Clinical Immunology 199 (2019) 57–61

Contents lists available at ScienceDirect

Clinical Immunology

journal homepage: www.elsevier.com/locate/yclim

The long-term prognostic significance of sarcoidosis-associated pulmonary hypertension – A cohort study

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ARTICLE INFO

Keywords:
Sarcoidosis
Pulmonary hypertension
Cohort
Survival
Prognosis

ABSTRACT

Background: Sarcoidosis is a multisystem, chronic, progressive, granulomatous disease. Sarcoidosis-associated pulmonary hypertension is a well described, but not common, complication of sarcoidosis. In small scale studies, it has been previously described as manifestation of advanced disease and was found to be associated increased morbidity and mortality. This study sought to assess the long-term prognostic significance of sarcoidosis-associated pulmonary hypertension (SAPH) by using data obtained from a large population-based registry which contains longitudinal follow-up data.

Methods: Utilizing the records of the largest healthcare provider in Israel, we extracted a cohort consisting of sarcoidosis patients and age-and-sex matched controls. Dates of sarcoidosis registration, pulmonary hypertension and death, as well as anthropometric information and medical comorbidities, were extracted from the database. A multivariate logistic regression model was used to find variables associated with pulmonary hypertension. Cox proportional hazards method and log-rank test were used for survival analysis.

Results: The cohort included 3993 sarcoidosis patients and 19,856 controls. Pulmonary hypertension was observed among 269 sarcoidosis patients (6.74%) vs. 400 controls (2.01%). Sarcoidosis was found as independently associated with pulmonary hypertension (OR 3.17). After a mean follow-up of 7.49 years (median 7.24, maximum 17.88 years), 710 (17.8%) of the sarcoidosis patients and 2121 (10.7%) of the controls had died. Both sarcoidosis and pulmonary hypertension were found to be significantly associated with an increased risk of all-cause mortality (HR 1.82 and HR 2.31, respectively).

Conclusions: SAPH is associated with a poor prognosis. Proper screening methods may assess whether early identification and treatment improve life expectancy.

1. Introduction

Sarcoidosis is a multi-system, chronic, progressive, granulomatous disease with a predilection for female gender. Lung involvement is common among sarcoidosis patients and may contribute to the deterioration of lung function and the eventual development of end-stage pulmonary fibrosis [1]. To date, the pathogenesis of sarcoidosis has yet to be completely understood. Several mechanisms have been proposed, suggesting that immune system dysregulation is invovled in the formation of non-caseating granulomata, the hallmark of the

Abbreviations: BMI, Body mass index; CHS, Clalit Health Services; CI, Confidence interval; FVC, Forced vital capacity; HR, Hazard ratios; IHD, Ischemic heart disease; mPAP, Mean pulmonary arterial pressure; OR, Odds ratio; PH, Pulmonary hypertension; SAPH, Sarcoidosis-associated pulmonary hypertension; SD, Standard deviation; SES, Socioeconomic status; WHO, World Health Organization

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https://doi.org/10.1016/j.clim.2018.12.012

Available online 10 December 2018

disease. Multiple clinical phenotypes of the disease have been observed, which differ with regard to presentation, involved organs, disease duration and severity. Pulmonary manifestations are present in about 90% of cases according to chest X-ray, either alone or in association with extrapulmonary localizations in around 50% of cases [2].

Pulmonary hypertension (PH) is defined by an increased mean pulmonary arterial pressure (mPAP) greater than or equal to 25 mmHg at rest, as documented on right-sided heart catheterization. Sarcoidosis-associated pulmonary hypertension (SAPH) is a well-known, yet uncommon complication of sarcoidosis. It is defined as part of group 5 in the Updated Clinical Classification of Pulmonary Hypertension [3]. In small scale studies, SAPH was previously described as a manifestation of advanced disease and was found to be associated with increased morbidity and mortality [4]. It manifests as severe dyspnea accompanied by reduced lung diffusion capacity and possibly low oxygen saturation [5]. Symptoms may vary between patients and are sometimes described as “out of proportion” with the degree of lung parenchymal involvement [6]. Over 70% of sarcoidosis patients who are lung transplant candidates have significant PH [7]. In less advanced, but still symptomatic patients, pulmonary arterial hypertension has been noted in up to 50% of the cases [7].

