

Epidemiology of sarcoidosis in the Isle of Man—1: A case controlled study

STEPHANIE A PARKES, S B de C BAKER, R E BOURDILLON, C R H MURRAY,
M RAKSHIT*

From the Postgraduate Medical Centre, Noble's Hospital, Douglas, Isle of Man

ABSTRACT A case controlled study of 96 cases of sarcoidosis has been carried out in the Isle of Man. Age and sex matched controls were selected at random from the pathology and radiology records, which cover 85% of the resident population, and a second control group was drawn from a tuberculosis register. Special efforts were made to achieve a high level of ascertainment. In this study most cases occurred in young adults. It affected the sexes equally and occurred more frequently in the indigenous Manx population. Thirty eight cases (39.6%) had been in contact with the disease before diagnosis, compared with two (1.2%) of the combined controls. These contacts included members of the same household, colleagues at work, and close friends. A bias may have been introduced as patients would inevitably be more aware of the disease and be more likely to mention previous contact than the controls. Nevertheless, the evidence is considered to support the view that sarcoidosis is a communicable disease.

Case controlled studies offer the best hope of identifying the important factors contributing to the development of sarcoidosis,¹ but few have been undertaken. A recent review of reports published worldwide on the epidemiology of the disease² concludes that it is a disease affecting young adults; it occurs more commonly in the black population than in the comparable white community of the United States; it is more common in people living in rural areas; it occurs in family aggregations and there is probably a higher incidence in women than in men.

Two factors could account for the slow progress of the epidemiology of sarcoidosis. Firstly, the disease can affect almost any body system, so that cases are referred to a wide range of specialists; secondly, the disease may be subclinical or the symptoms so mild that even if medical advice is sought referral to a specialist clinic is unnecessary. Both of these factors produce serious under-recording of cases,³ which reduces the chance of finding a link between cases that might give a lead to the aetiology of the disease.

This paper describes the epidemiology of 96 cases

of sarcoidosis diagnosed from 1962 to 1983 in a clearly defined community well documented by a regular census. From 1977 to 1983 special efforts were made to improve the level of ascertainment, which were associated with an apparent fourfold increase in incidence.³

Methods

The cases of sarcoidosis are those diagnosed in the resident population of the Isle of Man from 1962 to 1983 inclusive. For cases occurring from 1962 to 1976, the records of inpatients and outpatients were searched. Since 1977 general practitioners have been requested to refer all cases of possible sarcoidosis to an appropriate consultant for verification. The cases are those previously reported in an incidence study, for which the diagnostic criteria and case collection methods have already been defined.³

THE ISLE OF MAN AND ITS POPULATION

The Isle of Man is about 50 × 18 km and is divided into 26 towns, village districts, and parish districts for the five yearly census⁴ and into four divisions (North, South, East, and West) for morbidity records. The population, 64 679 in 1981, is enumerated and classified by age, sex, country of birth, residence, and occupation. The Island has its own health service, which is run on similar lines to that in the UK, and

*Dr Rakshit died in January 1986.

Address for reprint requests: Dr SB de C Baker, Noble's Hospital, Douglas, Isle of Man.

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the standard of medical care is uniform throughout.

The indigenous Manx are of Celtic and Norse origin. In the last two decades there has been considerable immigration from the UK and ABO gene frequency differences have been detected during this period.⁵ In this study we have accepted those with a minimum of three grandparents born in the Isle of Man as being of Manx ancestry.

CONTROLS

For each case of sarcoidosis a general control of the same sex and age (within one year) was chosen by random numbers from the files of the pathology and radiology departments. These files contain cards, one for each person, with name, date of birth, and abbreviated records of some 70 000 people investigated since 1954; each card is updated with fresh results as they arise. Comparison with a random sample of the Island's health services register showed that 85% of the population are represented in the files. There are more names than there are residents, since it is not always possible to update the files for people leaving the Island permanently. Every effort was made to locate the first person chosen; failing this, the next suitable match was selected. The control group was compared with the census for place of birth, region of residence, social class, and occupation and no important differences were detected.

For each case of sarcoidosis a second control, matched for age (within four years) and sex was selected from the hospital tuberculosis register. No attempt was made to match the date of diagnosis of tuberculosis with the date of diagnosis of sarcoidosis in the matched pair. Fifteen people refused to be interviewed (seven general controls and eight tuberculosis controls). We could obtain only 68 suitably matched tuberculosis controls.

