Cardiac Sarcoidosis: Epidemiology, Characteristics and Outcome over

25 Years in a Nationwide Study

Running title: Kandolin et al.: Cardiac Sarcoidosis

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Abstract

Background—This study was designed to assess the epidemiology, characteristics and outcome of cardiac sarcoidosis (CS) in Finland.

Methods and Results—We identified in retrospect all adult (>18 yr) patients diagnosed with histologically confirmed CS in Finland between 1988 and 2012. Totally 110 patients (71 women) aged 51 ± 9 yr (mean ± SD) were found and followed for outcome events to the end of 2013. The annual detection rate of CS increased more than 20-fold during the 25-year period reaching 0.31/10^5 adults between 2008 and 2012. The 2012 prevalence of CS was 2.2/10^5. Nearly two thirds of patients had clinically isolated CS. Altogether 102 of the 110 patients received immunosuppressive therapy and 56, an intracardiac defibrillator. Left ventricular (LV) function was impaired (ejection fraction < 50 %) in 65 patients (59 %) at diagnosis and showed no overall change over 12 months of steroid therapy. During follow-up (median, 6.6 years), 10 patients died of a cardiac cause, 11 underwent transplantation and another 11 patients suffered an aborted sudden cardiac death. The Kaplan-Meier estimates for 1-, 5- and 10-year transplant-free cardiac survival were 97 %, 90 % and 83 %, respectively. Heart failure at presentation predicted poor outcome (log rank p=0.0001) with a 10-year transplant-free cardiac survival of only 53 %.

Conclusions—The detection rate of CS has increased markedly in Finland over the last 25 years. With current therapy, the prognosis of CS appears better than generally considered but patients presenting with heart failure still have poor long-term outcome.

Key words: cardiac sarcoidosis, epidemiology, treatment, prognosis, myocardial cardiomyopathy disease
Described first more than 80 years ago, cardiac sarcoidosis (CS) continues to puzzle clinicians for many reasons, not least for it’s representing a disease the cause(s) and innermost nature of which remain unknown. Further, its manifestations are protean with a range from silent myocardial granulomas, that yet may lead to sudden death, to symptomatic conduction disturbances, ventricular arrhythmias and progressive heart failure. CS is reported to involve only 2 to 5% of patients with systemic sarcoidosis, but both autopsy studies and modern cardiac imaging suggest that clinically manifest cases may represent just the top of an iceberg in CS. There is also much evidence indicating that sarcoidosis can be clinically confined to the heart, which may delay its detection.

Assessing prognosis and planning treatment in CS are no less of a challenge. CS is considered a serious condition with 60% to 75% 5-year survival most often quoted in the literature. The available outcome data are much more heterogeneous, though, the reported prognosis varying from 73% 1-year mortality to 100% 10-year survival in the absence of left ventricular (LV) dysfunction. The problem here is that, due to the rarity of CS, the prognostic data are derived from small and selected CS populations with varying number of cases detected only at autopsy or posttransplantation. Lack of high-quality research complicates the planning of treatment, too. Although steroid therapy is considered mandatory, its efficacy has never been proven beyond limited and uncontrolled observations. For these reasons it is not surprising that experts in this field disagree on several aspects of diagnosis and treatment of CS.

With the uncertainties about CS in mind we decided to collect data on all cases of histologically confirmed CS seen in Finland over the last 25 years. Our work focused on the epidemiology, characteristics and long-term outcome of CS. Here we report data that
demonstrate a continuing increase in the detection rate of clinically manifest CS and show that its overall prognosis may be somewhat better than generally considered. Presentation with heart failure seemed to predict poor long-term outcome, however. LV function was commonly impaired and showed little overall change with steroid therapy.

Methods

Study Outline

The Myocardial Inflammatory Diseases in Finland (MIDFIN) study group is a cardiology research network of the 5 Finnish university hospitals that focuses on CS and giant-cell myocarditis. For the present work, cases of CS from the year 1988 onwards were identified from the discharge, pathology and device registries of our network’s member institutions and also from 17 central hospitals covering the whole Finland. Possible patients were first screened using the ICD-10 code I41.8*D86.8 (sarcoidosis of heart) and the code D86 (sarcoidosis) combined with one of the codes I42 (cardiomyopathy), I44.1-2 (second or third degree atroventricular block), I45.3 (trifascicular block), I46 (cardiac arrest), I47.2 (ventricular tachycardia), I49.0 (ventricular fibrillation), I49.3 (premature depolarization), I50 (heart failure) or R00.1 (bradycardia). Thereafter one investigator (RK) visited each site having potential adult (>18 years) CS patients and scrutinized the pertinent hospital charts for data on patients’ demographics, symptoms, initial and later clinical manifestations, results of diagnostic imaging and laboratory studies, invasive procedures and details of treatment with drugs and devices. The investigator also studied the records of follow-up visits for results of serial echocardiographic studies, with particular focus on LV ejection fraction (EF), as well as for changes in treatment and occurrence of adverse cardiac events and side effects of treatment. The work started in 2008
and thus the collection of data was fully retrospective for the years 1988 - 2008 but partly prospective thereafter. The last patients were included in February 2012 and adverse events were recorded up to the end of December 2013. The mortality data were double-checked from the official Finnish Population Register in January 2014. The causes of death were determined by hospital chart review. The study had the approval of the national ethical review board (STM/1219/2009). A subpopulation of this nationwide study, the patients seen at Helsinki University Central Hospital between 2000 and 2010, has been reported earlier.17

