Sapporo Med. J. 61 (3) 167~174 (1992)

Sarcoidosis in Hokkaido and Finland

— Results of Comparative Studies —

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ABSTRACT **Two comparative Finnish-Japanese sarcoidosis studies were carried out. One study compared the frequencies of sarcoidosis in 1984 in Hokkaido and Finland. We found a significantly and approximately four times higher prevalence and incidence of sarcoidosis in Finland than in Hokkaido ; prevalence 28.2/100,000 in Finland and 7.2/100,000 in Hokkaido ; incidence 11.4/100,000 in Finland and 2.8/100,000 in Hokkaido, The other study compared the clinical picture and prognosis of sarcoidosis in two large hospital series ; 686 patients in Sapporo and 571 patients in Mjölbolsta, Finland. The sex ratio was the same with a slight female predominance in both hospitals. The Japanese patients were younger at the time of diagnosis (mean age 30 years in Sapporo compared with 42 years in Mjölbolsta), although 50% of the patients in both series had been detected via routine health screening procedures. Among the symptomatic patients the mode of presentation of the disease varied considerably with eye symptoms as the dominating in Sapporo, but with respiratory symptoms and Löfgren's syndrome in Finland. Stage I disease was more frequent in Sapporo, (57% of the patients compared with 48% in Finland) whereas more Finnish patients had parenchymal lesions. Extrapulmonary manifestations of sarcoidosis were more often diagnosed in Sapporo ; mainly because of the eye lesions. The prognosis of pulmonary sarcoidosis in Finland was significantly less favourable than the prognosis of the Japanese patients.**

(Received February 17, 1992 and accepted April 7, 1992)

Key werds : Incidence, Prevalence, Prognosis, Sarcoidosis

Introduction

Finland and Hokkaido resemble each other in several aspects. Both areas have a four season climate with cold winters and cool summers. There are approximately 5 million inhabitants in both places. The frequency of tuberculosis has been the same over the years ; in 1983 the incidence of tuberculosis in Finland was 39.2/100,000 and in Hokkaido 44.0/100,000.

In 1963 the prevalence of sarcoidosis was reported to be the same in Finland and Japan (5.1-5.6/100,000) but these figures were based on the detection of 8 cases in Finland and 11 in Japan[1]. Later reports, based on large number of patients, and presented at international conferences on sarcoidosis in Paris in 1966[2,3] and Tokyo in 1972[4,5] have indicated that the frequency of sarcoidosis in Finland is higher than in Japan. Within Japan the island of Hokkaido has reported a high prevalence of sarcoidosis compared with other areas[5-7]. Also a local outbreak of the disease has been seen in Furano on

the Hokkaido island[8]. There also seem to be differences in the clinical picture and prognosis of sarcoidosis in Finland and Japan[9,10].

In order to find out if the reported differences were true we decided to perform a series of comparative studies. The work started at the Department of Internal Medicine, Section 3, Sapporo Medical College, when one of us (OS) got the opportunity of visiting Sapporo for two months in 1989[11]. This became true as a result of the international exchange programme between Sapporo Medical College and the Paulo Foundation in Finland. A close collaboration was established with the Sapporo Hospital of the Hokkaido Railway Company and with members of the Japan Society of Sarcoidosis.

The frequency of sarcoidosis in Finland and Hokkaido

In 1984 a nation wide sarcoidosis study had been carried out in Japan[12]. From that survey we got the data of all Hokkaido patients (n=208). By using a similar questionaire we then in Finland performed the Finnish part of the study by evaluating all records of patients seen in Finnish hospitals in 1984 with a diagnosis of sarcoidosis. Out of 2,158 cases we found 1,378 Finnish patients who fulfilled the diagnostic criteria of sarcoidosis. The crude prevalence of sarcoidosis was then 28.2/100,000 in Finland

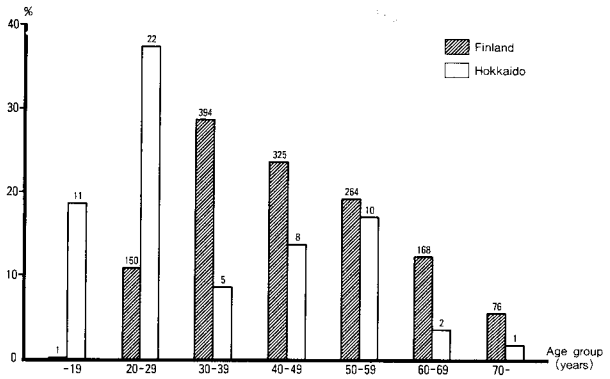

Fig. 1 Age distribution of sarcoidosis patients in Finland and Hokkaido in 1984.

