Research Brief

Stroke in cardiac sarcoidosis: Need to worry?

Muthiah Subramanian a, Sachin Yalagudri a, Daljeet Saggu a, Jugal Kishore b, Muralidhar Reddy c, Calambur Narasimhan a, *

a Department of Electrophysiology, Asian Institute of Gastroenterology, Gachibowli, Hyderabad, India
b Department of Rheumatology, Care Hospitals, Banjara Hills, Hyderabad, India
c Department of Neurology, Care Hospitals, Banjara Hills, Hyderabad, India

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ABSTRACT

Objectives: The occurrence of stroke in patients with cardiac sarcoidosis (CS) is an under-recognized entity. The objective of this study is to evaluate the clinical presentation, risk factors, etiology, temporal relationship and management of stroke in patients with CS.

Methods: The data of 111 patients with CS from the Granulomatous Myocarditis Registry was analyzed. Clinical data regarding the clinical presentation, risk factors for vascular disease, electrocardiogram, echocardiogram and 18 Fluorodeoxyglucose (FDG) PET-CT were extracted from the registry database.

Results: Among the 111 patients with CS, 8 patients (7.2%) had a history of ischemic stroke. Six of the eight patients with ischemic stroke were young (<50 years) without conventional risk factors for vascular disease. In five patients, stroke occurred prior to the diagnosis of CS. In all except one patient the ischemic stroke occurred in the anterior cerebral circulation. LV dysfunction was noted in all patients at the time of stroke, with the presence of an LV apical clot in four of the eight patients. Atrial fibrillation was documented in 2 patients. Two patients received thrombolysis and mechanical thrombectomy, while the others were treated with standard antiplatelets and statins. There was a significant improvement in the LV Ejection fraction (33.6 ± 15.2 to 49.1 ± 13.8%, p = 0.043) following immunosuppression. Two patients developed refractory HF and respiratory sepsis, respectively, and succumbed following prolonged ICU admissions.

Conclusions: Ischemic stroke in patients with CS can be attributed to a cardioembolic phenomenon. A high index of clinical suspicion is needed for early diagnosis and management of these patients.

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1. Research brief

1.1. Introduction

Cardiac involvement in sarcoidosis occurs in 20–30% patients and is a leading cause of death in these patients. In contrast, ischemic neurological insults are exceedingly rare in patients with sarcoidosis despite the frequent granulation infiltration identified by post-mortem studies. In this report we describe our experience in the clinical recognition of ischemic stroke in eight patients with cardiac sarcoidosis (CS). We believe this association is an under-recognized entity and a high clinical suspicion can lead to more prompt diagnosis and treatment.

1.2. Case series

One hundred-and-eleven patients with cardiac sarcoidosis were enrolled in the Granulomatous Myocarditis Registry from January 2013 to December 2018. Of these patients, 8 (7.2%) had a history of stroke. The methods of diagnosis, data collection, and management of patients with cardiac sarcoidosis in this registry have been described by our group previously. In brief, the diagnosis of clinical CS was made with 18 Fluorodeoxy glucose positron emission tomography scan (18FDG-PET CT scan) and histological evidence of extra cardiac sarcoidosis. These criteria are in accordance with the recent guidelines for the diagnosis of extra cardiac CS.

Six of the eight patients presenting with ischemic stroke were young patients (less than 50 years) without conventional risk factors increasing their risk for vascular disease (Table 1). In five patients, the stroke occurred prior to the diagnosis of CS. In addition, in all except one patient the ischemic stroke occurred in the...
### Table 1
Characteristics of stroke in patients with cardiac sarcoidosis.

