Characteristics of sarcoidosis-associated pulmonary hypertension at the National Pulmonary Hypertension Unit


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Abstract

Aim
There is a paucity of data regarding the characteristics of sarcoidosis-associated pulmonary hypertension (SAPH) in Ireland and the aim of this retrospective cohort study was to address this knowledge gap. Patients diagnosed with SAPH at the National Pulmonary Hypertension Unit between January 2010 and December 2020 were included for further analysis.

Methods
Nineteen patients were diagnosed during the study period. This translates to an estimated annual incidence of 0.36 per million population and a calculated prevalence of 2.98 per million population in 2020. There was a male preponderance (68%, n=13) and the mean age at diagnosis was 54 (±12) years.

Results
The interval between sarcoidosis diagnosis and subsequent SAPH being identified was 15 (±15) years. There was evidence of interstitial lung disease in 16 (84%) and fibrosing mediastinitis in 5 (26%). PH specific therapy was prescribed in 14 (74%) and sarcoid directed therapy in 13 (68%) in the first 12 months following diagnosis. One patient underwent pulmonary artery stent insertion and a further patient underwent double lung transplantation during the study period. The cumulative survival at one- and five- years was 84% and 67% from the time of SAPH diagnosis.

Discussion
This study highlights the characteristics of SAPH in Ireland and underscores the importance of clinical phenotyping to guide complex treatment decisions.
Introduction

Sarcoidosis is a multisystem granulomatous disease of unclear aetiology. Sarcoidosis-associated pulmonary hypertension (SAPH) is defined by co-existent sarcoidosis and pulmonary hypertension (PH) and is associated with considerable morbidity and mortality. The prevalence of SAPH is incompletely defined, and may effect between 5.7% and 28.3% of patients with sarcoidosis.

A diagnosis of sarcoid is typically one of exclusion, usually requiring radiology (CT), clinical correlation and a biopsy confirming non-caseating granulomas. Moreover, a diagnosis of SAPH can be suggested by clinical features including a loud pulmonary component of the second heart sound or signs of right heart failure. Radiology may reveal a main pulmonary artery (PA) to thoracic aorta ratio greater than one and pulmonary function tests can show disproportionate reductions in diffusion capacity for carbon monoxide (DLCO). Echocardiography remains the screening tool of choice, though MRI and PET-CT have evolving roles in the field. A definitive diagnosis of PH requires right heart catheterisation (RHC) and demonstration of a mean pulmonary artery pressure (mPAP) greater than 20mmHg. SAPH typically seen presents in prevalent patients with more advanced pulmonary sarcoidosis.

Patients with SAPH are assigned to World Health Organisation (WHO) group 5 PH classification to reflect the multifaceted nature of this disease. However, it is essential to carefully phenotype these cases, as diverse SAPH phenotypes have been described. These include a primary pulmonary arterial vasculopathy, driven by granulomatous inflammation, that mimics the characteristics and trajectory of idiopathic pulmonary arterial hypertension (IPAH). Patients with sarcoidosis can also have cardiac involvement resulting in a group 2 PH phenotype. However, the most common cause of PH in sarcoidosis is related to interstitial lung disease (ILD) resulting in a group 3 phenotype. Furthermore, patients with sarcoidosis associated fibrosing mediastinitis can present with PH due to extrinsic compression of pulmonary vessels. Therefore treatment of SAPH is guided by the clinical phenotype and includes various combinations of sarcoid directed immunosuppressive therapy, PH specific therapy, pulmonary arterial stents, optimisation of comorbidities and ultimately may require lung transplantation.

There is a paucity of data regarding SAPH internationally and the aim of this retrospective study was to characterise SAPH seen at the National Pulmonary Hypertension Unit in Ireland.

Methods

This retrospective cohort study received ethical approval from the institutional ethical review board (IRB:1/378/2176TMR). Patients referred to the National Pulmonary Hypertension Unit (NPHU) between January 2010 and December 2020 were assessed for a diagnosis of SAPH using the hospital electronic database (PatientCentre). Data regarding patients with SAPH were fully anonymised and
included for further analysis. Confirmed cases of SAPH required RHC and a mPAP threshold greater than 20mmHg was chosen to define PH. Data regarding patient characteristics, treatment within 12 months of SAPH diagnosis and cumulative survival were collected retrospectively. The estimated incidence and calculated prevalence of SAPH were calculated using population estimates provided by the central statistics office for the Republic of Ireland. 6

Statistical analysis was performed using GraphPad online statistical software. Continuous variables were expressed as mean ± standard deviation and categorical variables as n (%). Survival estimates were made using the Kaplan-Meier method.