**Inclusion Criteria**

As in our previous works,17,26 the criteria for the diagnosis of CS, and for inclusion in the present study, were either sarcoidosis histology in an endomyocardial biopsy (EMB) or extracardiac histologic verification of sarcoidosis associated with both clinical manifestations indicative of a myocardial disease and abnormalities compatible with CS in either gadolinium enhanced cardiac magnetic resonance imaging (Gd-MRI), 18-F-fluorodeoxyglucose positron emission tomography (18F-FDG PET) or echocardiography.7,27,28 As earlier,17,26 the histologic diagnosis of sarcoidosis required the presence of non-necrotizing epithelioid cell granulomas with isolated giant cells and absence of both myocardial necrosis and more than solitary eosinophils.

**Statistical Analysis**

Differences between patient groups were assessed using Mann–Whitney U test, Student’s t test and the chi-square test or Fisher’s exact test, as appropriate. Changes in LVEF over the first year of steroid therapy were analyzed with Student’s paired t-test. Survival curves were plotted by the Kaplan–Meier method, and factors influencing survival were analyzed by the log-rank test and by Cox regression analysis. Survival was calculated from the time of first CS manifestation that
was considered to be the date of first contact with health care professionals due to symptoms compatible with CS. The following events were taken as outcome end points in these analyses: 1) cardiac death, 2) a composite of cardiac death and transplantation, whichever came first, and 3) a composite of cardiac death, transplantation and aborted sudden cardiac death. The analyses were made both in the total population and after excluding cases diagnosed only at transplantation or autopsy. In all tests, a 2-tailed P<0.05 was considered statistically significant. The analyses were performed using SPSS version 21 for Windows (SPSS Inc; Chicago, IL).

Results

Detection Rate and Prevalence of CS

A total of 110 patients aged 27 to 69 years fulfilled the criteria of CS and were included in the present work. Additionally 34 patients with a clinical diagnosis of CS were identified at screening (see Methods) but were ultimately excluded due either to lack of histologic proof of sarcoidosis (n=21) or to missing confirmative cardiac imaging (n=13). Ninety-seven of the 110 patients came from the 5 university hospitals. There was a remarkable increase over time in the number of new CS diagnoses (Figure 1). The annual detection rate of CS was 0.31/10^5 adults (>18 years) between years 2008 and 2012. The prevalence of CS in 2012 was 2.2/10^5.

The Paths to CS Diagnosis

There were variations both across hospitals and over time in the methods used to diagnose CS. All 110 patients had undergone echocardiography and 66 and 59 patients had undergone ^18^F-FDG PET and cardiac Gd-MRI, respectively. Coronary angiography or coronary computed tomography had been done in 71 patients, of whom 3 individuals were found to have angiographically significant coronary artery disease in association with CS. These individuals
were retained in our analyses. Most patients (92/110) had undergone one or several (up to 3) EMB sessions of the right or left ventricle, or of both ventricles. Ultimately, EMB confirmed the CS diagnosis in 55 patients. In the remaining 55 patients, sarcoid histology was obtained from PET-positive mediastinal lymph nodes in 18 cases and from biopsies of lung (n=11), peripheral lymph nodes (n=8), skin (n=5), liver (n=3) and central nervous system (n=2) in the remaining 29 cases. Lastly, 6 cases were diagnosed from native hearts removed at transplantation and 2 cases only at autopsy. Of the 47 patients with extracardiac confirmation of sarcoid histology, 38 had typical abnormalities in cardiac 18F-FDG PET and/or Gd-MRI. The remaining 9 patients had either global LV dysfunction (EF < 50 %), local thinning or thickening of the basal interventricular septum or an LV aneurysm at echocardiography.

Patient Characteristics, Modes of Presentation and Findings at Initial Imaging and Laboratory Studies

At presentation, 71 of the 110 patients (65 %) had clinically isolated CS defined here as cardiac involvement with neither past history nor any current signs or symptoms of extracardiac sarcoidosis by initial clinical examination, routine blood tests and plain chest x-rays. In the remaining 39 patients (35 %), CS was associated with known or clinically manifest extracardiac sarcoidosis at presentation. Seven of the 8 cases identified from cardiac explants or at autopsy were in the subgroup of clinically isolated CS. Table 1 summarizes the patients’ demographics, presenting manifestations and key findings at the initial imaging and laboratory studies for the whole population and separately for the above subgroups. The median time from the first cardiac manifestation to diagnosis was 9.0 months (range, 0.3-168 months) in the 102 patients diagnosed prior to transplantation or autopsy. In patients diagnosed after transplantation or at autopsy, the median delay from first manifestation was 41.5 months (range, 5-85 months).
Treatment with Drugs and Devices