| Patient No. | Age | Sex | Stroke Syndrome | Imaging Findings | Temporal Relationship of Stroke to Diagnosis of CS (Prior/Later) (Months) | Conventional Risk Factors for Stroke | Management of Stroke | Outcome |
|-------------|-----|-----|-----------------|------------------|-------------------------------------------------------------------------|-------------------------------------|---------------------|---------|
| 1           | 49  | M   | Right lower limb monoparesis | Left ACA infarct | Later (<1 month) | x x x x x | Aspirin, Astatine | Completely recovered |
| 2           | 62  | M   | Left hemiparesis | Right parietal MCA infarct | Later (<1 month) | ✓ x x x x | Aspirin, Rosuvastatin | Died to refractory heart failure and respiratory sepsis |
| 3           | 40  | M   | Right hemiparesis | Left corona radiata infarct | Prior (13 months) | x x x x x | Thrombolysis with Alteplase | Died due to respiratory sepsis |
| 4           | 43  | M   | Right upper limb monoparesis | Left MCA infarct | Prior (14 months) | x x x x x | Aspirin, Atorvastatin | Completely recovered |
| 5           | 42  | M   | Right hemiparesis | Right medial temporal and basal ganglia infarct with ICA occlusion | Prior (<1 month) | x x x x x | Mechanical thrombectomy for stroke | Completely recovered |
| 6           | 45  | M   | Right sided facial palsy | Left high frontoparietal cortex infarct | Prior (19 months) | x x x x x | Aspirin, Rosuvastatin | Completely recovered |
| 7           | 33  | M   | Left hemiataxia (CS) | Left cerebellar infarct | Prior (3 months) | x x x x x | Aspirin, Atorvastatin | Completely recovered |
| 8           | 66  | F   | Left hemiparesis | Right MCA infarct | Later (<1 month) | ✓ x x x x | Aspirin, Rosuvastatin | Completely recovered |

MCA - Middle Cerebral Artery; ACA - Anterior Cerebral Artery; HTN - Systemic Hypertension; DM - Diabetes Mellitus; DLP - Dyslipidemia; PVD - Peripheral Vascular Disease.

### Table 2
Presentation and outcome of patients with stroke and cardiac sarcoidosis.

| Patient No. | Age | Sex | Initial Clinical Presentation of Cardiac Sarcoidosis | LV Function (at time of stroke) | LA volume (at the time of stroke) | Device Implantation | Documented Atrial Arrhythmia (Clinical + Silent) | Outcome of Cardiac Sarcoidosis |
|-------------|-----|-----|-----------------------------------------------------|--------------------------------|----------------------------------|---------------------|-----------------------------------------------|-----------------------------|
| 1           | 49  | M   | Recurrent Ventricular Tachycardia                    | Mild LV Dysfunction (EF 45%) with LV Apical Clot | 39 ml                            | ICD                 | No                                            | Rx with immunosuppressive therapy, underwent RFA for ventricular storm, doing well on follow up |
| 2           | 62  | M   | Heart Failure and Recurrent Ventricular Tachycardia  | Severe LV Dysfunction (EF 31%) | 75 ml                            | CRT-D              | Atrial Fibrillation on OAC (VKA)               | Died to refractory heart failure and respiratory sepsis |
| 3           | 40  | M   | Recurrent Ventricular Tachycardia                    | Severe LV Dysfunction (EF 29%) | 120 ml                           | ICD                 | No                                            | Died due to respiratory sepsis |
| 4           | 43  | M   | Heart Failure                                        | Severe LV Dysfunction (EF 26%) with LV Clot | 65 ml                            | None                | No                                            | Rx with immunosuppressive therapy, doing well on follow up |
| 5           | 42  | M   | Heart Failure                                        | Severe LV Dysfunction (EF 33%) | 115 ml                           | CRT-D              | Yes (Atrial Flutter/Fibrillation) on OAC (VKA) | Rx with immunosuppressive therapy, doing well on follow up |
| 6           | 45  | M   | Recurrent Ventricular Tachycardia                    | Mild LV Dysfunction (EF 45%) | 137 ml                           | ICD                 | No                                            | Rx with immunosuppressive therapy, doing well on follow up |
| 7           | 33  | M   | Heart Failure                                        | Severe LV Dysfunction (EF 32%) with LV Apical Clot | 99 ml                            | ICD                 | No                                            | Rx with immunosuppressive therapy, doing well on follow up |
| 8           | 66  | F   | Heart Failure                                        | Severe LV Dysfunction (EF 28%) with LV Apical Clot | 65 ml                            | None                | No                                            | Rx with immunosuppressive therapy, doing well on follow up |