Large-scale data analyses regarding the exact magnitude and prognosis of SAPH are lacking. Therefore, the aim of our study was to describe the epidemiology and long-term prognostic significance of SAPH by utilizing the database of Israel's largest healthcare provider.

2. Methods

This study is one of a series of explorative and analytic studies based on the chronic disease registry of Clalit Health Services (CHS), the largest healthcare maintenance organization in Israel, which provides service for roughly 50% of the population. The CHS chronic disease registry receives input data from pharmaceutical, medical and administrative computerized operating systems. Various patient data are continuously extracted from the database, allowing the conduction of a wide-scale epidemiological study on a real-time heterogeneous population in an effective manner. Using the CHS's computerized database, we extracted a cohort consisting of sarcoidosis patients and compared them with age- and sex-matched controls. The data drawn from the database was recorded continuously since the beginning of the utilization of computerized systems in the CHS, approximately from the year 2000 until the year 2016.

Sarcoidosis patients were defined as such if they had at least one documented diagnosis of sarcoidosis as an outpatient, either by a primary care physician or a specialist in their medical records, or who were diagnosed with sarcoidosis in their hospital discharge papers. All sarcoidosis patients detected in the CHS database were included in this study. Controls were randomly selected from the CHS database, with the exclusion of sarcoidosis patients. Five controls were matched by age and gender for each sarcoidosis patient. Data available from the CHS database included age, sex, socioeconomic status (SES), body mass index (BMI) and diagnoses of chronic diseases (Fig. 1). The definition of PH, similar to that of sarcoidosis, was based on a documented diagnosis of PH in medical records, as registered in the CHS database. Dates of registration in the medical records of sarcoidosis (or alternatively for controls, start of follow-up), PH and death, as well as anthropometric information, smoking status (ever smoked) and medical comorbidities, were extracted from the database. Index date was defined as the first documentation date of sarcoidosis diagnosis for each sarcoidosis patient and its matched controls. SES was defined based the address of residency, according to the Israeli central bureau of statistics publication in aggregation to 3 groups (low, medium, high). The validity of the different diagnoses in the registry was found to be high in previous studies [8–10].

The Chi-square test was used to assess the distribution of categorical sociodemographic and clinical parameters, such as SES and gender, between sarcoidosis patients and controls, while the *t*-test was applied for continuous parameters such as age. To reflect a nonlinear relation between BMI and dependent variables, BMI was broken into 4 categories: < 20,20-25, 25-30 and > 30 kg/m^2.

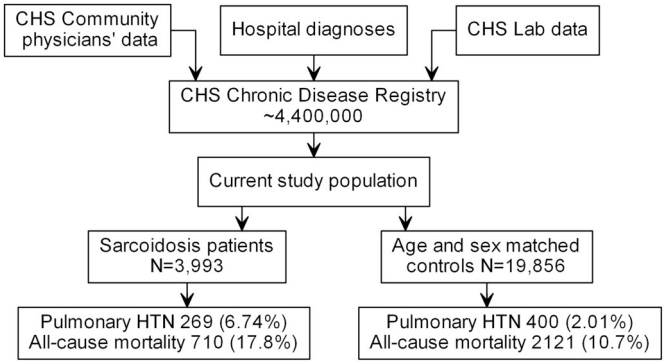

Fig. 1. Study flowchart.
Legend: CHS: Clalit health services; HTN: Hypertension.

Rates of PH were compared between sarcoidosis patients and controls in the study sample group.

We performed a cross sectional analysis regarding the association between sarcoidosis and PH, using multivariate logistic regression model, adjusting for possible confounders. In this analysis, we treated indifferently PH diagnosed before or after sarcoidosis, because we assumed that PH may be one of the initial signs of sarcoidosis.

