Global Spotlights

The cardiac sarcoidosis consortium: elucidating a mysterious disease through collaborative research

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Introduction

Cardiac sarcoidosis (CS) is an inflammatory disease of unknown aetiology that can lead to life-threatening arrhythmias, heart failure, and death. The hallmark pathophysiology involves the development of noncaseating granulomas in cardiac tissue disrupting normal electrical signalling and ultimately impairing cardiac pump function. Advanced cardiac imaging has improved the clinician’s ability to detect the disease, and there has been a significant rise in the number of patients diagnosed with this disorder in the last 20 years. Critical knowledge gaps remain in the domains of aetiology, genetic basis, and immunological mechanisms. There is also uncertainty as to the most appropriate diagnostic criteria, risk stratification, and treatments. The CS literature is mostly comprised of case reports and small retrospective studies; high-quality data from randomized controlled trials are lacking.

Creation of the cardiac sarcoidosis consortium and its goals

After collaborating on a multicentre analysis of safety and efficacy of implantable cardioverter defibrillator (ICD) in CS, the founding members [Dr Thomas Crawford and Dr Frank Bogun (University of Michigan), Dr William Sauer (then at the University of Colorado), and Dr Kenneth Ellenbogen and Dr Jordana Kron (Virginia Commonwealth University)] established an international, prospective registry, the Cardiac Sarcoidosis Consortium (CSC). The consortium identified five primary aims (Figure 1). The CSC has advocated for inclusion of CS sessions at major national and international meetings and proposed and championed the development of the first CS-specific guidelines, which resulted in the 2014 Heart Rhythm Society Expert Consensus Statement on the Diagnosis and Management of Arrhythmias Associated with Cardiac Sarcoidosis. Since the inception of the CSC, we have witnessed an increase in academic interest in CS at national meetings and in research publications.

Progress to date

Twenty-five centres across the world are actively enrolling patients in the registry (Figure 2). A total of 696 registry participants have at least the baseline entry. The registry allows enrolment of patients who have clinical and imaging appearance of CS, but who do not currently fit into any previously proposed criteria, often for want of a positive tissue biopsy. In the registry, 594 patients with CS meet at least one of the following diagnostic criteria: 1993 Japanese criteria, 2006 updated Japanese criteria, 2014 Heart Rhythm Society (HRS) criteria, and 2017 Japanese criteria. The mean age at diagnosis is 52 years and ~40% are females. The racial composition in the registry is 59% white, 31% black/African-American, 6% Asian, and 1% Hispanic.

Analyses from the CSC registry have already led to significant insights into CS diagnosis, treatments, and outcomes. Patients experienced an average delay of 22 ± 52 months from the time of symptom onset to definitive diagnosis underscoring the need for an elevated index of suspicion for this under-recognized disorder. Among CS patients treated with immunosuppressants, more than half are on a steroid-sparing agent, either in conjunction with steroids or as a stand-alone agent, most commonly methotrexate. Data from patients who had at least one 24 h Holter revealed high rates of arrhythmias, including nonsustained ventricular tachycardia (NSVT) in 34% and premature ventricular contraction burden ≥ 5% in 22%.

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Analysis of patients with sustained or nonsustained VT in the entire cohort, utilizing Holters, ambulatory monitors, implantable loop recorders, cardiac implantable electronic devices, and electrocardiograms showed that occurrence of VT or NSVT was associated with an almost three-fold higher risk of adverse events (death, left ventricular assistance device implantation, heart transplantation, and appropriate ICD shock or pacing), and ventricular fibrillation (VF) with almost four-fold increased risk of these outcomes. A study on ventricular tachycardia ablation in 158 patients showed catheter ablation was associated with reductions in defibrillator shocks and...
recurring VT storm, supporting the role of catheter ablation in conjunction with medical therapy in the management of ventricular arrhythmias in CS.5

The consortium presented an analysis of different published diagnostic schemes at the American College of Cardiology (ACC) 2022 Scientific Sessions. The 2014 HRS criteria were met by 82% of the subjects, while the 1993 and 2006 criteria identified about 53% of patients, and 2017 criteria only 19%.3 Meeting the 1993 criteria or the 2006 criteria was associated with adverse outcomes, but there was no difference between patients with and without an event in terms of meeting 2014 HRS or 2017 Japanese criteria. The meaning of this finding remains unclear, but it calls attention that these various criteria require further refinement. Also presented at ACC 2022 was the finding that traditional risk factors including hypertension, hyperlipidaemia, diabetes, chronic kidney disease, coronary artery disease, emphysema, and advanced heart failure are associated with poor outcomes in CS.6 The consortium also presented data at HRS 2022 showing that patients with CS who present with malaise, fatigue, VT/VF, and who had been treated with antiarrhythmic medication prior to CS diagnosis have an increased risk in adverse cardiovascular outcome.7

Healthcare disparities in sarcoidosis

Both the incidence and prevalence of sarcoidosis vary across the globe and are higher in patients of northern European and African-American descent.2 In the USA, sarcoidosis disproportionately affects women and African-American patients. In addition, minority patients have worse outcomes in the USA, including higher in-hospital mortality rates.8 Research approaches to understand CS should include identifying healthcare disparities in treatments and outcomes. The inclusion of patients from high-volume sarcoidosis centres in the USA, Europe, and Asia provides the opportunity to prospectively compare treatment strategies and adverse outcomes in patients with different racial backgrounds and from different geographic locations.

Looking forward

From the launch of the CSC, the founders envisioned creating a global network of CS researchers who would ultimately collaborate to design and execute prospective research. Two of the CSC centres (Virginia Commonwealth University and University of Michigan) have taken the first step towards the realization of this goal with the currently enrolling Multimodality Assessment of Granulomas in Cardiac Sarcoidosis—Anakinra Randomized Trial (MAGIC-ART; NCT04017936).3 This pilot randomized controlled trial is evaluating the feasibility and safety of interleukin-1 blockade with anakinra on top of standard of care compared with standard of care in patients with CS. Future studies should build on the existing network and resources of the CSC to explore new therapies for CS. Additionally, given the multidisciplinary nature of the evaluation and management of patients with CS, the consortium aims to broaden the scope of its expertise beyond heart rhythm specialists to include experts in heart failure and advanced cardiac imaging.

Conclusion

The CS is a mysterious and complex disease with poorly understood pathophysiology, aetiology, and genetics. Its variable presentation and patchy tissue infiltration pose diagnostic challenges, and the correct diagnosis requires vigilance and a high index of suspicion. Over the last several years, the CSC has made notable progress in the improvement of the clinical knowledge base. Much more study is needed to expand our understanding of the disease and to provide evidence-based treatments.

Conflict of interest: None declared.

References