Familial sarcoidosis in Finland and Hokkaido, Japan – a comparative study

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Two or more cases of sarcoidosis in one family is not unusual. To compare the frequencies of familial sarcoidosis in Finland and Hokkaido, Japan, and to analyse the type of associations reported, we collected data on all patients visiting hospitals for sarcoidosis in 1984 in Finland (1378 patients) and Hokkaido (208 patients), including information about familial sarcoidosis. We also analysed the familial cases seen among 571 sarcoidosis patients diagnosed at the Mjölbolsta hospital in Finland from 1955 to 1987 and among 686 Japanese patients seen in Sapporo from 1964 to 1988.

In 1984, 50 sarcoidosis patients visiting Finnish hospitals and nine sarcoidosis patients in Hokkaido reported as familial cases. Of the sarcoidosis patients seen in Finland at the Mjolbolsta hospital in 1955–1987, 27 had a family member with the same disease, while this number was 20 in the Sapporo hospital in 1964–1988.

Those surveys give a prevalence of familial sarcoidosis in Finland of 3.6–4.7% and in Hokkaido of 2.9–4.3%.

Among familial cases, the dominating relationships were sister–brother and mother–child relationships.

Introduction

Sarcoidosis is a multiorgan disease with a widely varying clinical picture and unknown aetiology. Both environmental and hereditary factors have been proposed to be involved in the pathogenesis of the disease.

The first report on a possible hereditary background of sarcoidosis was published more than 70 years ago (1). Since then, several studies on familial sarcoidosis have been published and more than 300 familial sarcoidosis cases have been reported (2–5). Brennan et al. reported an Irish population comprising 114 sarcoidosis patients with a sibling pool of 534 individuals. Twenty-four siblings from 11 families were identified as having sarcoidosis, providing a prevalence of familial sarcoidosis of 9.6% (6). A similar prevalence was reported by Buck and McKusick (7). In Germany, Jörgensen surveyed 2471 sarcoidosis cases and found 40 families with two or more family members with sarcoidosis, indicating a prevalence of familial sarcoidosis of 2% (5). Wiman, in Sweden, studied 299 sarcoidosis patients and found 20 with familial occurrence, indicating a prevalence of familial sarcoidosis of 6.9% (8). These family sarcoidosis studies seem to indicate that sarcoidosis has a higher than expected occurrence in blood-relatives (6,7,9).

We have previously shown that the prevalence of sarcoidosis is lower in Japan than in Finland (five vs. 28 cases per 100 000 inhabitants) (10). Also the mode of presentation of sarcoidosis differs between Finland and Hokkaido. In Finland, sarcoidosis most often starts with lung symptoms or signs while early sarcoidosis in Hokkaido is frequently associated with ocular manifestations (11).

Earlier sarcoidosis studies from Finland include only a few reports on familial sarcoidosis. Elo (12) and Poukkula (13) performed epidemiological studies on sarcoidosis in two circumscribed areas of Finland. They reported a frequency of familial sarcoidosis ranging from 3.4 to 6%. Grönhagen-Riska et al. described the familial presentation of sarcoidosis and Crohn’s disease in Finland with an association to HLA B8 and DR3 (14). Selroos et al. reported a pair of identical twins with a prognostically similar sarcoidosis despite the fact that one of the twins had corticosteroid treatment during the disease and the other did not (15).

In Japan, several epidemiological studies have been performed but only a few have dealt with familial sarcoidosis. Kawabe et al. reported a mother-daughter pair with sarcoidosis with an interval of 9 years. The authors concluded that both inhaled contagious factors and hereditary disposition may conceivably constitute a cause of sarcoidosis (16). Ito et al. reported 16 familial sarcoidosis cases among 2700 sarcoidosis patients, giving a prevalence of familial...
sarcoidosis in Japan of 0.6% (17). Hiraga et al. reported a local outbreak in 1972–1976 of 16 sarcoidosis cases in northern Japan (Furano Basin, Hokkaido), including three cases belonging to three generations in a single family (18). The authors proposed that a genetic factor could be one of the reasons for such a local accumulation. A follow-up study in the area covering the period up to 1990 discovered three additional familial instances (sister–sister, mother–child, husband–wife) among a total of 40 cases (19).

Tachibana et al. reviewed sarcoidosis cases from four areas in Japan, Hokkaido, Nagoya, Osaka and Fukuoka, and presented 72 sarcoidosis families (20). A brother–sister relationship was observed in 44 families, parent–child in 18 and other connections in 10 families. In a later paper they added eight more families, including two pairs of identical twins (21).