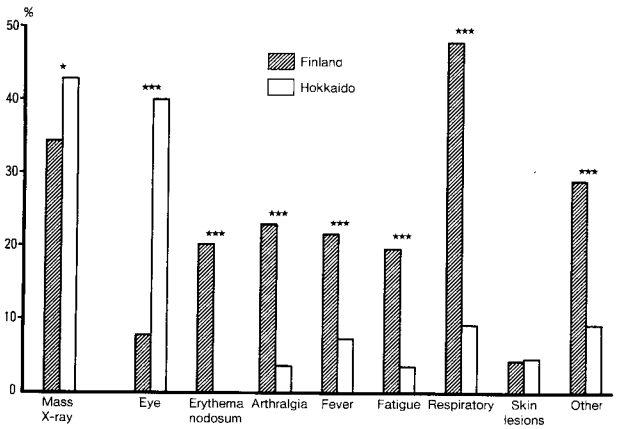

Fig. 2 Modes of presentation of sarcoidosis in Finland and Hokkaido in 1984 based on 1378 Finnish and 208 Japanese patients. The p-values for statistically significant differences are shown: *=$p<0.05$, ***=$p<0.001$.

and 3.7/100,000 in Hokkaido. Depending on different response rates from the hospitals the estimated prevalences were calculated to be the same in Finland (28.2/100,000) but 7.2/100,000 in Hokkaido. The annual incidence of new cases in 1984 was 11.4/100,000 in Finland and 1.0/100,000 in Hokkaido (estimated incidence 2.8/100,000).

There were more female than male patients in both series: 63% in Finland and 67% in Hokkaido. This difference is not statistically significant ($p=0.25$). The patients in Hokkaido were younger at the time of diagnosis: 40.2 ± 16.1 years (mean±SD) compared to 45.6 ± 13.7 years for the Finnish patients. This difference is statistically highly significant ($p<0.001$). The median ages were 38 and 44 years respectively. The age distribution within the two series is shown in Figure 1.

A substantial part of the patients had been detected via mass X-ray surveys: 43% in Hokkaido and 34% in Finland. Thus, symptomatic patients were significantly more frequent in Finland ($p<0.05$). The Finnish patients most frequently fall ill with respiratory symptoms such as dyspnoea, cough and chest pain, and with fever, joint pain and erythema nodosum. In Hokkaido eye symptoms were the most prevalent. The modes of presentation in the two series are shown in Figure 2.

At the time of diagnosis 82% of the Finnish and 84% of the Hokkaido patients had bilaterally enlarged hilar lymph nodes on their chest radiographs. Parenchymal shadows were more often seen in the Finnish patients (49%) than in the Hokkaido patients (25%), and the same was true of peripheral lymphadenopathy; 16% in Finland vs 8% in Hokkaido.

The clinical picture of sarcoidosis in Finland and Hokkaido

In order to compare sarcoidosis more in detail in Finland and Hokkaido we compared two large clinical series: the Hiraga collection in Hokkaido comprising 686 patients seen in 1964-1988 at the Sapporo Hospital of the Hokkaido Railway Company and the Mjölbolsta Hospital series in Finland including 571 patients seen in 1955-1987. The Hiraga collection represents approximately 50% of all sarcoidosis patients seen in Hokkaido during the period in question. The Mjölbolsta hospital in Finland diagnoses approximately 75% of all sarcoidosis patients within its area of southern Finland. Of the Finnish patients 58% were female, the corresponding Japanese figure being 55%. At the time of diagnosis the Japanese patients were 30.0 ± 15.4 (mean±SD) years old, whereas the Finnish patients were 41.5 ± 13.0 years old. This difference is statistically significant ($p<0.001$). 28% of the Japanese patients were smokers compared to only 16% in the Finnish series. This difference is also significant ($p<0.001$). In both hospital series half of the patients (50%) had been detected symptom-free at mass X-ray surveys or other routine examinations. Again the initial symptoms varied. In the Sapporo series 256 patients had eye symptoms (37%), followed by cough in 14 patients (2%) and fever in 10 patients (1.5%). The eye symptoms were thus the clearly dominating initial symptom and show the necessity of having an ophthalmologist included in the clinical staff. At Mjölbolsta hospital the following initial symptoms were registered: cough in 189 (33%), fever in 121 (21%), general malaise in 118 (21%), erythema nodosum in 103 (18%), dyspnoea in 102 (18%) and joint pain in 89 patients (16%). Only 27 patients had initial eye symptoms (5%). Thus sarcoidosis in Finland is more respiratory dominated and the syndrome with erythema nodosum-joint pain-fever is common whereas these are very rare initial symptoms in Japanese patients seen in Hokkaido. It is interesting to note that erythema nodosum did not appear at all as an initial symptom in this large Japanese series.