QUESTIONNAIRE

A questionnaire was designed to obtain data relating to a wide range of factors: medical and family history, occupation, recreational activities, social habits, and domestic circumstances. Each subject (or close relative in three cases) was visited in his or her own home by one of the authors (SAP) and the questionnaire completed by her during an interview lasting about two hours. Information was sought about a history of contact with various diseases, including tuberculosis, sarcoidosis, Crohn's disease, multiple sclerosis, and rheumatoid arthritis. Contacts were classified into the following categories: (1) occupying the same household for at least six months or visiting the household regularly as a member of the family; (2) working in the same building for at least six months, having regular contact during that time; (3) near neighbours having regular contact for at least six months; (4) regular

recreational meetings for at least six months; (5) long-standing close friends.

In the analysis of the control questionnaires "the time of diagnosis" was equated with that of the matched index case of sarcoidosis.

DISTRIBUTION OF RESIDENCES AT DIAGNOSIS

The distribution of the cases of sarcoidosis was compared with that of the controls. The housing density around each subject's residence was measured by counting the number of buildings in a circle of one hectare centred on the house on Ordnance Survey maps; 1:25 000 was used for rural areas and 1:1 250 for towns.

STATISTICS

The sarcoidosis and tuberculosis groups were separately compared with the controls and, where possible, the census population for various factors. These comparisons used the χ^2 test (with Yates's correction for 2×2 tables) for categorical variables and the Student's *t* test for comparisons of continuous variables with those in the controls and the census population.

Many statistical tests have been performed on these data, but no adjustment for the number of tests has been made and for this reason *p* values should be interpreted with caution.

Results

AGE AND SEX DISTRIBUTION

The male/female ratio of the sarcoidosis cases (1:1.18) was similar to that in the mean 1961–81 census population, corrected for age (1:1.08); 63.5% of cases occurred in the 20–39 age group which comprises 23% of the census population (fig 1). The mean age at diagnosis was 41.5 yrs for men and 38.6 yrs for women. There were two deaths (2.1%) attributable to sarcoidosis.

GEOGRAPHICAL DISTRIBUTION

The geographical distribution of sarcoidosis and the controls is shown in table 1. There was no detectable difference between the three groups. Comparison of the total number of cases occurring in the towns and village districts with those in the rural parishes showed no difference between the sarcoidosis group and the general controls, but tuberculosis occurred more frequently in urban areas ($\chi^2 = 4.27$, 1 df; $p < 0.05$)—see table 2.

HOUSING DENSITY

There was no apparent difference between the sarcoidosis group and the general controls in the density of housing, but more cases of tuberculosis came from

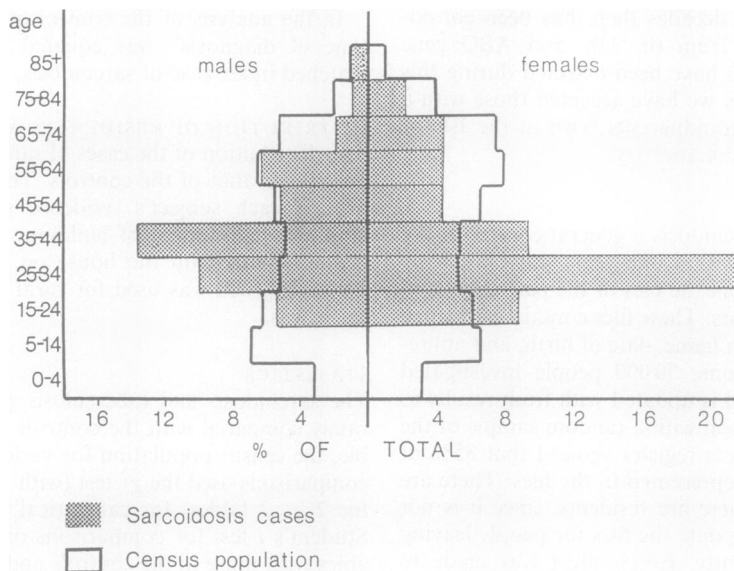


Fig 1 Age distribution of patients with sarcoidosis at diagnosis, compared with that of the Island census population (mean for 1961-81).

Table 1 Distribution of cases of sarcoidosis, general controls, and tuberculosis (TB) controls by the divisions of the Island at onset

| Division | Sarcoid (n = 91) No | Control (n = 90) No (expected) | TB control (n = 68) No (expected) | Census (n = 55 248*) |
|----------|------------------------|-----------------------------------|--------------------------------------|-------------------------|
| Western | 11 | 12 (9.9) | 5 (7.4) | 6 125 |
| Northern | 12 | 12 (14.0) | 7 (10.6) | 8 580 |
| Eastern | 52 | 50 (49.4) | 44 (37.3) | 30 311 |
| Southern | 16 | 16 (16.6) | 12 (12.6) | 10 232 |

*Mean population 1961-81.