Totally 102 of the 110 patients (i.e. all apart from the ones detected at autopsy or transplantation) underwent disease-modifying immunosuppressive therapy. All received steroids with the initial prednisone-equivalent doses varying from 30 to 80 mg per day, being <60 mg and ≥60mg in 42 and 60 patients, respectively. Although the dosing schedule was not uniform, the prednisone-equivalent dose was usually tapered to 10 mg/day within 6 months of treatment. In 48 of the 102 patients steroids were used uninterrupted until the end of follow-up or death or transplantation. The remaining 54 patients were given steroids intermittently due to fluctuation of disease activity or steroid side effects. In 4 patients corticosteroids were discontinued permanently due to intolerable adverse effects (severe myopathy, psychosis, aseptic joint necrosis, severe insomnia with hypokalemia and diarrhea). Of other immunosuppressants, azathioprine was used in 50 patients, methotrexate in 6 patients, mycophenolate mofetil in 3 patients, cyclosporine in 2 patients and infliximab in 1 patient. Symptomatic drugs included beta-blockers in 104 patients, angiotensin converting enzyme inhibitors or angiotensin receptor blockers in 89 patients, diuretics in 48 patients and amiodarone in 25 patients. An intracardiac cardioverter defibrillator (ICD) was implanted in 59 patients (54%) and another 28 patients (25 %) received a permanent pacemaker for atrioventricular conduction block.

Outcome

Follow-up time from the first clinical manifestation of CS varied from 12 to 303 months (median, 79 months). A total of 10 patients died of a cardiac cause and 6 patients suffered a non-cardiac death (1 breast cancer, 1 colon cancer, 1 mesothelioma, 1 stroke, 1 Lewy body dementia and 1 gastrointestinal perforation). Eleven patients underwent cardiac transplantation and 2 additional patients were awaiting transplantation at the close of our study in December 2013.
Two of the 11 transplanted patients died within 30 days of surgery and another 2 patients died of allograft failure, without signs of recurrent CS in the graft, 3 and 5 years posttransplantation. Thus, altogether 20 of the 110 patients had died and 7 patients were alive with a transplanted heart after a median follow-up of 6.6 years. Of the 102 biopsy-diagnosed patients, 19 died or underwent transplantation during follow-up.

Of the 10 cardiac deaths as first outcome event, 9 were sudden (2 in cases diagnosed at autopsy) and 1 due to terminal heart failure. Another 11 patients experienced an aborted sudden death as the first event, i.e. they were either successfully resuscitated from VF (n=8) or VF was terminated by an ICD shock (n=3). Furthermore, an appropriate ICD treatment for sustained VT was recorded in 15 additional patients during follow-up, but these events were not included in the outcome analyses of the present work. The Kaplan-Meier curves for cardiac survival, cardiac survival free of transplantation, and cardiac survival free of transplantation and aborted sudden death are shown for the total CS population in Figure 2A and for patients who were identified clinically and underwent immunosuppressive treatment in Figure 2B. The Kaplan-Meier estimates of 1-, 5- and 10-year survival are given in Table 2.

Predictors of Outcome

Cardiac survival free of transplantation

In the total population of 110 patients having 21 events, transplant-free cardiac survival was independent of age (p=0.469, Cox regression), sex (log rank p=0.163) and the type of CS (log rank p=0.132) but was strongly related to heart failure as the first clinical manifestation of CS (log rank p=0.0001, Figure 3A). In patients presenting with heart failure, the 1-, 5- and 10-year Kaplan-Meier survival probabilities were 90 % (95 % CI, 66.9-98.2 %), 75 % (95% CI, 50.6-90.4 %) and 52.5 % (95% CI, 29.9-74.2 %), respectively. Transplant-free cardiac survival was
also related to initial LVEF (p=0.006 by Cox regression and p=0.011 by log-rank, Figure 3B) and to NYHA class (log rank p=0.023, Figure 3C).

Analyzed in the clinically diagnosed 102 patients with 13 outcome events, transplant-free cardiac survival was related only to heart failure as the mode of CS presentation (log rank p=0.025, Figure 4).

Cardiac survival free of transplantation and aborted sudden death

There were altogether 32 events in 110 patients. Event-free survival was independent of age and sex as well as of heart failure as the first CS manifestation (log rank p=0.093) but was related to the CS type (log rank p=0.005, Figure 5A) and to LVEF (p=0.017 by Cox regression and p=0.046 by log rank, Figure 5B).

In the clinically diagnosed 102 patients having 24 events, CS type was the only predictor of event-free cardiac survival (log rank p=0.015, Figure 6).

Changes in LV Function and Atrioventricular Conduction during Steroid Therapy

In the 102 patients receiving immunosuppression, LVEF averaged 44.9 ± 12 % at diagnosis and 45.4 ± 11 % after on average 12 months of steroid therapy (p=0.532). Table 3 shows the data on LVEF before and after treatment by subgroups of LV function. The data suggest that patients with severe LV impairment at diagnosis (EF <35%) had an improvement in LV function with steroid therapy. Altogether 74 of the 110 patients (67 %) either had LV dysfunction (EF <50 %) at diagnosis (n=65) or developed it later during the disease course (n=9).