The chest X-rays taken at the time of diagnosis gave the following information as shown in Figure 3: bilaterally enlarged hilar lymph nodes (BHL) were found in 48% of the Finnish patients and in 57% of the Sapporo patients. This difference is statistically significant ($p<0.01$). Stage II lesions (BHL+ parenchymal lesions) were seen in 39% of the Finnish and in 20% of the Sapporo patients. Stage III

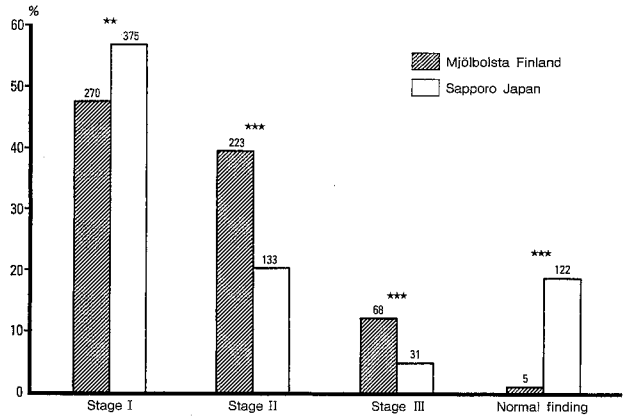

Fig. 3 Initial chest radiographic findings among 571 Finnish and 686 Japanese patients. The p-values for statistically significant differences are shown: **=$p<0.01$, ***=$p<0.001$.

change (parenchymal lesions without lymph node enlargement) were found in 12% in the Finnish patients and in 5% of the Sapporo patients. Also the differences in radiographic stages II and III are statistically significant ($p=0.0000$). Interestingly, at the time of diagnosis only 1% of the Finnish patients had a normal chest X-ray compared to 18.5% of the Japanese patients.
The last mentioned patients had only eye and/or skin lesions.

The most common extrapulmonary manifestations of sarcoidosis in Finland were peripheral lymphadenopathy in 25%, eye lesions in 7% and skin lesions in 5%. In Sapporo 50% of the patients had eye lesions, followed by skin lesions in 7% and suspected myocardial sarcoidosis in 5%.

Lung function tests showed more airway obstruction of the Japanese patients. As mentioned, they also smoked significantly more. No differences in diffusion capacity were found.

Table 1 *Family relationships within the two hospital series of sarcoidosis patients.*

	Mjölbolsta Finland	Sapporo Hokkaido
No of familial cases	27	21
In % of all cases	4.7%	3.1%
Siblings	13	9
Sister-sister	3	2
Brother-brother	1	2
Sister-brother	9	5
Mother-child	8	6
Mother-child-sister	1	
Father-child	2	
Father-child-grandchild	1	
Cousins		2
Nieces	1	2
Nephews	1	1
Husband-wife		1

Occurrence of familial sarcoidosis

Within the Hiraga and Mjölbolsta collections of sarcoidosis patients the occurrence of sarcoidosis in family members was also registered. In the Mjölbolsta series 27 familial cases out of 571 (4.7%) were found, the corresponding Sapporo figure being 21 cases out of 686 (3.1%). Of all possibilities sarcoidosis in siblings and in mother-child were the clearly dominating relationships in both series. Familial sarcoidosis therefore seems to occur in a similar way in the two regions. The family relationships are shown in the Table 1.

Within the two series findings among the familial cases were statistically compared with the rest of the series. No statistically significant differences were found when comparing modes of presentation, chest radiographic findings, organ involvement, biochemical activity markers at the time of diagnosis, need of corticosteroid therapy, course and prognosis.