Results

Study population

Nineteen patients were diagnosed with SAPH during the study period and were included in the final analysis. This translated to an estimated annual incidence of SAPH of 0.36 per million population and calculated prevalence of 2.98 per million population in 2020.

Sixty eight percent (n=13) of this cohort were male and the mean age at SAPH diagnosis was 54 (±12) years. All patients reported dyspnoea at diagnosis, 53% (n=10) had evidence of right heart failure and 74% (n=14) reported New York Heart Association (NYHA) functional class (FC) III symptoms.

The mean interval between sarcoidosis and subsequent SAPH diagnosis was 15 (±15) years. The mean 6-minute walk distance (6MWD) was 312 (±82) meters and b-type natriuretic peptide (BNP) was 266ng/L (± 419). There was evidence of left heart disease on echocardiography or heart catheterisation in 21% (n=4) in keeping with a group 2 phenotype. Baseline investigations are highlighted in Table 1.

At RHC mPAP was 39mmHg (±12), pulmonary vascular resistance (PVR) was 6.9 Wood Units (±5.2) and pulmonary artery wedge pressure (PAWP) was 12.5mmHg (±7). The diagnosis of sarcoidosis was biopsy proven in 69% (n=13) of cases. There was evidence of interstitial lung disease in 84% (n=16) and fibrosing mediastinitis in 26% (n=5). The mean forced vital capacity (FVC) was 71% (±24) of predicted values and the mean DLCO was 38% (±16). All patients were classified as group 5 PH.

Treatment

Treatment consisted of combinations of supplemental oxygen therapy, sarcoid and PH specific therapy, pulmonary artery stenting and double lung transplantation. Regarding sarcoid therapy, 68% (n=13) were prescribed oral corticosteroid at the time of SAPH diagnosis and 3 of these were
also receiving steroid sparing agents. PH specific therapy was prescribed in 74% (n=14) in the first 12 months following SAPH diagnosis and consisted of monotherapy in 53% (n=10) and double combination therapy in 21% (n=4). Those prescribed double combination therapy (21%, n=4) were in the latter years of the study (2017-2020). One patient underwent pulmonary artery (PA) stenting to manage extrinsic PA compression from fibrosing mediastinitis. Additional treatment characteristics are highlighted in Table 2.

**Survival**

Cumulative survival in the entire cohort at one- and five- years was 84% and 67% from the date of SAPH diagnosis. This is illustrated in Figure 1.

**Table 1.**

<table>
<thead>
<tr>
<th>Patient Characteristics</th>
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<tbody>
<tr>
<td><strong>Sex, n (%): Male</strong></td>
<td>13 (68)</td>
</tr>
<tr>
<td><strong>Age (years), mean ± SD: at PH diagnosis</strong></td>
<td>54 ±12</td>
</tr>
<tr>
<td><strong>Non caseating granulomas on biopsy, n (%)</strong></td>
<td>13 (68)</td>
</tr>
<tr>
<td><strong>Supplemental oxygen therapy at SAPH diagnosis, n (%)</strong></td>
<td>10 (53)</td>
</tr>
<tr>
<td><strong>Smoking history &amp; pack years</strong></td>
<td></td>
</tr>
<tr>
<td>% Current smoker/ Ex-smoker/ Non-smoker</td>
<td>6/50/44</td>
</tr>
<tr>
<td>Pack years, mean ± SD</td>
<td>20±7</td>
</tr>
<tr>
<td><strong>Time (years) between sarcoid diagnosis and PH diagnosis, mean ± SD</strong></td>
<td>15.33 ±14.75</td>
</tr>
<tr>
<td><strong>Serum adjusted calcium (mmol/l), mean ± SD</strong></td>
<td>2.38 ±0.11</td>
</tr>
<tr>
<td><strong>BNP (ng/L), mean ± SD</strong></td>
<td>266 ±419</td>
</tr>
<tr>
<td><strong>6MWD (metres), mean ± SD</strong></td>
<td>312 (±82)</td>
</tr>
<tr>
<td><strong>WHO functional class (FC), % I/II/III/IV</strong></td>
<td>0/21/74/5</td>
</tr>
<tr>
<td><strong>Risk stratification (ESC/ERS), % Low/ Intermediate/ High risk</strong></td>
<td>5/63/32</td>
</tr>
<tr>
<td><strong>CXR Scadding Stage % 0/1/2/3/4</strong></td>
<td>6/0/6/6/82</td>
</tr>
<tr>
<td><strong>RHC</strong></td>
<td></td>
</tr>
<tr>
<td>mRAP (mmHg)</td>
<td>6.7± 5.8</td>
</tr>
<tr>
<td>mPAP (mmHg)</td>
<td>39±12</td>
</tr>
<tr>
<td>PAWP (mmHg)</td>
<td>12.5±7</td>
</tr>
<tr>
<td>CO (L/min)</td>
<td>4.9±1.5</td>
</tr>
<tr>
<td>PVR (WU)</td>
<td>6.9±5.2</td>
</tr>
<tr>
<td>PA saturation (%)</td>
<td>70±6</td>
</tr>
<tr>
<td><strong>PFT</strong></td>
<td></td>
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<tr>
<td>FVC predicted (%)</td>
<td>71±24</td>
</tr>
<tr>
<td>FEV1 predicted (%)</td>
<td>50±18</td>
</tr>
</tbody>
</table>
Table 1: mRAP: mean right atrial pressure; mPAP: mean pulmonary artery pressure; PAWP: pulmonary artery wedge pressure; CO: cardiac output; PVR: pulmonary vascular resistance; PA saturations: pulmonary artery saturation; RVSP: right ventricular systolic pressure; RAP: right atrial pressure; TAPSE: tricuspid annular plane systolic excursion; FVC: forced vital capacity; FEV1: forced expiratory volume in 1 second; DLCO: diffusing capacity for carbon monoxide; CT: computed tomography