Initiation of steroids resulted in recovery of cardiac conduction (defined as < 10 % ventricular pacing during follow-up) in 7 out of 35 patients (20%) with a pacemaker implanted due to a complete atrioventricular block.

Since the patients not receiving immunosuppression were the ones diagnosed from
Explants or at autopsy, analyses of the effect of steroids (yes/no) on outcome were omitted as meaningless. Among patients receiving steroids, there was no difference in transplant-free cardiac survival by the initial dose of prednisone (< 60 mg vs ≥ 60 mg/day, log rank p = 0.561) or by the delay from symptom onset to starting steroids (< 6 months vs ≥ 6 months, log rank p = 0.867).

**Discussion**

With a 25-year nationwide coverage the present work provides a representative view to the characteristics and outcome of clinically manifest and histologically confirmed CS in an adult white Northern European population. Most conspicuous among our findings were the more than 20-fold increase in the annual detection rate of CS over the study period, the predominance of disease clinically isolated to the heart at presentation and the high cumulative frequency of LV dysfunction during the disease course. Yet, the 10-year estimate of transplant-free cardiac survival was as high as 91% in patients who were diagnosed clinically and received contemporary immunosuppressive and device therapy.

**Epidemiology of CS**

With an annual detection rate of 0.31 per 10⁵ adults, and with a prevalence of 2.2 per 10⁵, clinically manifest CS remains a very rare condition in today’s Finland. No figures from elsewhere specific to CS exist for comparison. However, since the reported general incidence of sarcoidosis in Finland is close to the incidence in other white populations²⁹,³⁰ the present epidemiologic data should be even more widely representative. Ethnic differences in the frequency of cardiac involvement are possible, however. An earlier comparative autopsy study revealed myocardial granulomas in 68% of Japanese patients with sarcoidosis vs in 21% of
African-Americans and in 14 % of Caucasians.\textsuperscript{31} We admit that our data most likely underestimate the true frequency of CS because we excluded a number clinically diagnosed cases due to lack of confirmatory histology or cardiac imaging and because systematic cardiac screening of patients with extracardiac sarcoidosis was not practiced in Finland during the period of our study. Further, the ICD-10 classification was introduced in Finland no earlier than in 1996 so that our screening may have missed solitary patients diagnosed after 1988 but lost from follow-up prior to 1996. Findings by other groups, too, suggest that the true prevalence of CS (manifest and silent but detectable cases combined) may be several times higher than what the number of clinical diagnoses suggest.\textsuperscript{3-5,11-14}

The observed increase in the annual detection rate of CS was surprisingly high. We think that improved diagnostic methods combined with better awareness of CS and heightened resolution in pursuit of diagnosis\textsuperscript{17} may explain this change without a true increase in disease incidence. Of note, the largest step-up in the number of new diagnoses (\textit{Figure 1}) followed the introduction of Gd-MRI and \textsuperscript{18}F-FDG PET into the routine clinical assessment of myocardial diseases in our country.

\textbf{CS without Clinically Manifest Sarcoidosis in Other Organs}

Cardiac involvement without known or clinically apparent extracardiac sarcoidosis (isolated CS) has been reported both in studies of CS populations\textsuperscript{3,4,6,15,17,32} and in case histories.\textsuperscript{16,18,19,33-36} In our work, 71 of 110 patients (65 %) presented with clinically isolated CS which proportion is close to the figure (57 %) reported by Okura et al.\textsuperscript{15} from an international registry. Although cardiac involvement is the only clinically apparent manifestation of sarcoidosis at presentation, hidden involvement of other organs can be found by \textsuperscript{18}F-FDG PET or at autopsy.\textsuperscript{3,4,6,17,27} In our isolated CS subgroup, silent extracardiac FDG uptake was common (\textit{Table 1}), but still 9 out of
the 30 patients undergoing whole-body PET (30 %) had no signs of active sarcoidosis outside the heart. At the outmost clinical case, exclusive involvement of the heart delays the diagnosis until transplantation or autopsy. We had 7 such cases (7 % of our study population) while in the study by Okura et al.\textsuperscript{15} totally 12 of 42 patients (29 %) had isolated CS detected at transplantation or autopsy. Similar experiences have been reported by others, too.\textsuperscript{35,36} Although the existence of a truly isolated CS can be questioned, we feel that recognition of this entity is important to the cardiology services where these patients present with acute cardiac problems without any clues to the etiology by history, chest X-rays or routine blood tests.

There were conspicuous differences between isolated CS and CS with manifest extracardiac disease (see Table 1). Thus, isolated CS was associated with a female preponderance and a more severe LV involvement judging from the higher frequency of LV dysfunction and septal abnormalities at echocardiography and from the higher prevalence of late enhancement at Gd-MRI. While the difference in sex distribution is difficult to explain the one in LV involvement suggests that CS was detected in a more advanced stage of the disease when it was clinically isolated. There were also differences in serum angiotensin converting enzyme, serum lysozyme and daily urinary calcium excretion, all pointing towards a heavier burden of granulomatous changes in CS with manifest extracardiac disease. Isolated CS predicted worse event-free survival when aborted sudden death was included in the composite outcome end point together with cardiac death and transplantation (Figs 5A and 6). One explanation is that there was a marked cluster of early aborted sudden arrhythmic deaths in isolated CS related to the frequency of ventricular arrhythmias at presentation (see Table 1).