The prognosis of sarcoidosis in Finland and Hokkaido

The clinical course of sarcoidosis was compared in patients followed-up for at least 5 years. The development is seen in Figure 4. The Japanese patients had a significantly better prognosis than the Finnish patients. At all yearly time points the differences are statistically significant. The Finnish patients with erythema nodosum had a prognosis almost as good as that of the Japanese patients from Hokkaido. However, after the first year of observation the difference in favour of the Japanese patients was significant ($p<0.001$).

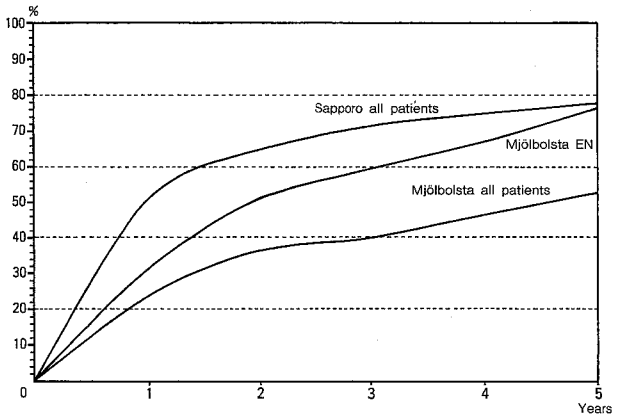

Fig. 4 Course of pulmonary sarcoidosis shown as complete clearing of chest radiographic findings. The patients in Sapporo had a significantly higher clearing rate at all time points compared with the Finnish patients of the Mjölbolsta Hospital.

Of patients with initial stage I disease (BHL) an abnormal chest X-ray was still seen in 23% of the 252 Finnish patients, and in 13% of the 336 Japanese patients. The Finnish figure is high, especially when considering that this series included the patients with Löfgren's syndrome (BHL+erythema nodosum) who have a very good prognosis with spontaneous complete recovery usually within one year[12]. 22% of the Finnish patients and 13% of the Japanese patients developed parenchymal lesions during the follow-up.

Of the patients with stage II-III lesions at the time of diagnosis 33% of the 268 Finnish patients and 24% of the Japanese patients had still an abnormal chest X-ray 5 years later.

Extrapulmonary lesions were initially diagnosed in 284 Finnish and in 589 Japanese patients. During the 5-year follow-up new extrapulmonary lesions were noted in 42 Finnish and 111 Japanese patients.

Thus pulmonary sarcoidosis seems to have a less favourable course in Finland than in Hokkaido, whereas extrapulmonary lesions are more frequent in Hokkaido than in Finland, but still not affecting unfavourably the outcome of the disease. Exceptions are the Japanese patients who develop myocardial or CNS-lesions during the follow-up. They seem to develop a chronic sarcoidosis with poor prognosis.

Discussion

These comparative studies of sarcoidosis in Finland and Hokkaido have been carried out by using identical techniques. They clearly show that there is a real difference in the frequency, and that sarcoidosis is a much more common disorder in Finland than in Hokkaido. Finland has usually been compared with Scandinavia, and it has been found that the occurrence of sarcoidosis in Finland is similar to that in Norway and Denmark, but less frequent than in Sweden[13]. However, a recent Finnish investigation showed very high figures (a mean prevalence of 102/100,000 for the period 1971-1980) for the south-western part of Finland[14]. The Finnish part of the actual frequency study showed a prevalence which was in between the earlier reported[9] and the most recent one[14]. Consequently, it seems appropriate to consider the Finnish prevalence figure of 28.2/100,000 accurate and not too high. Compared with all these Finnish figures the Japanese figures in general are significantly lower. Also Hokkaido, the Northern island of Japan with the same climate as Finland and with the same frequency of pulmonary tuberculosis, has a four times lower occurrence of sarcoidosis than Finland.

The clinical picture of sarcoidosis was very different in Finland and Hokkaido. In Finland acute sarcoidosis with erythema nodosum, arthralgia and fever is common, whereas this clinical picture is rare in Japan. It has earlier been found that Löfgren's syndrome, i. e., erythema nodosum with bilateral hilar lymphadenopathy is associated with the occurrence of the HLA type B 8[15]. This HLA type is very uncommon in Japan[16]. This could explain why the clinical expression of sarcoidosis with erythema nodosum is so different in the two areas in question.

