LETTER

Evidence for association between sarcoidosis and pulmonary embolism from 35-year record linkage study

In the last year, we have observed large pulmonary embolisms (PEs) in four of 85 patients that attended the Oxford Sarcoidosis Clinic. In addition, we note a few case reports of PEs and unprovoked thrombotic events in patients with sarcoidosis (only one referenced here), leading us to question if, compared with normal populations, patients with sarcoidosis have a higher risk of developing PE.

To explore this possibility, we performed a retrospective cohort analysis using data from the well-established Oxford Record Linkage Study. This is a database of statistical records, spanning 35 years, of all hospital admissions (including day cases) to National Health Service (NHS) hospitals, and all deaths, regardless of where they occurred, in defined populations within the former Oxfordshire NHS region. The database and methods used for studying disease associations have been described and can also be found in the Supplementary data. The sarcoidosis cohort was assembled by identifying admissions during the study period where sarcoidosis was recorded as the principal diagnostic reason for admission. The reference cohort comprised patients admitted for the first time for various medical and surgical conditions as the principal diagnostic reason for admission and who presented with PE or other CVDs within a year of the index admission. We also re-analysed the data excluding patients who presented with PE or other CVDs within a year of the index admission to reduce any surveillance bias (see Supplementary data).

Within these cohorts, we searched the database for any subsequent NHS hospital care for, or death from, (1) PE and (2) other cardiovascular disorders (CVDs) (see table 1). In subset analyses, we applied an age restriction of 65 for the sarcoidosis and reference cohort to minimise confounding co-morbidities. We also re-analysed the data excluding patients who presented with PE or other CVDs within a year of the index admission to reduce any surveillance bias (see Supplementary data).

Rate ratios were calculated, comparing rates of PE or other CVDs in the sarcoid cohort with rates in the reference cohort. We also re-analysed the data excluding patients who presented with PE or other CVDs within a year of the index admission to reduce any surveillance bias (see Supplementary data).

The risk of PE was significantly higher in sarcoidosis patients (rate ratio 2.0, 95% CIs 1.1 to 3.4, for the under 65 year olds, table 1). We also found an increased risk of heart failure but the risk of other CVDs was not significantly increased. A similar profile was found after excluding cases of CVD and PE in the first year, and where no age restrictions were applied (see table 1).

Our observation comes from a well-established epidemiological data set comprising large numbers collected over a long period of time (1963–1998), in a defined population. The data set was collected by a team trained in the coding of clinical data. The population is stable, with respect to migration, forming a homogenous cohort, and has a standardised mortality ratio of 85, indicating a relatively healthy population. One limitation is the lack of scope for validation. We know little about the patients other than their International Classification of Diseases (ICD) codes (eg, sarcoidosis, PE). We have no data on diagnostic criteria, or potential confounding factors—for example, corticosteroid treatment for sarcoidosis, smoking status and other risk factors for thrombosis. In addition, these are hospitalised patients, and many sarcoidosis patients are not admitted even when the disease is active. One caveat is that this probably was not always the case, particularly early on during the cohort period when patients may have been admitted for Kveim testing.

Our data show that the incidence of heart failure was also higher than expected in the sarcoidosis group. It is known that as many as 25% of patients with sarcoidosis have cardiac involvement in which sudden cardiac death and congestive cardiac failure are features. It may be that in the cohort of patients with disease severe enough to require admission there is a greater degree of systemic involvement, in which cardiac manifestations are present.

The cause for this potential increase in risk of PE is speculative, but could include use of corticosteroids, hitherto unrecognized presence of procoagulant factors (macrophages and activated leucocytes are known to increase activation of thrombin and fibrin formation) and co-existence of sarcoidosis and antiphospholipid syndrome. Anti-phospholipid antibodies occur in 2–5% of the general population, but in up to 38% patients with sarcoidosis, correlating with poorer prognosis.

Overall, our findings would be viewed as hypothesis generating, providing a platform for further study, and supportive of the anecdotal observations made in our Sarcoidosis Clinic. Despite the limitations discussed above, PE should be considered in patients with sarcoidosis when there is sudden deterioration in dyspnoea.