**Long-Term Outcome**

The Kaplan-Meier estimates of cardiac survival shown here (Table 2) suggest an outlook for CS
that is somewhat more favourable than what is generally presented and much better than the worst prognostic data hitherto. In 1978, Roberts et al. reported from a clinicopathologic study of 113 patients that only 27% of patients were alive 1 year from symptom onset. A British study from the 1980’s reported a 40% 5-year survival in CS. In a study of 95 patients collected from 40 Japanese hospitals, 5-year survival was 60% overall and 75% in the subgroup of patients diagnosed prior to autopsy. In the international multicenter study by Okura et al., transplant-free 5-year survival was 60% overall and 70% in clinically diagnosed patients. In two small Japanese studies, 5-year survival exceeded 90%, and finally, a French study reported only one CS-related death among 41 patients followed-up for nearly 5 years on average. All these works were retrospective in design. Recently, a few small studies have reported outcome data from cardiac screening and prospective follow-up of patients with known extracardiac sarcoidosis. Patel et al. found a 19% cardiac mortality (4 of 21 patients) in less than 2 years in patients with LV late enhancement at Gd-MRI. In a similar work, Greulich et al. followed a group of 39 patients with cardiac symptoms and LV late enhancement and found an 8% cardiac mortality (3 of 39 patients) over a mean of 2.6 years. By contrast, Mehta et al. found no mortality or adverse events during 2 years follow-up in 24 sarcoidosis patients having cardiac symptoms and either PET or Gd-MRI indicative of CS. Altogether these reports indicate that CS is a potentially fatal disease, but how fatal it really is remains uncertain due to the marked disparities in the methods and results of these works.

Although the 5-year survival probability of clinically diagnosed CS appears clearly better in our study (95%) than in the two most widely cited previous works (70-75%), the data are not directly comparable since we reported transplant-free cardiac survival while Okura et al. reported transplant-free overall survival and Yazaki et al. the mere overall survival. Further,
since most of our patients were from a later era, it is possible that, due to improved diagnostic
methods, they had less advanced cardiac involvement than what was studied in the earlier
works. Differences in the ethnic composition of the study groups also confound any
comparisons since Japanese CS patients have been reported to have a markedly higher cardiac
mortality than CS patients of African-American or Caucasian origin. Finally, there were
differences in treatment, too, for instance in the frequency of ICD implantations which was
highest in our study.

Our survival analyses indicated that heart failure as the first clinical CS manifestation
predicted poor transplant-free cardiac survival along with impaired LV function at diagnosis.
This is understandable due to the prognostic notoriety of heart failure in general and it also
accords well with earlier data showing that dilated LV size and impaired EF predict increased
mortality and life-threatening arrhythmias in CS. In our study, event-free cardiac survival was
impaired in patients with severe LV dysfunction (EF < 35%) but there was little difference in
outcome between patients with moderately depressed or normal LV function (EF 35-50 % vs
>50 %) (Figs 3B and 5B). The significance of isolated CS as a predictor of poor outcome was
discussed above.

Reflections on Steroid Therapy

Corticosteroid therapy is generally considered mandatory in CS even though all evidence is
based on purely retrospective observations. Our work, though larger in size than many earlier
ones, could not add much to the knowledge about steroids and prognosis in CS. We found, like
Yazaki et al., that long-term outcome was independent of the initial dose of prednisone.
Outcome was also independent of the delay from the first disease manifestation to the onset of
treatment, but a potential confounder here is that patients with the most severe manifestations are
likely to undergo an expedited diagnostic process leading to shorter treatment delays.

Limited observational data from Japan suggest that administering steroids in CS prevents development of systolic LV dysfunction if EF is initially normal\(^{21,22,39}\) and, further, that it improves moderately depressed LV function\(^{21,40}\) but has no beneficial effects on severely impaired LV function (EF < 30-35 %).\(^{21,39}\) Our data, by contrast, indicated an improvement of LV function with immunosuppression in patients with severely impaired EF (<35 %) but no change if EF was normal or only moderately depressed at the start of treatment (Table 3). The weakness of all these works is that it remains unknown what the course of LV function had been without steroids.

