curve was plotted using the Kaplan–Meier method with the statistical significance examined by the log-rank test. The Cox proportional-hazards regression was used to compare the hazard ratios (HR), with 95% confidence intervals (CIs) for the outcomes. A multivariate analysis was used to identify the independent predictors of new-onset VT and mortality during the long-term follow-up. Potential confounders were adjusted via two models. Model 1: age and sex; Model 2: Model 1 plus HTN, DM, COPD, CKD, hyperlipidemia, and thyroid disease. The level of statistical significance was set at a 2-tailed alpha level of <0.05. Analyses were performed with SAS version 9.3 software (SAS Institute, Cary, NC).

3. Results

3.1. Patient characteristics

A total of 2237 cases with sarcoidosis and the same number of healthy controls were enrolled in the study (N = 4474). The baseline characteristics between the two groups were comparable except for chronic kidney disease (CKD), which was more frequent in patients with sarcoidosis than in the control group (sarcoidosis group [1.20%] vs. control group [0.31%], p < 0.001; Table 1).

Table 1
Patient characteristics.

Variables	Without sarcoidosis (n = 2237)	With sarcoidosis (n = 2237)	*p*-value*
Age (years, mean ± SD)	46 ± 18	45 ± 18	0.12
Gender (male)	949 (42.42%)	953 (42.60%)	0.90
Underlying disease			
HTN	190 (8.49%)	162 (7.24%)	0.12
DM	118 (5.27%)	124 (5.54%)	0.69
COPD	110 (4.92%)	122 (5.45%)	0.42
Hyperlipidemia	20 (0.89%)	21 (0.94%)	0.88
Thyroid disease	8 (0.36%)	13 (0.58%)	0.12
CKD	7 (0.31%)	27 (1.20%)	<0.001

Values are stated as the n, %. A *p*-value < 0.05 was considered to indicate statistical significance.
HTN indicates hypertension; DM, diabetes mellitus; COPD, chronic obstructive pulmonary disease; CKD, chronic kidney disease.

3.2. Incidence of events

After a mean follow-up of 11.4 ± 2.15 years (IQR: 12, 11.3–12), the crude incidence of VT in the sarcoidosis group was higher than that in the control group (0.94% [85 per 100,000 person-year] in the sarcoidosis group, and 0.09% [8 per 100,000 person-year] in the control group) (see Table 2). The future risk of ICD implantations for secondary prevention, and cardiovascular death did not significantly differ between the two groups even after a multivariate adjustment including the sex, age, underlying disease such as hypertension, diabetes mellitus, and other comorbidities. The crude incidence of all-cause mortality was higher in patients with sarcoidosis, but did not significantly differ from the control group (14.48% [1295 per 100,000 person-year] vs 13.32% [1187 per 100,000 person-year]).

3.3. Cardiovascular outcome

The Kaplan–Meier estimates for new-onset VT, CV mortality, all-cause mortality, and defibrillator implantations between the patients with sarcoidosis and the control group are shown in Fig. 1A–D. In the patients with sarcoidosis, there is an increased risk for new-onset VT (cumulative incidence of 0.94% in the sarcoidosis group vs. 0.09% in the control group) with significantly decreased survival compared to the control group (log rank p < 0.001, Fig. 1A). The cumulative incidence of the over-all mortality did not significantly differ between those who had sarcoidosis and the control group (14.48% in patients with sarcoidosis vs 13.32% in control group, p = 0.26). Device implantation between the 2 groups was also similar with cumulative incidence of 0.13%. The event-free survival for the CV mortality (log rank p = 0.27), over-all mortality (log rank p = 0.27), and defibrillator implantations (log rank p = 0.99) between the 2 groups did not significantly differ. The mean time to the onset of VT and mean time to ICD implantation after the diagnosis of sarcoidosis were 5.58 ± 3.5 years and 9.11 ± 3.68 years, respectively.

In Table 3, after adjusting using a multivariate regression, the study showed a higher future risk for VT events in patients with sarcoidosis (adjusted hazard ratio [HR]: 12.7 (95% confidence interval [CI]: 2.82–56.9); p < 0.001). These patients also had a higher risk for mortality (adjusted HR: 1.19 (95% CI: 1.01–1.40); p = 0.03) compared to the control group. In patients with sarcoidosis who had VT also had a higher risk for CV mortality (Odds ratio (OR): 13.5 (95% CI: 4.33–42.0), p < 0.001) compared to those diagnosed with sarcoidosis who did not have VT events.

3.4. Predictors of the occurrence of ventricular arrhythmias

The characteristics of the patients with sarcoidosis with and without new-onset VT are shown in Table 4. The sarcoidosis patients with new-onset VT events were significantly older (62 ± 16 years of age for the patients with new-onset VT vs. 44 ± 18 years of age for patients without