Note: data from some variables were incomplete. Data regarding smoking history was available in 94% (n=18); pack years in 50% (n=5); year of sarcoid diagnosis in 94% (n=18); time between sarcoid and PH diagnosis in 89% (n=17); age at diagnoses in 94% (n=18); duration of symptoms prior to sarcoid diagnosis in 37% (n=7) and PH diagnosis in 42% (n=8); duration of sarcoid diagnosis in 94% (n=18); 6MWD in 37% (n=7); evidence of RHF in 94% (n=18); evidence of ILD 94% (n=18); BNP was available in 94% (n=18); serum calcium in 84% (n=16); mRAP in 63% (n=12); mPAP in 94% (n=18); PAWP in 57% (n=11); CO in 63% (n=12); PVR in 53% (n=10); PA saturation in 32% (n=6); RVSP + RAP in 57% (n=11); RA area in 63% (n=12); RV size in 68% (n=13); LV size in 63% (n=12); EF in 68% (n=13); FVC pred. in 79% (n=15); FEV1 pred. in 79% (n=15); FEV1/FVC in 68% (n=13); DLCO pred. in 74% (n=14); scadding stage in 84% (n=16); CT in 89% (n=17); PA compression in 53% (n=10).

Table 2.

<table>
<thead>
<tr>
<th>Treatment</th>
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<tbody>
<tr>
<td>Supplemental oxygen therapy at SAPH diagnosis, n (%)</td>
<td>10 (53)</td>
</tr>
<tr>
<td>Sarcoid targeted therapy, n (%):</td>
<td>13 (68)</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>10 (53)</td>
</tr>
<tr>
<td>Corticosteroids + Methotrexate</td>
<td>1 (5)</td>
</tr>
<tr>
<td>Corticosteroids + Adalimumab</td>
<td>1 (5)</td>
</tr>
<tr>
<td>Corticosteroids + Hydroxychloroquine</td>
<td>1 (5)</td>
</tr>
</tbody>
</table>
PH Therapy, n (%): | 14 (74)
---|---
**Single Agent Therapy** | 10 (53)
PDE5i/sGC | 8 (42)
ERA | 2 (11)
PGI2 | 0 (0)
**Double Combination Therapy** | 4 (21)
PDE5i + ERA | 3 (16)
PDE5i + PGI2 | 1 (5)
**Triple combination Therapy** | 0 (0)
PA stent, n (%) | 1 (5)
Lung Transplant | 1 (5)

Table 2. PDE5i (phosphodiesterase type 5 inhibitor), sGC (soluble guanylate cyclase) ERA (endothelin receptor antagonists); PGI2 (prostacyclin); PA: Pulmonary Artery

Discussion

Sarcoidosis is a multisystem granulomatous disease of uncertain aetiology, that can also involve the pulmonary circulation. SAPH is typically assigned to WHO group 5 PH, reflecting its heterogeneous nature. Internationally, there are a limited number of registries describing the characteristics of SAPH.1 This is the first study characterising SAPH in the National Pulmonary Hypertension Unit, Ireland. In our cohort, SAPH was typically diagnosed in patients with established sarcoidosis, with an average disease duration of 15 years, similar to the published experience of the French Reference Centre for Severe Pulmonary Hypertension.4 There was a male preponderance and the mean age at diagnosis was 54 years. Furthermore, 84% (n=16) had established ILD on imaging. These characteristics are consistent with published reports.4

In the Republic of Ireland, the prevalence of sarcoidosis is estimated to be as high as 850 per million population, one of the highest worldwide.7 In this study period, the calculated incidence and prevalence of SAPH in the Republic of Ireland were 0.36 and 2.98 per million population respectively. This suggests that SAPH effects only 0.35% of all patients with sarcoidosis in the Republic of Ireland. While the epidemiology of SAPH is incompletely defined, it is estimated to effect between 5.7 and 28.3% of all patients with sarcoidosis.1 However, patients with sarcoidosis and PH are not automatically referred to the National PH Unit unless there is the possibility of medical or surgical intervention and this very likely explains the observed low incidence and prevalence.