Limitations

Some of the limitations of our work are self-explanatory, like the retrospective design with its inherent problems, the lack of standardized diagnostic and treatment practice in all participating hospitals and the change over time in the diagnostic methods. Further, although we tried to collect a comprehensive nationwide clinical series it is possible that some patients with manifest CS were missed due to deficiencies in both hospital registries and in our screening. In the epidemiologic sense it is a major limitation that our series only covers clinically manifest CS. Systematic screening of patients with sarcoidosis for silent cardiac involvement was not done, and CS presenting first as an unexpected sudden death in the community also remained outside our work. Although with 110 patients our study is one of the largest works on long-term outcome of CS, in strict statistical sense the number of patients and events remained small. This limits the interpretation of our survival analyses and may also partly explain why there were differences in the statistically significant predictors of different composite end points. The inclusion in survival analyses of cases diagnosed postmortem or posttrasplantation assumes that there is no really
benign form of CS and that the diagnosed cases are representative of all those who contract the disease. Since this assumption can be questioned we calculated the survival data also after excluding these cases from the analyses. Similar dual analysis strategy has been used also in the prior key survival studies in CS.\textsuperscript{15,20}

**Conclusions**

The number of patients with manifest CS seen annually in Finland increased more than 20-fold from 1988 to 2012, most likely due to improved diagnostic methods and heightened diagnostic activity. The majority of patients had clinically isolated CS which was characterized by female preponderance, more severe LV involvement and less frequent elevations in the common laboratory markers of sarcoidosis. The 10-year probability of transplant-free cardiac survival was 83\% overall and 91\% under immunosuppressive treatment. Heart failure at presentation, marked LV dysfunction at diagnosis (EF <35\%) and isolated CS type predicted impaired event-free outcome. Although the overall prognosis of CS was better than generally considered, LV dysfunction was common and poorly responsive to steroid therapy. Improvement in disease modifying treatment is clearly needed but presupposes prospective controlled trials which, due to the rarity of CS, should be organized internationally.

**Addendum:** From February 2012 through August 2014, i.e. after the inclusion of the last patient in the present follow-up work, we have diagnosed totally 57 new histologically confirmed cases of CS in Finland. This gives a current annual detection rate of 0.53 per 10^5 adults, which is clearly more than reported above for the period from 2008 to 2012.
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Conflict of Interest Disclosures: None.

References:


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### Table 1. Key characteristics of the CS population at the time of diagnosis (or at first disease manifestation in cases diagnosed at transplantation or at autopsy).

<table>
<thead>
<tr>
<th></th>
<th>All CS patients</th>
<th>Clinically isolated CS</th>
<th>CS with known extracardiac disease</th>
<th>p*</th>
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<tbody>
<tr>
<td></td>
<td>n = 110</td>
<td>n = 71</td>
<td>n = 39</td>
<td></td>
</tr>
<tr>
<td>Age, years (mean ± SD)</td>
<td>51 ± 9</td>
<td>51 ± 9</td>
<td>50 ± 9</td>
<td>0.463</td>
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<tr>
<td>Gender, n of females</td>
<td>71 (65%)</td>
<td>53 (75%)</td>
<td>18 (46%)</td>
<td>0.003</td>
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<tr>
<td>First clinical manifestation</td>
<td></td>
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<tr>
<td>Symptomatic atrioventricular conduction block</td>
<td>48 (44%)</td>
<td>34 (48%)</td>
<td>14 (36%)</td>
<td>0.016</td>
</tr>
<tr>
<td>Ventricular tachycardia or fibrillation¶</td>
<td>36 (33%)</td>
<td>27 (38%)</td>
<td>9 (23%)</td>
<td></td>
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<tr>
<td>Heart failure</td>
<td>20 (18%)</td>
<td>8 (11%)</td>
<td>12 (31%)</td>
<td></td>
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<tr>
<td>Others†</td>
<td>6 (6%)</td>
<td>2 (3%)</td>
<td>4 (10%)</td>
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<td>New York Heart Association class</td>
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<tr>
<td>1</td>
<td>62 (56%)</td>
<td>40 (56%)</td>
<td>22 (56%)</td>
<td></td>
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<tr>
<td>2</td>
<td>33 (30%)</td>
<td>22 (31%)</td>
<td>11 (28%)</td>
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<tr>
<td>3 - 4</td>
<td>15 (14%)</td>
<td>9 (12 %)</td>
<td>6 (15 %)</td>
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<td>Findings at 12-lead electrocardiogram</td>
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<tr>
<td>No abnormalities</td>
<td>15/107 (14%)</td>
<td>8/69 (12%)</td>
<td>7/38 (18%)</td>
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<td>2 -3° atrioventricular block</td>
<td>48/107 (45%)</td>
<td>34/69 (49%)</td>
<td>14/38 (37%)</td>
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<tr>
<td>RBBB</td>
<td>40/107 (37%)</td>
<td>30/69 (43%)</td>
<td>10/38 (26%)</td>
<td>0.079</td>
</tr>
<tr>
<td>LBBB</td>
<td>22/107 (21%)</td>
<td>16/69 (23%)</td>
<td>6/38 (16%)</td>
<td>0.365</td>
</tr>
<tr>
<td>Findings at echocardiography</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left ventricular dilatation‡</td>
<td>43/102 (42%)</td>
<td>27/64 (42%)</td>
<td>16/38 (42%)</td>
<td>1.000</td>
</tr>
<tr>
<td>Left ventricular systolic dysfunction (EF &lt; 50 %)</td>
<td>65/110 (59%)</td>
<td>49/71 (69%)</td>
<td>16/39 (41%)</td>
<td>0.004</td>
</tr>
<tr>
<td>Interventricular septal thinning or thickening</td>
<td>63/109 (58%)</td>
<td>48/70 (69%)</td>
<td>15/39 (38%)</td>
<td>0.002</td>
</tr>
<tr>
<td>Findings at Gd-MRI</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myocardial late enhancement</td>
<td>49/59 (83%)</td>
<td>36/38 (95%)</td>
<td>13/21 (62%)</td>
<td>0.002</td>
</tr>
<tr>
<td>Findings at ¹⁸F-FDG PET</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Focally increased cardiac FDG uptake</td>
<td>48/66 (73%)</td>
<td>34/46 (74%)</td>
<td>14/20 (70%)</td>
<td>0.743</td>
</tr>
<tr>
<td>FDG uptake in mediastinal lymph nodes</td>
<td>30/42 (71%)</td>
<td>22/31 (71%)</td>
<td>8/11 (73%)</td>
<td>1.000</td>
</tr>
<tr>
<td>FDG uptake outside heart and mediastinum</td>
<td>16/39 (41%)</td>
<td>12/30 (40%)</td>
<td>4/9 (44%)</td>
<td>1.000</td>
</tr>
<tr>
<td>Laboratory findings</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elevated serum ACE</td>
<td>22/90 (24%)</td>
<td>9/59 (15%)</td>
<td>13/31 (42%)</td>
<td>0.005</td>
</tr>
<tr>
<td>Elevated serum lysozyme</td>
<td>40/74 (54%)</td>
<td>21/48 (44%)</td>
<td>19/26 (73%)</td>
<td>0.016</td>
</tr>
<tr>
<td>Elevated urinary calcium</td>
<td>22/45 (49%)</td>
<td>9/24 (38%)</td>
<td>13/21 (62%)</td>
<td>0.029</td>
</tr>
</tbody>
</table>

