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Epidemiology of sarcoidosis in the Isle of Man—2: Evidence for space-time clustering

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ABSTRACT The case-control test for space-time clustering developed by Pike and Smith was applied to 96 cases of sarcoidosis diagnosed in the Isle of Man from 1962 to 1983. There were significantly more links between cases separated by time intervals of less than 10 years and distances of less than 100 metres than between the others. Analysis of the type of links indicated that clusters consisted of pairs whose contact was by place of residence or work. More linked cases were diagnosed less than three years apart than would be expected by chance. These findings lend support to the idea that sarcoidosis is a communicable disease.

Apparent clusters of patients with sarcoidosis were observed during a study of the disease in the Isle of Man.[1] Many of the patients had a history of previous contact with sarcoidosis. This paper attempts to interpret the importance of these findings by examining links between patients that are not subject to bias (such as the bias caused by patients' recollection of previous cases). Experimental evidence for a transmissible agent in human sarcoid tissue has previously been reported.[2 3]

An earlier study in the Isle of Man[4] reported a high incidence of the disease (14·7 per 100 000). It was suggested that this high incidence was partly due to clinical efforts to improve the recognition of sarcoidosis, and thus cases were detected that might otherwise have gone unnoticed. This high rate of detection of cases, the defined boundary of the Island, and the relatively small changes in population make it an ideal place to study links between patients.

There is no available evidence about the length of any latent period for sarcoidosis. It was apparent from this study (and has previously been mentioned[5 6]) that the disease may be diagnosed some years after initial symptoms develop. Hence we had to look at links between the cases covering some time before diagnosis to investigate any evidence of a transmissible agent. We also had to collect information on the number of links expected between people on a small island, where many spurious links could occur by chance.

For transmission of a disease individuals must be in close proximity at a particular time. Knox[7–9] has proposed a test that supposes that evidence of space-time clustering is provided by an excess of pairs of cases that are close in space and time (measured relatively to pairs of cases distant in space and time). The method of Knox has been extensively used and modified, but is not really appropriate for a disease with a long latent period. Pike and Smith[10] give an alternative approach, which determines whether patients with a disease can be linked more frequently with each other than a matched set of controls without the disease. The method of Pike and Smith was considered more appropriate for this study.

Methods

PATIENTS AND DATA

Ninety six patients with sarcoidosis diagnosed in the Isle of Man from 1962 to 1983 were each matched for age and sex with a control. (Details of entry criteria for the study, choice of controls and matching have been given elsewhere.[1 4]) The characteristics of the control group closely followed those of the census population. Each case and control (or a close relative in three cases) were interviewed by one of the authors (SAP) to provide information about their past histories. Grid references were taken of the school they had attended, their place of work at diagnosis, their place of predominant recreation in the two years before diagnosis, and their places of residence during the

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period from five years before diagnosis to two years after (this was the postulated "infective period"). The time of diagnosis of each control was taken to be the same as that of the patient with whom they were matched.

The study had two distinct periods: from 1962 to 1976 cases were detected retrospectively from hospital records, while from 1977 to 1983 special efforts were made to detect cases and the incidence rate was higher.[4]

STATISTICAL METHODS

The links between cases of sarcoidosis and between controls whose diagnoses were within 10 years of each other were counted for five different types of contact: (*a*) they attended the same school and their attendance periods overlapped; (*b*) their places of work at diagnosis were within 50 metres; (*c*) their places of predominant recreation in the two years before diagnosis were within 50 metres; (*d*) their places of residence had been within 100 metres for any part of the overlap of the postulated (arbitrary) infective periods (that is, from five years before diagnosis to two years after it), and (*e*) their places of residence *at diagnosis* were within 500, 100, 50, or 10 metres.

Pike and Smith[10] have given a method for testing if the observed number of case to case links is different from that expected. This method consists of examining pairs in the study groups. Each pair can be one of three types: case and case, control and control, or case and control. For each pair a link is said to occur if a contact is detected between members of the pair according to the above criteria.

If Z is the sum of the links for all types of pair, then the expected numbers of the different types of link will be as follows:

case	→	case	$Z/4$
case	→	control	$Z/2$
control	→	control	$Z/4$.

The variance of Z can be evaluated but is complicated because the links are not independent. Details are given by Pike and Smith,[10] who also provided FORTRAN-4 subroutines to perform the calculations. An approximate significance level is then found by taking the difference between the observed and expected number of case to case links divided by the variance to be a standard normal deviate and using a one sided test.

For the links concerned with place of work, place of recreation, and place of residence *at diagnosis*, it is possible (and indeed likely) that spurious links will be detected, because participants may have moved during the course of the study; there is, however, no reason for there to be more spurious links in the sarcoidosis group than in the control group.

A histogram was drawn of the time intervals between the diagnoses of linked cases whose places of residence at diagnosis were within 1 km, to examine any evidence for a specific latent period. In this study the distribution of these intervals on the hypothesis of no clustering is complicated because of the different incidence rates during the two periods of the investigation; in an attempt to overcome this problem, the histogram included only pairs diagnosed in the latter part of the study (1977–83).