Formal recommendations to guide the screening of patients with sarcoidosis for PH are currently lacking and the diagnosis can be delayed. 4 5 The World Association for Sarcoidosis and Other Granulomatous Diseases (WASOG) committee summarised current SAPH related knowledge but fall short of making formal guidelines to support clinical practice. 5 SAPH can be an incidental finding,
suggested by radiological evidence of PA dilatation or unexplained reductions in DLCO. Notably, the
DLCO was markedly reduced in all patients with SAPH in our cohort, with a mean value of 38%. This
underscores the clinical utility of DLCO as a biomarker, as significant reductions should alert
clinicians to the possibility of SAPH, even in the absence of established parenchymal lung disease.
Echocardiography is advised to screen for the disease and may be prompted by clinical features such
as a high BNP, a worsening of New York Heart Association-FC (without modification of FVC), a 6MWD
<300m and/or desaturation >5% or the above radiological or PFT findings. Cardiac MRI is
increasingly employed with late gadolinium-enhanced (LGE) cardiac MRI having increased sensitivity
for detecting cardiac sarcoid with LGE often in the basal septum wall and subepicardial layer. Overall, right heart catheterisation remains the gold standard to confirm the diagnosis of SAPH and
assess the haemodynamic features. Positron emission tomography (PET) has an evolving role in the
management of these cases, as increased mediastinal node avidity may suggest a role for
augmenting immunosuppressive therapy.

It is important to carefully phenotype these cases, as treatment varies depending on the clinical
characteristics. Patients with SAPH can present with a progressive pulmonary vasculopathy that
mimics WHO group 1 pulmonary arterial hypertension (PAH) and can benefit from pulmonary
vasodilator therapy. It may also present as WHO group 3 PH, driven by hypoxia and interstitial lung
disease (ILD) requiring supplemental oxygen and consideration of immunosuppressive therapy.
The recently published INCREASE trial has demonstrated evidence for the role of inhaled pulmonary
vasodilators in these cases, which preferentially vasodilate well ventilated lung tissue. Another
phenotype includes patients with sarcoidosis-associated fibrosing mediastinitis. In these cases PH
is caused by extrinsic compression of PAs by calcified lymphadenopathy and mediastinal fibrosis,
and may benefit from mechanical intervention such as pulmonary angioplasty and stent insertion.
Diverse SAPH phenotypes were identified in our cohort in keeping with the heterogeneity of
sarcoidosis. These often displayed overlapping features from different WHO PH groups. In our
cohort, PH specific therapy was prescribed in 74% (n=14) in the first 12 months following SAPH
diagnosis and one patient with mediastinal fibrosis underwent PA stent insertion.

The clinical characteristics, treatment and survival of our patient cohort mirrors that of international
experience. The one and five year cumulative survival of our entire cohort was 84% and 67%
respectively from the time of SAPH diagnosis. The one, three and five year cumulative survival for
SAPH in the French Pulmonary Hypertension Registry was 93%, 74% and 55%, respectively.

There are a few important limitations to this study. Firstly, not all patients with SAPH are referred
to the NPHU. Referrals to the Unit are more commonly WHO group 1 and group 4 for consideration
of PH targeted therapy rather than patients with parenchymal lung disease or left heart disease.
Moreover, the definitions for PH at the 6th World Symposium, to include patients with mPAP of 20-
24mmHg, were updated in 2019 and patients who fit this criteria were not referred before this
period. Therefore, it is likely that these figures significantly underestimate the prevalence of SAPH
in Ireland. Further limitations include missing data and the retrospective, observational nature of this study. Nevertheless we highlight important aspects of SAPH in Ireland, including the importance of phenotyping these complex cases.

This study provides insight into the characteristics of SAPH in Ireland and underscores the importance of a national registry to improve our understanding of the disease and further studies to guide sarcoid specific diagnostic and treatment algorithms, to aid the identification and management of these cases.

Figure 1
Kaplan-Meier curve, highlighting the cumulative survival of patients diagnosed with SAPH between 2010 and 2020.

Declarations of Conflicts of Interest:
None declared.

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