LV - Left Ventricle; EF - Ejection Fraction; ICD - Implantable Cardioverter Defibrillator; CRT-D - Cardiac Resynchronization Therapy + Defibrillator; OAC - Oral Anticoagulation; VKA - Vitamin K Antagonist.
anterior cerebral circulation. None of the patients suffered from a hemorrhagic stroke. Other than one patient who presented with a complete internal carotid artery occlusion, imaging of the carotid arteries did not reveal evidence of atherosclerotic plaques or stenosis in the rest of the cohort. Half of the reported patients presented with incessant ventricular tachycardia and the others presented with congestive heart failure. LV Dysfunction was noted in all patients at the time of stroke, with the presence of an LV apical clot in four of the eight patients (Table 2). Atrial fibrillation was documented in 2 patients. Although there were no clinical or silent (documented atrial high rate episodes on device interrogation) atrial arrhythmias in the other 4 patients, echocardiography revealed increased LA volumes in 3 of them at the time of stroke.

With regards to management of the ischemic stroke, two patients received thrombolysis and mechanical thrombectomy, while the others were treated with standard antiplatelets and statins. All patients with CS were treated with immunosuppressive therapy according to institutional protocols. There was a significant improvement in the LV Ejection fraction (mean 33.6 ± 15.2 to 49.1 ± 13.8%, p = 0.043) and freedom from ventricular arrhythmias with therapy in the majority of patients, although two patients developed refractory HF and respiratory sepsis, respectively, and succumbed following prolonged ICU admissions. During a mean follow up of 22 ± 9 months, there was no recurrence of stroke in any of these patients.

2. Discussion

The mechanism of ischemic stroke in patients with CS may be attributed to a cardioembolic phenomenon. Underlying atrial arrhythmias have been reported in 13–32% of patients with CS. The cause appears to be a combination of granulomatous involvement of the atrium and raised end-diastolic pressures from sarcoid involvement of the lung and left ventricle. However, in our study only 2 patients (25%) had documented atrial fibrillation and 4 patients (50%) had a normal LA volume. A LV apical clot was present in 50% of our patients and may be an important etiology for cardioembolic stroke in CS. Although the etiology of LV thrombus formation may be attributed to sarcoid cardiomyopathy, the strong inflammatory bed of cytokines in sarcoidosis may also serve as a nidus in this “thrombo-inflammatory” cascade. Surgical removal of left ventricular thrombus in patients with CS and cardioembolic stroke is a potential treatment option.

There is increasing evidence that the inflammatory cytokines released by the sarcoid granuloma may also have an independent role in the propagation of ischemic stroke. More specifically, IFN gamma and IL-12, the most important cytokines in the initiation and maintenance of granulomatous inflammation in sarcoidosis, have also been shown to play a key role in the pathogenesis of brain infarction in cerebral ischemia. In addition, given the myriad of presentations of ischemic lesions in psychoneurosis it is difficult to rule out the possibility of large vessel inflammation or small vessel diverticulitis.

Our observations suggest that ischemic stroke in patients with cardiac sarcoidosis is more than a coincidence. It may be prudent to investigate all young patients with stroke and unexplained LV dysfunction for cardiac sarcoidosis. In addition, the role of anti-coagulation of high-risk CS patients who are in sinus rhythm needs to be investigated further. A high index of clinical suspicion is necessary for early diagnosis and optimal management of these patients.

Declaration of competing interest

All authors have none to declare

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