Table 2 Distribution of residence at the time of diagnosis (numbers with percentages in parentheses)

| | Sarcoid (n = 96) | Control (n = 96) | TB control (n = 68) | Census (n = 55 248)* |
|------------------|---------------------|---------------------|------------------------|-------------------------|
| Parish districts | 30 (31.3) | 22 (22.9) | 7 (10.3) | 15 460 (28.0) |
| Towns, villages | 61 (63.5) | 68 (70.8) | 61 (89.7) | 39 788 (72.0) |
| Elsewhere | 5 (5.2) | 6 (6.3) | 0 (0.0) | 0 (0.0) |

*Mean population 1961-81.

Tuberculosis (TB) v control: $\chi^2 = 4.27, 1 \text{ df}; p < 0.05$.

crowded areas ($\chi^2 = 11.42$; 3 df; $p < 0.01$)—see table 3.

PLACE OF BIRTH AND ANCESTRY

A larger proportion of the sarcoidosis group than of either the controls ($p < 0.001$) or of the census population were born in the Isle of Man (table 4) and more of the sarcoidosis group were of Manx ancestry ($p < 0.025$) than could have been expected by chance. Everyone in this study who was of Manx ancestry was born in the Isle of Man. There was no apparent difference in the duration of residence on the Island between the patients with sarcoidosis and the controls not born on the Isle of Man (table 5).

OCCUPATIONS

The occupation categories of the economically active Manx residents listed in the census contained the expected number of cases of sarcoidosis and controls, with two exceptions: there were more nurses with sarcoidosis and more tuberculosis controls in unskilled occupations than expected ($p < 0.005$)—see table 6.

Table 3 *Housing density at diagnosis (numbers with percentages in parentheses)*

| No of houses/ hectare | Sarcoid (n = 96) | Control (n = 96) | TB control (n = 68) |
|--------------------------|---------------------|---------------------|------------------------|
| 1-10 | 33 (34.4) | 34 (35.4) | 11 (16.2) |
| 11-20 | 26 (27.1) | 25 (26.0) | 22 (32.4) |
| 21-30 | 30 (31.3) | 28 (29.2) | 19 (27.9) |
| 31+ | 7 (7.3) | 9 (9.4) | 16 (23.5) |

Tuberculosis (TB) v control: $\chi^2 = 11.42$, 3 df; $p < 0.01$.

CONTACT HISTORIES

Fifty four patients had been in contact with sarcoidosis. Of these, the contact was before the patient's diagnosis in 23 cases, after diagnosis in 15, and before and after in 15. Thus 38 patients had been in contact with sarcoidosis before their diagnosis (table 7). In contrast, there were five contacts in the combined controls, two before and three after "diagnosis".

The 54 patients comprised 49 contact pairs or "links". Forty three of them were within the study group (fig 2); 14 were with members of the same household (category 1), nine being blood relatives; 19

Table 5 *Duration of Isle of Man residence of non-Manx born*

| Residence (y) before diagnosis | Nos (%) born outside Island | |
|-----------------------------------|-----------------------------|------------------|
| | Sarcoid (n = 33) | Control (n = 57) |
| 0-5 | 10 (30.3) | 18 (31.5) |
| 6-20 | 16 (48.5) | 32 (56.1) |
| 21+ | 7 (21.2) | 7 (12.2) |

were at work (category 2); two were between next door neighbours (category 3); and 14 were between recreational contacts or close friends (categories 4 and 5). There were no husband-wife pairs. The mean time between the diagnoses of the linked cases was 2.1 (SD 1.3) years. Among the general controls there were two people who had been in contact with sarcoidosis through work and three people (two acquaintances and one blood relative) among the tuberculosis controls. There was no statistical difference between the numbers of people reporting contact with tuberculosis in the three groups.

Discussion

Sarcoidosis in the Isle of Man occurs predominantly in young adults, as reported elsewhere.² We found the sex ratio to be the same as in the age corrected census population and there was no appreciable rural or urban preponderance. Sarcoidosis was more common among those of Manx ancestry and a high proportion of patients gave a history of previous contact with other cases of the disease.