Apart from age, the data are numbers (%) of patients with positive findings, or number of positive findings/number of studied patients.

* p-values for comparison between the 2 subgroups; ‡ 31 patients with ventricular tachycardia and 5 patients with ventricular fibrillation; † 4 patients with multiple ventricular premature beats, 1 patient with mitral regurgitation and 1 patient with pericardial effusion; ‡ left ventricular diastolic diameter > 60 mm in men or > 55 mm in women.

ACE= angiotensin converting enzyme; EF= ejection fraction; ¹⁸F-FDG PET = 18-F-fluorodeoxyglucose position emission tomography; Gd-MRI= gadolinium enhanced cardiac magnetic resonance imaging; LBBB= left bundle branch block; LZM= lysozyme; RBBB= right bundle branch block.
Table 2. Survival probabilities in all 110 CS patients and in the 102 patients diagnosed prior to transplantation or autopsy.

<table>
<thead>
<tr>
<th></th>
<th>Cardiac survival</th>
<th>Cardiac survival free of transplantation</th>
<th>Cardiac survival free of transplantation and aborted sudden death</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-year survival, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N=110</td>
<td>99.1 (94.3 - 99.9)</td>
<td>97.3(91.6-99.3)</td>
<td>89.1 (81.3-93.9)</td>
</tr>
<tr>
<td>N=102</td>
<td>100 (95.5 – 100)</td>
<td>99.0 (93.9 – 99.9)</td>
<td>89.2 (81.1 – 94.2)</td>
</tr>
<tr>
<td>5-year survival, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N=110</td>
<td>93.5 (86.7 – 97.1)</td>
<td>90.0(82.4-94.6)</td>
<td>77.7 (68.5 - 84.8)</td>
</tr>
<tr>
<td>N=102</td>
<td>97.0 (90.9 – 99.2)</td>
<td>95.1 (88.4 – 98.2)</td>
<td>82.0 (72.9 – 88.7)</td>
</tr>
<tr>
<td>10-year survival, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N=110</td>
<td>89.3 (81.6 – 94.2)</td>
<td>83.1(74.5-89.3)</td>
<td>70.4 (60.8 - 78.5)</td>
</tr>
<tr>
<td>N=102</td>
<td>92.5 (85.1 – 96.5)</td>
<td>90.6 (82.7 – 95.2)</td>
<td>77.2 (67.6 – 84.7)</td>
</tr>
</tbody>
</table>

The figures are Kaplan-Meier survival estimates (95 % confidence intervals)

Table 3. LV function before and after an average of 12 months of immunosuppressive treatment in patients with CS.

<table>
<thead>
<tr>
<th>Initial LV function</th>
<th>EF before treatment, %</th>
<th>EF after 12 months of steroid therapy, %</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal (EF ≥ 50 %), n = 44</td>
<td>56.8 ± 5.6</td>
<td>54.9 ± 7.6</td>
<td>0.145</td>
</tr>
<tr>
<td>Moderately impaired (EF 35-49 %), n=36</td>
<td>40.9 ± 4.1</td>
<td>40.8 ± 6.4</td>
<td>0.979</td>
</tr>
<tr>
<td>Severely impaired (EF&lt; 35 %), n=22</td>
<td>27.9 ± 4.1</td>
<td>34.1 ± 8.3</td>
<td>0.005</td>
</tr>
</tbody>
</table>

The data are mean ± SD

*p paired t-test

EF = ejection fraction; LV = left ventricular
Figure Legends:

Figure 1. The number of new cases of CS diagnosed within the 5-year periods between 1988 and 2012.