Table 1 Occurrence of PE compared with other cardiovascular events in patients admitted to hospital with sarcoidosis, compared with a reference cohort

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Expected</th>
<th>RR</th>
<th>Lower CI</th>
<th>Upper CI</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All ages</td>
<td>2.00</td>
<td>2.70</td>
<td>0.75</td>
<td>0.09</td>
<td>2.72</td>
</tr>
<tr>
<td>AAA</td>
<td>44.00</td>
<td>37.80</td>
<td>1.00</td>
<td>0.73</td>
<td>1.35</td>
</tr>
<tr>
<td>Heart Failure</td>
<td>21.00</td>
<td>11.80</td>
<td>1.78</td>
<td>1.10</td>
<td>2.72</td>
</tr>
<tr>
<td>MI</td>
<td>33.00</td>
<td>28.60</td>
<td>1.15</td>
<td>0.79</td>
<td>1.62</td>
</tr>
<tr>
<td>PE</td>
<td>14.00</td>
<td>7.30</td>
<td>1.92</td>
<td>1.05</td>
<td>3.23</td>
</tr>
<tr>
<td>DVT</td>
<td>5.00</td>
<td>5.00</td>
<td>1.00</td>
<td>0.32</td>
<td>2.34</td>
</tr>
<tr>
<td>All ages excluding SAH</td>
<td>21.00</td>
<td>18.30</td>
<td>1.15</td>
<td>0.71</td>
<td>1.76</td>
</tr>
<tr>
<td>SAH</td>
<td>2.00</td>
<td>2.20</td>
<td>0.91</td>
<td>0.11</td>
<td>3.31</td>
</tr>
<tr>
<td>Under 65 years</td>
<td>2.00</td>
<td>2.60</td>
<td>0.78</td>
<td>0.09</td>
<td>2.82</td>
</tr>
<tr>
<td>AAA</td>
<td>36.00</td>
<td>37.80</td>
<td>0.95</td>
<td>0.67</td>
<td>1.32</td>
</tr>
<tr>
<td>Heart Failure</td>
<td>18.00</td>
<td>8.20</td>
<td>2.22</td>
<td>1.31</td>
<td>3.51</td>
</tr>
<tr>
<td>MI</td>
<td>25.00</td>
<td>23.90</td>
<td>1.04</td>
<td>0.68</td>
<td>1.54</td>
</tr>
<tr>
<td>PE</td>
<td>13.00</td>
<td>6.60</td>
<td>1.98</td>
<td>1.05</td>
<td>3.39</td>
</tr>
<tr>
<td>DVT</td>
<td>5.00</td>
<td>4.10</td>
<td>1.23</td>
<td>0.40</td>
<td>2.88</td>
</tr>
<tr>
<td>Heart Failure</td>
<td>17.00</td>
<td>12.60</td>
<td>1.35</td>
<td>0.79</td>
<td>2.17</td>
</tr>
<tr>
<td>SAH</td>
<td>2.00</td>
<td>2.00</td>
<td>1.02</td>
<td>0.12</td>
<td>3.72</td>
</tr>
</tbody>
</table>

Patients in the reference cohort were drawn from a group who were admitted to hospital with squint, otitis media, haemorrhoids, deflected septum, nasal polyps, impacted tooth, ingrowing toenail, bunions, sebaceous cyst, superficial injury and appendicectomy. AAA, abdominal aortic aneurysm; CHD, coronary heart disease; DVT, deep vein thrombosis; PE, pulmonary embolism; RR, rate ratio; SAH, subarachnoid haemorrhage.

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A P Crawshaw,1,2 C J Wotton,3 D G R Yeates,3 M J Goldacre,2 L-P Ho1,2
1Oxford Sarcoidosis Clinic, Oxford Centre for Respiratory Medicine, Oxford Radcliffe Hospitals NHS Trust, UK; 2MRC Human Immunology Unit, Weatherall Institute of Molecular Medicine, Oxford; 3Unit of Health-Care Epidemiology, Department of Public Health, University of Oxford, UK

Correspondence to Dr Ling-Pei Ho, MRC Human Immunology Unit, Weatherall Institute of Molecular Medicine, Oxford OX3 9DS, UK; ling-pei.ho@imm.ox.ac.uk

Additional data are published online only. To view these files please visit the journal online (http://thorax.bmj.com).

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Competing interests None.

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Provenance and peer review Not commissioned; externally peer reviewed.

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