Other authors^{6,7} have shown that sarcoidosis occurs more commonly in rural areas. Although our findings do not show this, it should be noted that by some standards⁷ the Isle of Man would be considered entirely rural. Clusters might have been expected in new housing estates, where young adults are concentrated; but any suspected clustering occurred outside these estates.

The higher incidence of sarcoidosis in people of Manx ancestry can be compared with the increased susceptibility reported in young Irish women (also of Celtic origin) emigrating to London⁸ and young Negro men entering the United States forces.⁹ The

Table 4 *Place of birth and ancestry (numbers with percentages in parentheses)*

| | Sarcoid (n = 96) | Control (n = 96) | TB control (n = 68) | Census (n = 55 913)* |
|-------------------------|---------------------|---------------------|------------------------|-------------------------|
| Born in the Isle of Man | 63 (65.6) | 39 (40.6) | 41 (60.3) | 26 986 (48.3) |
| Three Manx grandparents | 44 (45.8) | 26 (27.1) | 27 (39.7) | — |

*Age standardised census population (1981).

Manx born—sarcoidosis v control $\chi^2 = 11.06$, 1 df; $p < 0.001$. Manx ancestry—sarcoidosis v control $\chi^2 = 6.50$, 1 df; $p < 0.025$.

Table 6 Occupations of economically active population (numbers with percentages of those economically active in each group)

| Occupation | Sarcoid | Control | TB control | 1981 Census |
|------------------------------|-----------|-----------|------------|-------------|
| Professional (except health) | 6 (8.7) | 14 (19.4) | 3 (6.3) | 5299 (19.2) |
| Health workers | 13 (18.8) | 3 (4.2) | 2 (4.2) | 1328 (4.8) |
| Agricultural | 10 (14.5) | 13 (18.1) | 2 (4.2) | 4068 (14.8) |
| Clerical | 10 (14.5) | 12 (16.7) | 3 (6.3) | 3941 (14.3) |
| Production | 14 (20.3) | 13 (18.1) | 11 (22.9) | 4484 (16.3) |
| Unskilled | 16 (23.1) | 17 (23.6) | 27 (56.3) | 8444 (30.6) |
| Economically inactive | 27 | 24 | 20 | 37115 |
| Total | 96 | 96 | 68 | 64679 |

Sarcoidosis v control v tuberculosis (TB): $\chi^2 = 34.6$, 10 df; $p < 0.005$.

Table 7 Histories of contact with tuberculosis (TB) and sarcoidosis before diagnosis (numbers with percentages in parentheses)

| Contact reported with | Sarcoid (n = 96) | Control (n = 96) | TB control (n = 68) |
|-----------------------|------------------|------------------|---------------------|
| Sarcoidosis | 38 (39.6) | 1 (1.1) | 1 (1.6) |
| Tuberculosis (TB) | 31 (32.3) | 33 (34.4) | 29 (42.6) |

Sarcoidosis v control: $\chi^2 = 38.68$, 1 df; $p < 0.0005$.

possibility that Manx people are at greater risk because of their longer residence on the Island is unlikely because there is no detectable relationship between duration of residence and the development of sarcoidosis in those born elsewhere.

A comparison of living conditions of the three groups was consistent with well documented facts concerning tuberculosis. These people had a lower economic status and lived in higher density urban housing than either of the other study groups.