We also performed a longitudinal analysis, taking into account existence of sarcoidosis and/or PH and association with all-cause mortality. Survival analysis using Kaplan-Meier curves, log-rank test and multivariate cox proportional hazards method was performed to detect variables associated with an increased risk of all-cause mortality, adjusting for possible risk factors. As opposed to the cross-sectional analysis, here the follow-up started at the index date and until all-cause mortality or end of follow-up, whichever came first.

Statistical analysis was performed using R Statistical Software (version 3.3.0; R Foundation for Statistical Computing, Vienna, Austria). Odds ratios (ORs), hazard ratios (HRs) and 95% confidence intervals (CIs) are presented.

The study was approved by the ethics committee of CHS, located in Soroka Medical Center, Be’er Sheva, Israel.

3. Results

The cohort included 3993 sarcoidosis patients and 19,856 age-and-sex matched controls (Table 1), which corresponds to a prevalence rate of 90.75 per 100,000 enrollees. The mean age of both groups was about 64 years, and the percentage of females in both groups was 63%. Age at diagnosis of sarcoidosis was 56 years. BMI was lower among sarcoidosis patients in comparison with controls (28.9 vs. 29.7 kg/m^2, respectively). Hypertension and ischemic heart disease (IHD) were present at a higher frequency among sarcoidosis patients, whereas smoking was not. PH was observed among 269 sarcoidosis patients (6.74%) vs. 400 controls (2.01%), $p < .001$. On multivariate analysis (Table 2), sarcoidosis and female gender were found to be independently associated with PH (OR 3.17, 95%CI 2.66–3.76 and OR 1.41, 95%CI 1.15–1.72, respectively). Hypertension and IHD (yet not smoking) were also found to be associated with PH. After a mean follow-up of 7.49 years (median 7.24, maximum 17.88 years), 710 (17.8%) sarcoidosis patients had died, in comparison with 2121 (10.7%) controls ($p < .001$). The study accumulated 28,310 and 150,311 person-years for sarcoidosis patients and controls, respectively, with rate ratio of 1.78 for all-cause mortality for sarcoidosis patients. The median survival time from sarcoidosis diagnosis until the end of follow-up was 5.72 years for patients with PH, as opposed to 6.83 years for patients without PH. Fig. 2 shows a Kaplan-

Table 1
Characteristics of sarcoidosis patients and age-and-sex matched controls.

Characteristic	Controls without sarcoidosis N = 19,856	Sarcoidosis patients N = 3993	p
Age (Mean ± SD)[a]	64.1 ± 15.7	64.2 ± 15.7	0.871
Age at diagnosis (Mean ± SD)[b]	56.0 ± 15.2	56.0 ± 15.2	0.874
Gender: Female	12,527 (63.1%)	2522 (63.2%)	0.933
BMI (Mean ± SD)	29.7 ± 19.4	28.9 ± 11.7	0.815
SES:			
Low	7376 (37.7%)	1654 (41.9%)	Reference
Medium	8029 (41.0%)	1569 (39.8%)	< 0.001
High	4168 (21.3%)	723 (18.3%)	< 0.001
Hypertension	8451 (42.6%)	2026 (50.7%)	< 0.001
Smoking	6949 (35.0%)	1342 (33.6%)	0.092
IHD	2999 (15.1%)	856 (21.4%)	< 0.001
Pulmonary Hypertension	400 (2.01%)	269 (6.74%)	< 0.001

SD: Standard deviation; BMI: Body mass index (kg/m^2); SES: Socioeconomic status; IHD: Ischemic heart disease.
[a] Current age at time of study production.
[b] Age at diagnosis represents the age of sarcoidosis diagnosis registration, for sarcoidosis patients, and the age of start of follow up for controls.

Table 2
Multivariate logistic regression assessing covariates associated with pulmonary hypertension.