Eye symptoms were very frequent in Hokkaido (50% of the patients had eye symptoms at some stage of their disease), and some patients have eye lesions as their only manifestation of sarcoidosis. The rare occurrence of eye lesions in the Finnish series (7%) was not due to insufficient examinations as almost all patients had been seen by an experienced ophthalmologist. However, another Finnish investigation in 281 sarcoidosis patients and performed by an ophthalmologist showed a frequency of eye lesions in 28% of her Finnish patients with conjunctival lesions as the most frequent (17%), followed by reduced lacrimal secretion (13%), uveitis (8%) and band keratopathy (4%)[17]. So also with these Finnish figures in mind eye sarcoidosis seems to be much more prevalent in Hokkaido.

In Hokkaido many patients (18.5%) had extrapulmonary sarcoidosis but without intrathoracic lesions as determined by a normal chest radiogram. This situation was rare in Finland; only 1% of the patients exhibited a normal chest picture. On the contrary, Finnish patients had more often not only enlarged hilar lymph nodes but also - and more importantly - pulmonary parenchymal lesions.

It is well known that sarcoidosis patients with pulmonary parenchymal lesions at the time of diagnosis have a poorer prognosis than patients with only stage I disease[4,9]. This could explain why the Finnish patients had a less favourable prognosis compared with the Japanese patients. However, a difference which must be kept in mind is that approximately 50% of the patients had been detected via mass screening procedures. These have been carried out every year in Japan but usually only every three years in Finland. As many patients are detected at a symptom-free stage it could well be that a substantial part of the Finnish patients have had their disease for two to three years before diagnosis.

At least a part of the patients with asymptomatic stage I disease and with a good prognosis have probably never been detected in Finland. This also means that the true frequency of sarcoidosis in Finland should be higher than that found in this study, and probably more close to the high figures reported from the south-western part of Finland[14].

Familial sarcoidosis has been reported in up to 10% of the patients[18]. In these series we found a lower but equal occurrence of familial cases. As in other series sarcoidosis in siblings and in mother-child were the dominating associations.

Comparative clinical investigations between countries are interesting and not only as art for the art's sake. They are important because the found differences may focus on factors involved in the pathogenesis of a disease, which still has an unknown aetiology.

Acknowledgement

The first author (Olof Selroos) wants to thank the Paulo Foundation in Finland and the Sapporo Medical College for the scholarship which made these studies possible. We are grateful to Östen Widjeskog, PhD, for performing the statistical analysis. The Finnish part of the studies has been supported by the Mjölbolsta Medical Research Foundation. The authors express their thanks to the Japan Society of Sarcoidosis, and especially to Momoko Yamaguchi, MD, and Yutaka Hosoda, MD, for their support and advice.

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北海道とフィンランドのサルコイドーシス

—比較研究の結果—

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フィンランドと日本のサルコイドーシスについて二つの比較研究を行った．ひとつは北海道とフィンランドの1984年における発生頻度と患者数の比較である．サルコイドーシスの発生頻度及び患者数は北海道よりもフィンランドで有意に約4倍多く，患者数はフィンランドでは人口10万対28.2，北海道では同じく7.2，また発生頻度はフィンランドでは人口10万対11.4に対して北海道では2.8であった。

もうひとつは札幌ＪＲ鉄道病院の686人とフィンランドのMjölbolsta病院の571人についてサルコイドーシスの臨床像と予後の比較を行った．男女比はほぼ等しく両病院ともやや女性が多かった．どちらの患者群でも50%の患者は定期検診で発見されているにも拘らず，札幌の患者の方が診断時の年齢は低かった（札幌では平均30歳に対してMjölbolsta病院では42歳）．症状のある患者での疾患の発現の様式は札幌では眼の症状が多いのに対して，フィンランドでは呼吸器症状とLofgren症候群が多く，著しく異なっていた．札幌ではＩ期が最も多かった（フィンランドの48%に対して札幌は57%）のに対してフィンランドの患者の方がより多く肺実質病変を伴っていた．肺外病変については札幌で主に眼病変が多く診断されているために頻度が高かった．肺サルコイドーシスの予後は札幌よりもフィンランドの方が有意に悪かった．