Figure 2. Kaplan-Meier curves for cardiac survival (line 1), cardiac survival free of transplantation (line 2), and cardiac survival free of transplantation and aborted sudden death (line 3), in all 110 CS patients (2A) and in the 102 patients who were identified clinically and received immunosuppressive treatment (2B).

Figure 3. Kaplan-Meier curves for transplant-free cardiac survival in all 110 CS patients by heart failure (HF) as the first clinical manifestation (3A), by LVEF at diagnosis (3B) and by the initial NYHA class (3C).

Figure 4. Kaplan-Meier curves for transplant-free cardiac survival by heart failure (HF) as the presenting manifestation in the 102 CS patients who were diagnosed clinically and underwent immunosuppressive therapy.

Figure 5. Kaplan-Meier curves for cardiac survival free of transplantation and aborted sudden death in the total population of 110 CS patients by the type of CS (5A) and by LVEF at diagnosis (5B). ICS = isolated cardiac sarcoidosis, CS+ECS = cardiac and extracardiac sarcoidosis.

Figure 6. Kaplan-Meier curves for cardiac survival free of transplantation and aborted sudden death by the type of CS in the 102 patients who were diagnosed clinically and underwent immunosuppressive therapy. For abbreviations, see the legend for Figure 5.
Figure 1
Figure 2A
Figure 2B

<table>
<thead>
<tr>
<th>N at risk</th>
<th>Time (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>102</td>
</tr>
<tr>
<td>2</td>
<td>102</td>
</tr>
<tr>
<td>3</td>
<td>102</td>
</tr>
<tr>
<td>1</td>
<td>64</td>
</tr>
<tr>
<td>2</td>
<td>63</td>
</tr>
<tr>
<td>3</td>
<td>51</td>
</tr>
<tr>
<td>2</td>
<td>27</td>
</tr>
<tr>
<td>2</td>
<td>27</td>
</tr>
<tr>
<td>3</td>
<td>15</td>
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<tr>
<td>2</td>
<td>7</td>
</tr>
<tr>
<td>2</td>
<td>7</td>
</tr>
<tr>
<td>3</td>
<td>5</td>
</tr>
</tbody>
</table>
log rank $p = 0.0001$

<table>
<thead>
<tr>
<th></th>
<th>HF-</th>
<th>HF+</th>
</tr>
</thead>
<tbody>
<tr>
<td>N at risk</td>
<td>90</td>
<td>20</td>
</tr>
<tr>
<td>Time (years)</td>
<td>57</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>25</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>1</td>
</tr>
</tbody>
</table>

Figure 3A
Figure 3B

<table>
<thead>
<tr>
<th>EF at Risk</th>
<th>N at Risk</th>
<th>Years 0-5</th>
<th>Years 5-10</th>
<th>Years 10-15</th>
</tr>
</thead>
<tbody>
<tr>
<td>EF &gt;50%</td>
<td>44</td>
<td>28</td>
<td>13</td>
<td>3</td>
</tr>
<tr>
<td>EF 35-50%</td>
<td>37</td>
<td>21</td>
<td>9</td>
<td>2</td>
</tr>
<tr>
<td>EF &lt;35%</td>
<td>29</td>
<td>16</td>
<td>5</td>
<td>2</td>
</tr>
</tbody>
</table>
log rank $p = 0.023$

<table>
<thead>
<tr>
<th>Condition</th>
<th>N at risk</th>
<th>Time (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NYHA I</td>
<td>62</td>
<td>38 17 3</td>
</tr>
<tr>
<td>NYHA II</td>
<td>33</td>
<td>20 6 3</td>
</tr>
<tr>
<td>NYHA III&amp;IV</td>
<td>15</td>
<td>9 4 1</td>
</tr>
</tbody>
</table>
Figure 4

Transplant-free cardiac survival

Nat risk
HF-
87
15
HF+
55
8
25
Time (years)
10
15

log rank p=0.025
Cardiac survival free of transplantation and aborted sudden death

Figure 5A
Cardiac survival free of transplantation and aborted sudden death

log rank

p = 0.136 overall

p = 0.046 for EF < 35% vs EF ≥ 35%

N at risk
EF > 50% 44
EF 35-50% 37
EF < 35% 29

Time (years)

Figure 5B
Cardiac survival free of transplantation and aborted sudden death

log rank p = 0.015

N at risk
CS+ECS  38  23  11  4
ICS  64  28  4  1

Figure 6
Cardiac Sarcoidosis: Epidemiology, Characteristics and Outcome over 25 Years in a Nationwide Study

Riina Kandolin, Jukka Lehtonen, Juhani Airaksinen, Tapani Vihinen, Heikki Miettinen, Kari Ylitalo, Kari Kaikkonen, Suvi Tuohinen, Petri Haataja, Tuomas Kerola, Jorma Kokkonen, Markus Pelkonen, Päivi Pietilä-Effati, Seppo Utriainen and Markku Kupari

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