Variable	OR	95% CI	p
Sarcoidosis	3.17	2.66–3.76	< 0.001
Age[a]	1.04	1.03–1.05	< 0.001
Gender: Female	1.41	1.15–1.72	< 0.001
BMI group[b]			
20–25	0.76	0.46–1.34	0.310
25–30	0.77	0.47–1.33	0.314
> 30	1.00	0.61–1.74	0.992
Hypertension	3.07	2.37–4.03	< 0.001
Smoking	1.05	0.87–1.27	0.580
IHD	3.86	3.23–4.63	< 0.001

OR: Odds ratio, BMI: Body mass index, kg/m^2; IHD: Ischemic heart disease.
[a] Per 1-year increment.
[b] Reference category is BMI < 20 kg/m^2.

Meier curve comparing all-cause survival rates between study groups. In a multivariate survival analysis (Table 3), both sarcoidosis and PH were found to be significantly associated with an increased risk for all-cause mortality (HR 1.82, 95%CI 1.65–2.01 and HR 2.31, 95%CI 2.03–2.62, respectively). IHD, smoking, hypertension and BMI < 20 kg/m^2 were also found to be associated with an increased risk for all-cause mortality. Furthermore, a BMI of 25–30 kg/m^2 was associated with a reduced risk for all-cause mortality, in comparison with normal range (20–25 kg/m^2) BMI.

Table 3
Multivariate cox model presenting survival analysis for covariates associated with all-cause mortality.

Variable	HR	95%CI	p
Age[a]	1.08	1.08–1.09	< 0.001
Gender: Male vs. Female	1.31	1.19–1.44	< 0.001
BMI group[b]			
< 20	2.03	1.66–2.48	< 0.001
25–30	0.86	0.77–0.96	0.009
> 30	1.00	0.9–1.12	0.97
Hypertension	1.38	1.23–1.55	< 0.001
Smoking	1.18	1.07–1.30	< 0.001
IHD	1.51	1.38–1.66	< 0.001
Sarcoidosis	1.82	1.65–2.01	< 0.001
Pulmonary hypertension	2.31	2.03–2.62	< 0.001

HR: Hazard ratio, BMI: Body mass index, kg/m^2; IHD: Ischemic heart disease.
[a] Per 1-year increment.
[b] Reference category is BMI 20–25 kg/m^2.

4. Discussion

This large-scale study demonstrates the significance and prognostic consequence of SAPH. We have shown that both sarcoidosis and PH are associated with increased risk of mortality, regardless of other risk factors. PH is recognized as a complication of pulmonary sarcoidosis and is associated with morbidity and mortality [7,11,12]. It is a major cause of death in patients with advanced pulmonary disease [11]. It is also a debilitating condition in sarcoidosis patients, which accounts for refractory dyspnea and reduced exercise capacity [13].

The epidemiology of SAPH has not been extensively studied. In the literature, the frequency of PH reported to accompany sarcoidosis is highly variable, depending, among others, on the severity of sarcoidosis pulmonary involvement, the presence of clinical symptoms and the diagnostic method for PH [14]. The gold-standard for diagnosis of SAPH remains right-sided heart catheterization, however echocardiography is usually used for screening. CT is also able to detect radiographic evidence of SAPH by calculating the pulmonary artery diameter