The aim of the present study was to compare the frequency of familial sarcoidosis in Finland and Hokkaido and to analyse the type of associations reported.

### Material and Methods

Finland, a northern European country, and Hokkaido, the northernmost island of Japan, resemble each other in several ways. Both areas have a four-season climate with cold winter and cool summer seasons. The populations are approximately equal, with about 5 million inhabitants. Also, the frequency of pulmonary tuberculosis was similar at the end of the study period in question; 39 per 100 000 in Finland and 35 per 100 000 in Hokkaido in 1983.

### Patients

We analysed the familial sarcoidosis cases and the types of family relationships seen among patients diagnosed at Mjölbolsta Hospital in Finland in 1955–1987 and among Japanese patients seen at the Sapporo Hospital of the Hokkaido Railway Company in 1964–1988 (11). Mjölbolsta hospital is one of the central hospitals for pulmonary diseases in southern Finland and caters for a population of approximately 450 000. The collaborating Sapporo Hospital is the unit in Hokkaido with a special interest in sarcoidosis and where the vast majority of all sarcoidosis patients in Hokkaido have been diagnosed and followed-up. The diagnostic criteria of sarcoidosis have been described previously in detail (10,11). In brief they included: 1. a chest radiographic finding with bilateral hilar lymphadenopathy (BHL); Stage II = BHL + parenchymal infiltrates; Stage III = parenchymal infiltrates without lymphadenopathy.

<table>
<thead>
<tr>
<th>Familial</th>
<th>Non-familial</th>
<th>Familial</th>
<th>Non-familial</th>
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<tr>
<td>Families (n)</td>
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<td>20</td>
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<tr>
<td>Patients (n)</td>
<td>56</td>
<td>544</td>
<td>40</td>
</tr>
<tr>
<td>Female/male ratio</td>
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<td>1.5</td>
<td>1.4</td>
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<tr>
<td>Mean age (years)</td>
<td>39.5</td>
<td>41.6</td>
<td>35.9</td>
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<tr>
<td>Chest radiography*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage I</td>
<td>14</td>
<td>256</td>
<td>38</td>
</tr>
<tr>
<td>Stage II</td>
<td>9</td>
<td>216</td>
<td>1</td>
</tr>
<tr>
<td>Stage III</td>
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<td>64</td>
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</tr>
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<td>0</td>
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<tr>
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<td>26</td>
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</tr>
<tr>
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<td>138</td>
<td>1</td>
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<td>2</td>
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<td>24</td>
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</tr>
<tr>
<td>Heart</td>
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</tr>
<tr>
<td>Other</td>
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<td>52</td>
<td>0</td>
</tr>
</tbody>
</table>

*Stage I = bilateral hilar lymphadenopathy (BHL); Stage II = BHL + parenchymal infiltrates; Stage III = parenchymal infiltrates without lymphadenopathy.
about half of the patients were asymptomatic at presentation. In Finland the symptomatic patients most often had respiratory symptoms, whereas in Hokkaido eye problems were more common. After a follow-up of 5 years, patients with pulmonary sarcoidosis had a better prognosis in Hokkaido than in Finland (22).

STATISTICAL ANALYSIS

The familial and non-familial cases in Finland and Hokkaido were compared using the chi-squared test, the Mann–Whitney U-test and the student’s t-test.

Results

STUDY POPULATION

The nationwide surveys performed in 1984 identified 1378 sarcoidosis patients in Finland and 208 in Hokkaido, Japan.


FREQUENCY OF FAMILIAL SARCOIDOSIS

In 1984, 50 sarcoidosis patients out of 1378 presenting to Finnish hospitals reported as familial cases, giving a cross-sectional occurrence of familial sarcoidosis of 3.6%. In Hokkaido, nine patients out of 208 (4.3%) included in the nationwide sarcoidosis survey had family members with sarcoidosis.

Of 571 sarcoidosis patients seen at Mjölbolsta Hospital in Finland from 1955 to 1987, 27 had a family member with the same disease. This gave a longitudinal frequency of familial sarcoidosis of 4.7%. Of 686 sarcoidosis patients seen in Sapporo from 1964 to 1988, 20 had a family member with sarcoidosis (2.9%).

FAMILY RELATIONSHIPS

There were 13 sibling pairs and 12 parent–child pairs in the Finnish hospital series. The corresponding Hokkaido figures were nine and six, respectively. No father–child combination was seen in the Hokkaido series. No cousins were found in the Finnish series, but two cases involving cousins were found in Japan. Two cases involving nieces and nephews were found in the Finnish series and three in the Japanese. The different family relationships are shown in Table 2.

