Sarcoidosis is a granulomatous disease of unknown pathogenesis that can affect virtually any organ system. Cardiac involvement results in significant morbidity and mortality, with some studies reporting that cardiac involvement accounts for up to 25% of all deaths from sarcoidosis in the United States and more than half of all deaths in Japan.1–3 Many deaths seem to be arrhythmogenic in nature and are potentially preventable. For example, recent studies4–6 in patients with cardiac sarcoidosis (CS) and an implantable cardioverter-defibrillator show high rates of appropriate implantable cardioverter-defibrillator discharges (≈10%–15% per year for primary prevention patients), which are more than double that reported in large randomized trials of heart failure patients.4

The event rates among LGE-positive patients as compared with LGE-negative patients. Cardiovascular mortality occurred in 10 LGE-positive versus 2 LGE-negative patients. A combined end point of death or ventricular arrhythmias, defined as appropriate implantable cardioverter-defibrillator therapy, ventricular fibrillation, or sustained ventricular tachycardia >30 seconds, occurred in 64 LGE-positive and 18 LGE-negative patients. The event rates among LGE-positive patients as compared with LGE-negative patients were consistently higher and statistically
significant for all outcomes. The relative risk was 3.4 ($P=0.04$), 10.7 ($P=0.03$), and 6.2 ($P<0.001$) for all-cause mortality, cardiovascular mortality, and the combined end point, respectively.

Strengths of the study by Hulten et al$^{13}$ include the multiple end points that were tested and the consistency of findings for these end points. There was no evidence of heterogeneity or small study effects for any of the outcomes. The author’s conclusion that “LGE is associated with future cardiovascular death and ventricular arrhythmia among patients referred to MRI for known or suspected cardiac sarcoidosis” appears sound. Nonetheless, the number of fatalities is few, and the magnitude of the effect is uncertain. For example, there were only 12 cardiovascular deaths, and the 95% confidence interval for relative risk was broad, ranging from 1.3 to 86.3.

Given the results of the study, is a change in clinical practice warranted? The HRS guidelines already indicate that an evaluation by CMR is appropriate (class 2a) in patients with extracardiac sarcoidosis who have signs or symptoms of cardiac involvement.$^{11}$ Still, the findings of the meta-analysis strengthen the body of evidence linking the presence of LGE with adverse outcomes and helps to support the HRS recommendation. Additionally, the meta-analysis highlights the potential role of CMR in influencing patient management. The data show that the absence of LGE was associated with low event rates. The annualized incidence of either death or ventricular arrhythmias was 0.6% in LGE-negative patients compared with 8.8% in LGE-positive patients. Given this reassuring event-free survival, the authors conclude that when LGE is absent, it has sufficiently high negative predictive value that no further testing is needed for the majority of patients. A caveat, of course, is that the warranty period of a normal scan in this patient population is unknown.

The HRS guidelines state that CMR is not recommended (class 3 indication) for patients without abnormalities on initial screening by symptoms (defined specifically as unexplained syncope, presyncope, or significant palpitations lasting >2 weeks), ECG, or echocardiography.$^{11}$ It is possible these criteria are too rigid. There are data to suggest that all 3 criteria are insensitive in detecting CS. Patel et al$^{17}$ recruited patients out of pulmonary, rheumatology, and general medicine clinics. Patients were not referred clinically for CMR. LGE was positive in 26% of patients, indicating cardiac involvement; however, the majority of these patients were asymptomatic and did not have any conventional signs of cardiac involvement after a thorough clinical evaluation. Murtagh et al$^{18}$ studied a cohort restricted to those with preserved left ventricular ejection fraction of >50% and found that 20% of their population was LGE positive. Although data regarding symptoms and signs are not reported, the authors state “a significant portion of the patients underwent the CMR examination as part of widespread screening, despite the absence of symptoms or ECG abnormalities.” Nagai et al$^{14}$ specifically investigated a cohort without signs or symptoms of cardiac involvement. The prevalence of LGE was 13% in their study.

These 3 studies were included in the meta-analysis by Hulten et al and reflect the heterogeneity in patient populations and different inclusion criteria used by the individual studies. Strictly speaking, it seems the meta-analysis was not limited to patients with known or suspected CS. Although the meta-analysis could not adjust for various patient factors, such as symptoms and ECG abnormalities, these data raise the possibility that CMR could potentially be used more broadly as a screening test in asymptomatic patients with the diagnosis of extracardiac sarcoidosis.

But if CMR’s ability to improve the diagnosis of CS is an important advance, it raises the natural question, what should a clinician do with a positive scan? Although the absence of LGE is reassuring, the magnitude of the effect of a positive scan is less clear, given the wide 95% confidence intervals for relative risks as stated earlier. Certainly, not all patients with LGE develop adverse outcomes, and there are no data to support the routine implantation of implantable cardioverter-defibrillators in this group.

A positive CMR scan needs to be evaluated in context of the clinical scenario. Although CS is considered a serious condition, there are several factors that likely modify the risk entailed by the diagnosis. For example, there seems to be significant differences in mortality depending on ethnicity. Yazaki et al$^{19}$ reported an overall survival of 60% at 5 years in Japanese patients. Although not directly comparable, Kandolin et al$^{12}$ observed a substantially better prognosis in Finnish patients and reported a transplantation-free cardiac survival of 90% at 5 years. Murtagh et al$^{18}$ enrolled patients at the University of Chicago of whom 59% were black. It is notable that within the LGE-positive group, all patients who experienced death or ventricular tachycardia were black.

Left ventricular ejection fraction is also known to modify the risk profile in patients with CS.$^{4,12}$ Yet other studies indicate that the extent of LGE is a better predictor of outcome than just simply the presence of LGE.$^{18,20}$ Unfortunately, these and many other covariates could not be assessed on a per patient basis in the meta-analysis.

Hulten et al have made an important contribution that extends our knowledge of this enigmatic disease. Their data clearly show that CMR can be used to stratify sarcoid patients with potential cardiac involvement into low- and high-risk categories and, by corollary, influence patient management. Moving forward, it will be important for future studies to precisely assess the adverse risk associated with a positive LGE CMR scan and the effect of other covariates that could modify risk. Also useful will be additional data in patients with isolated CS because the literature provides little guidance in its diagnosis. In the meta-analysis, <2% of patients did not already have a known diagnosis of extracardiac sarcoidosis. Finally, of particular value will be prospective studies in patients with sarcoidosis that evaluate the efficacy of patient management strategies guided by CMR that aim to improve patient outcomes.

Disclosures

None.

References


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Prognostic Value of Myocardial Damage in Patients With Sarcoidosis: Is Cardiac Magnetic Resonance What We Need?
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