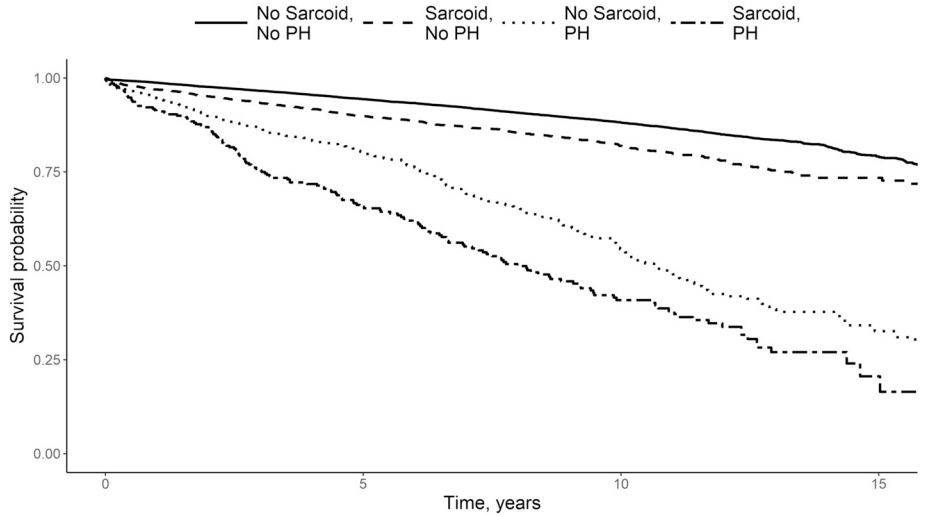

Fig. 2. Kaplan-Meier curve representing overall survival of study participants by group.
Legend: Sarcoid: Sarcoidosis; PH: Pulmonary hypertension.

indexed to body surface area [15]. Our study included all existing measures as a possible indication for PH diagnosis.

Nunes et al. [13] reported that PH affects 1% to 6% of patients with sarcoidosis. It was further shown that pulmonary arterial mean pressure was over 35 mmHg in half of the patients with sarcoidosis [16]. Other studies have demonstrated a prevalence of SAPH between 5 and 20% [11,12,17]. Baughman et al. [7] found that half of sarcoidosis patients who suffered from persistent dyspnea, in fact had undiagnosed PH. Shorr et al. [18] noted that PH was common, diagnosed in 73.8% of sarcoidosis patients who were listed for orthotopic lung transplantation [4]. A similar rate was observed by the Copenhagen lung transplant center. These reports were consistent with the observations of Gluskowski et al. [19], who found that 60% of those with stage III sarcoidosis have increased pulmonary arterial mean pressure. In our study, we observed a rate of 6.74% for SAPH. Thus, our findings are in line with those previously reported in the literature.

Handa et al. [20] found a univariate male predominance in SAPH patients, which differs from the findings of the current study which has demonstrated a robust female predominance. Other studies have not reported any gender preponderance, probably due to their limited study samples.

The pathogenesis of SAPH remains obscure. The advanced fibrous pulmonary disease may cause the destruction of distant capillary bed and leads to hypoxemia [20,21]. Mechanical compression of the pulmonary arteries by granulomata formation or by hilar lymphadenopathy, local vasculopathy and increased vasoreactivity may also generate PH. Additionally, there may be veno-occlusive disease caused by the direct infiltration of granulomata into the veins. In rare conditions, pulmonary embolism or porto-pulmonary hypertension secondary to hepatic involvement with sarcoidosis, is also a contributing factor [13,16,22–25].

It should be noted that PH among sarcoidosis patients can develop from other etiologies as well, e.g., secondary to left ventricular disease. We assume that the association between hypertension and IHD with PH demonstrated in our study was due to the inclusion of patients with other reasons for PH in the cohort (e.g., group 2, due to left heart disease) [3]. It should also be kept in mind that corticosteroid use by itself may promote the development of hypertension, diabetes and IHD and thus induce left heart disease PH.

The characteristics of the sarcoidosis patients in our study are similar to previously published, yet smaller, cohort studies. The gender ratio in our study was practically identical to the ACCESS study, a clinical center-based observational study whose percentage of female patients was 64% [26]. The prevalence of sarcoidosis in our study was far less than that reported in Sweden in 2016 in a register-based assessment (90.75 vs. 160 per 100,000, respectively) [27], however greater than the prevalence reported in Vermont in 2009 (66.1 per 100,000, according to insurance claims data) [28]. Nonetheless, the mean age of sarcoidosis patients in the current study is higher than that in the Swedish report (64 vs. 56 years, respectively), and the age of diagnosis in Sweden was 50 (compared to 56, in the present study). Our study did demonstrate slightly lower BMI and smoking rates among sarcoidosis patients, but without any statistical or clinical significance, hence we assume that these findings has no real-life implications.