CLINICAL PICTURE AND PROGNOSIS

Within the two hospital series, the familial cases were compared statistically with the rest of the sarcoidosis cases.

The female–male ratio was 0.93 among the Finnish familial sarcoidosis cases, but in both the Finnish and Hokkaido non-familial and Hokkaido familial sarcoidosis cases the ratio was greater than one (Table 1).

The mean ages of the Finnish familial and non-familial sarcoidosis patients were around 40 years, whereas the Hokkaido patients were younger (Table 1). Six (22%) of the Finnish familial sarcoidosis patients seen in the hospital and 96 (18%) of the non-familial cases had erythema nodosum. In the Hokkaido series there were only three erythema nodosum cases, which all occurred in the non-familial group. Conversely, eye involvement was prevalent among the Hokkaido sarcoidosis patients, in eight familial (20%) and 336 non-familial cases (51%). The corresponding Finnish figures for eye involvement were one and 26, respectively (Table 1).

The familial cases in both areas had a slightly less favourable prognosis (normalization of chest radiography) during 5-year follow-up than the non-familial cases. No statistically significant differences were found between the familial and non-familial series in either area, but both the Hokkaido familial and non-familial sarcoidosis patients had a significantly better prognosis than the Finnish patients. The clearing rates of chest radiographs of the patients in the two hospital series are shown in Table 3.

Discussion

As shown in earlier studies, the pattern of sarcoidosis differs between Finland and Hokkaido (10,11). Nevertheless, it appears that familial sarcoidosis is equally frequent in these areas; 3–5% in the present study. This frequency is within the range usually reported for familial sarcoidosis in larger series of Caucasian patients (2,3,6,23). Epidemiological studies performed in Afro-Americans have shown higher prevalences both for sarcoidosis and for familial sarcoidosis.
An Afro-American has a higher risk of developing sarcoidosis than a Caucasian if one family member already has the disease (24).

In the present study sarcoidosis among siblings was the most frequent family relationship. This result has been reported in earlier studies (2,5,6). An interesting finding in the present study was that the sister–brother relationship was more frequent than sister–sister or brother–brother. This may be the result of a chance finding due to the small number of cases, especially as the larger Japanese series showed the sister–sister relationship to be equally as prevalent as the sister-brother (20). However, in a study performed in London, U.K. and Los Angeles, U.S.A., with a total number of 33 family related sarcoidosis patients, a sister–brother predominance within the sibling group was also found (3). Monozygotic twins have a higher risk for sarcoidosis than dizygotic (5). The present study did not include any twin pairs.

A parent–child relationship was the next most frequent relationship. Within that entity a mother–child relationship was much more frequent than a father–child relationship. The same has been shown in previous non-Japanese (2,3) as well as in Japanese (17,20) studies (2,3). In fact, no father–child combination was found in the actual Hokkaidoan series. In another study from Japan including data from Hokkaido 18 parent–child associations were identified, 17 of which were mother–child combinations (20).

That sarcoidosis could be a contagious disease was postulated in a case-control study of 96 sarcoidosis cases from Isle of Man (25). However, in the present study, as in earlier studies (26,27), the occurrence of a husband–wife relationship was rare (only one husband–wife pair in the Hokkaidoan series outside the actual study analysis), supporting a genetic factor predisposing for the disease rather than an environmental factor.

Different opinions exist about the type of inheritance. A recessive genetic background (23) or a multigenic mechanism (5,9) as aetiological causes of sarcoidosis have been suggested. The same conclusion was reached in a HLA-analysis in 18 siblings with sarcoidosis (28).

No association between HLA types and the development of sarcoidosis could be found in a study of 14 Caucasian families with more than one sarcoidosis case per family. However, the HLA type may have an influence on the clinical picture of sarcoidosis (29). In Japan, two monozygotic twin pairs, two brothers and a mother–son pair were found to have HLA DRw52 (20). The HLA type may thus influence the inheritance of sarcoidosis, as well as of Crohn’s disease, as described in one family where all sick family members had the haplotype alleles B8 and DR3 whereas the healthy members did not (14). Also, in a study comparing 73 HLA-typed sarcoidosis patients with a race-matched control group, the relative risk of sarcoidosis was increased in patients with HLA-DR5. This study also concluded that an infectious agent cannot produce the disease without a suitable genetic background (30).

In the present study, the clinical picture and prognosis were similar in familial cases and non-familial cases of sarcoidosis. No such comparisons have been made in previous studies.

Studies on familial sarcoidosis are important as its aetiology and mechanisms of inheritance are still not fully understood. Additional family studies on sarcoidosis combining HLA-typing and genetic mapping are warranted.

### References