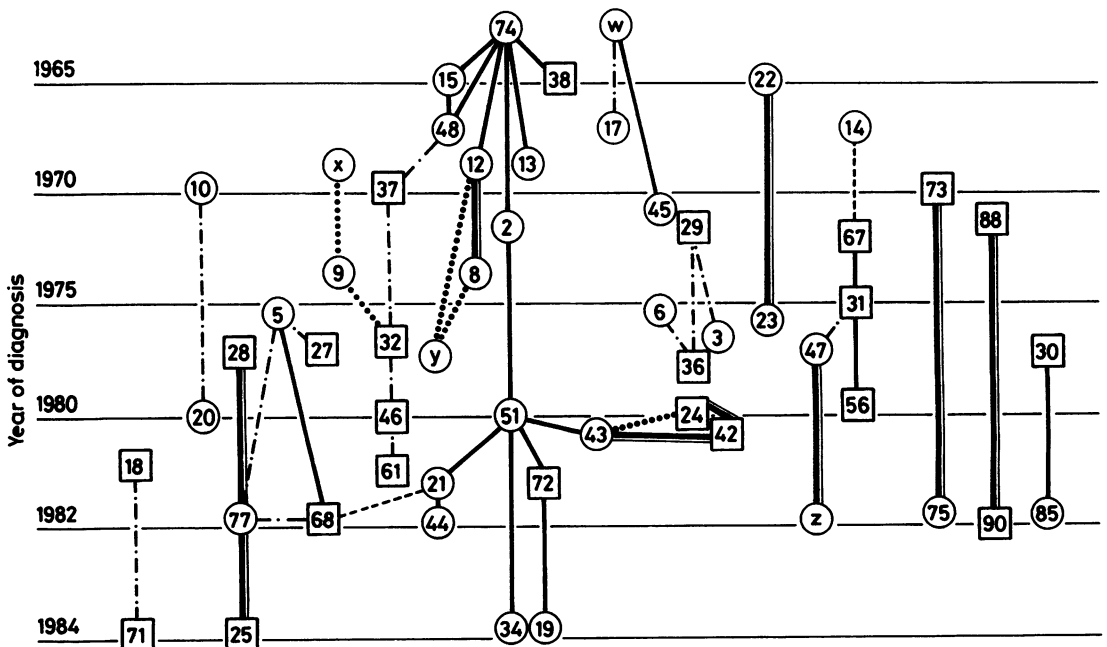


Fig 2 Diagram of links between cases of sarcoidosis by year of diagnosis and category of contact.

Household contacts: blood relatives ——— and other relatives ; work contacts ———; near neighbours - - - - - ; recreational and longstanding friends - · - · ; men □; women ○; proved cases outside the study group w, x, y, z.

The finding of greatest importance in this survey is that nearly 40% of the patients with sarcoidosis gave a history of previous close contact with a person who had the disease, compared with 1.2% in the combined controls. These contacts occurred within the family or domestic groups and among colleagues at work. There is a possible bias in the case history data: patients with sarcoidosis were alerted to the disease and might have been more likely than the controls to recall possible contacts. In contrast, many tuberculosis controls rejected the diagnosis of tuberculosis and were reluctant to discuss it. Consequently, the data relating to contact is likely to be distorted. We do not believe, however, that increased awareness of sarcoidosis among the patients can entirely account for the results of this study or alter the general conclusions reached. Space-time clustering studies, in which this bias has been eliminated, support this view.¹⁰ Significantly more cases were found in nurses, most of whom had lived at some time in the nurses' home. There is nothing to suggest that the nurses had better medical supervision than the rest of the population, which might have resulted in a higher level of ascertainment. One case among the nurses was detected by routine chest radiography, compared with three cases in the remainder of the group.

Increased numbers of cases within families have been reported for many years,¹¹⁻¹⁶ and it has been suggested that a genetic factor may be important.^{11-13 15 16} Nevertheless, no Mendelian mode of inheritance has been demonstrated and HLA studies have not detected any linkage between cases.¹⁷ If contact is an important factor, then members of a family containing a case must be at greatest risk; and if the closeness of contact is important, the pattern of contact in most families should lead to an excess of mother-child pairs over father-child pairs, as has been reported by Scadding *et al.*¹⁴ In these circumstances there would be no need to postulate an inherited factor (although an inherited factor might, of course, influence response). The arguments for a genetic component in sarcoidosis are similar to those of 100 years ago in relation to tuberculosis, then considered to be inherited.

No agent has been identified that has been associated regularly with sarcoidosis, but transmission of the disease has been suggested by Hosoda *et al.*¹⁸ on the basis of a local outbreak in Japan. Mitchell and Rees^{19 20} have shown that an agent that passes through a 0.2 µm filter and is destroyed by irradiation and autoclaving can be transferred to the foot pads of mice, producing a sarcoidosis type granuloma, and subsequently passaged in mice up to six times. These lesions are associated with a positive reaction to a Kveim test performed on the mouse's ear. Most epidemiological studies, however, have not produced

evidence to support any hypothesis about transmission. This could be related to considerable under-recording of cases,³ which, combined with a long latent period, would reduce the chances of detecting connections between cases. In this study many patients have been seen who would not normally have been referred to hospital; possibly we have in consequence been able to detect some "missing links."

There has been considerable immigration into the Isle of Man from the UK and the Commonwealth during the past 20 years; the population has increased by 26%, although the number of births has remained the same. If sarcoidosis is an infectious disease and the Manx people had hitherto been infrequently exposed to it, they might be expected to be more susceptible than the incoming, more mobile population. Our findings are consistent with a communicable disease, although the rarity of cases reported in both husband and wife still needs explanation. This study has avoided some of the difficulties found in larger areas, in which cases are scattered through ill defined and more mobile populations. Closer investigation of sarcoidosis clustering is needed to clarify the present findings.

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