We showed that sarcoidosis itself is associated with excessive mortality, regardless of PH, however, the Olmsted County study in Minnesota did not demonstrate differences in overall mortality from the general population [29].The variation in study population characteristics between nations can be attributed to the different methodologies of data gathering (e.g., population-based vs. clinic-based vs. insurance claims). Moreover, the significant genetic and environmental variance among studies poses an epidemiological challenge when seeking to compare findings. Israel is considered an immigrant state and thus, is genetically heterogeneous, despite its population being nearly entirely Caucasian. This may explain the similarities between the characteristics of the sarcoidosis patients in this study to those in other studies conducted on Caucasian populations.

In a prospective study conducted in a sarcoidosis clinic in Cincinnati, SAPH patients without left ventricular dysfunction who underwent right-sided heart catheterization demonstrated a median survival of 4.2 years [30]. In that study, which included sarcoidosis patients with a wide spectrum of pulmonary artery pressures as documented on right-sided heart catheterization, PH without left ventricular dysfunction was the strongest predictor of mortality, with a HR of 10.39, whereas PH with left ventricular dysfunction had a HR of 3.14. A French study by Nardi et al. [31] that retrospectively followed 142 stage IV sarcoidosis patients, reported that PH was observed in 29.7% of the patients. PH patients presented survival rates of 91.5% at 5 years, 84.1% at 10 years and 78.1% at 15 years, which was significantly poorer than those of the control population. In their study, PH was found to be independently associated with mortality, with a striking adjusted HR of 8.2. Those findings correlate with the results of our study, which also demonstrated lower survival rates among SAPH patients, as well as an independent association between PH and all-cause mortality.

The strengths of our study are derived from the large sample size and the high validity of diagnoses. It includes an extensive sarcoidosis cohort and is the largest SAPH study ever to be published. The study reflects the authentic characteristics of the sarcoidosis patients registered in the CHS. Due to is population-based nature, it avoids referral bias which afflicts center-based studies and depicts an accurate image of the natural history of SAPH.

Nevertheless, our study has several limitations. The design is observational and not experimental. Additionally, the dates taken into account reflect the dates of registration in the CHS database and not the true incidence dates. These limitations are inherent to any database study of this type. Moreover, the technique or criteria by which both sarcoidosis and PH were diagnosed were not standardized, and the study relied solely on documentation in medical records. We cannot ascertain that PH was diagnosed by right-sided heart catheterization or that sarcoidosis patients had indeed proven granulomas in biopsy. Selection bias is less probable in studies of that nature, because we included all of sarcoidosis patients registered in CHS. Misclassification of sarcoidosis patient may have occurred, but if so – it was non-differential and thus only may have reduced the strength of association described in the study. Residual confounding is also possible limitation due to non-included risk factors for sarcoidosis or PH, however we did try to include the majority of variables analyzed in previous studies.

In conclusion, PH may develop in sarcoidosis patients and is associated with a poor prognosis.

Future studies should explore whether screening, early identification and treatment improve life expectancy.

Disclosures

The abstract of this paper was presented at the 2017 EULAR conference as an oral presentation with interim findings. DOI: https://doi.org/10.1136/annrheumdis-2017-eular.4464

Conflicts of interest

Arnon Cohen received research grants from Novartis. Other relationships: In the last 3 years, Prof. Arnon Cohen served as a consultant, advisor or speaker to Abbvie, Dexcel pharma, Janssen, Novartis, Perrigo, Pfizer, and Rafa.

Howard Amital received research grants from Pfizer, Abbvie, Yansen. Other relationships: In the last 3 years, Howard Amital served as a consultant, advisor or speaker to Abbvie, Yansen, Novartis, Perrigo, Pfizer, MSD, Neopharm and Sanofi.

All other authors have no conflicts of interest to disclose.

All authors had access to the data and played a role in writing this manuscript.

Funding

None.

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