Results

More cases than controls were born on the island ($Z = 3{\cdot}399$; $p < 0{\cdot}006$), went to school on the island ($Z = 3{\cdot}487$; $p < 0{\cdot}0004$), and lived on the island two years after their diagnosis ($Z = 2{\cdot}221$; $p < 0{\cdot}027$) (table 1); but at all other times there were no differences between the numbers of cases and controls resident on the island (Z values are standardised normal deviates for comparison between two proportions).

Table 2 shows the results from the eight different tests performed. No excess of links between cases was detected when looking at schools attended, places of recreation, or places of residence for links within 500 metres. There was an excess of links between cases according to places of residence within 100, 50, and 10

Table 1 *Numbers of cases and controls resident in the Isle of Man*

	On the Island		*Not on the Island*		*Missing*	
	Cases	*Controls*	*Cases*	*Controls*	*Cases*	*Controls*
Place of residence						
At birth	62	41	30	54	4	1
5 y before diagnosis	84	80	12	16	—	—
2 y before diagnosis	85	87	11	9	—	—
At diagnosis	92	89	4	7	—	—
2 y after diagnosis	93	85	3	11	—	—
Place of work						
At diagnosis	91	87	4	9	1	—
Place of recreation	88	87	5	9	3	3
School	67	46	25	50	4	—

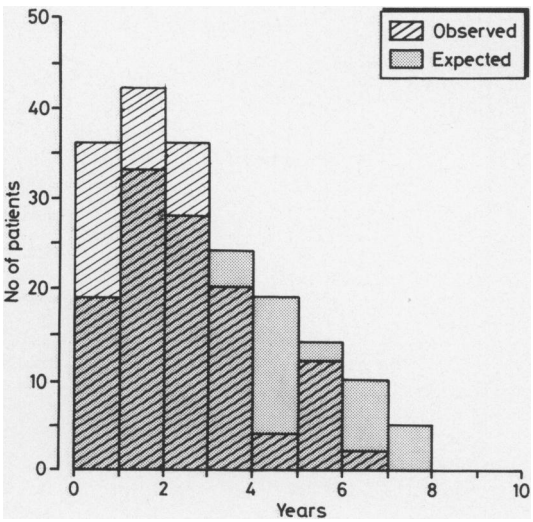
Table 2 *Number of links between cases and between controls*

Type of contact	*No of links between cases*	*Expected No*	*Variance*	*Approximate p value*
School	26	24·25	29·31	0·37
Work	42	17·50	48·12	0·0003
Recreation	17	14·75	37·94	0·36
Residences within 100 m during "infective" period	17	8·00	7·25	0·0005
Residences at diagnosis within:				
500 m	113	98·50	379·00	0·23
100 m	13	6·25	6·19	0·0034
50 m	8	2·75	3·31	0·0020
10 m	6	1·75	2·31	0·0026

metres and for contacts within the postulated "infective" period. Bias could, however, have arisen in the last result owing to the excess of cases over controls resident on the Island two years after diagnosis.

Further investigation revealed a large cluster of patients with sarcoidosis centred on Noble's Hospital in Douglas. Contacts in this cluster occurred between residents in the nurses home, workers in the hospital, and three patients who lived close to a hospital worker. Fourteen cases could be linked to the hospital cluster according to the criteria living closer than 100 metres during the "infective" period, having a place of residence at diagnosis closer than 100 metres, and working closer than 50 metres. Eight smaller clusters were detected: one of seven cases, one of six, three of three and three linked pairs.

The figure shows the distribution of the time intervals between the diagnoses of linked cases in which the places of residence at diagnosis were less than 1 km apart. This distribution is different from the distribution observed under the hypothesis of no time clusters (χ^2 = 25·90; 6 df). Most of this difference is concentrated on an excess of pairs diagnosed within one year of each other and a deficit of pairs diagnosed between three and four years apart; more generally, the number of pairs diagnosed within three years is greater than expected and the number whose diagnoses were further apart than three years is less than expected.



Numbers of years separating the diagnoses of linked cases of sarcoidosis in which places of residence were within 1 km (1977–83).

Discussion

This study has found evidence of space-time clustering of sarcoidosis cases in the Isle of Man. No environmental reasons for the clustering became apparent when we searched for common factors between the cases, neither did the site of the clusters indicate a reason. The suggestion is therefore that sarcoidosis could be a communicable disease.

Tests for the detection of clusters for different types of contact did not reveal a significant excess of links between cases that were spatially distant or for short periods of time (places of recreation or of residence within 500 metres at diagnosis). An excess of links between cases was discovered for close contacts over long periods of time (places of work, or of residence within 100 metres). This evidence suggests that if transmission of sarcoidosis from person to person occurs it requires prolonged close contact. No excess of links by schools attended was apparent (although more patients with sarcoidosis than controls had attended school on the Island), which suggests that important links occur after school leaving age. Sarcoidosis is known to be a disease affecting young adults.[11] Thus if it is a communicable disease a high incidence would be expected among young adults in close proximity to each other, such as the large cluster of young nursing staff in the hospital.

Some evidence was found to support an excess of pairs diagnosed within three years of each other. The presence of clustering can, however, produce an

excess of pairs diagnosed within a short interval of time (independently of the latent period) because an unlinked pair of cases that are both associated with a third case will introduce a spurious short link. In some cases moreover the time interval between the contraction of sarcoidosis and its diagnosis was of uncertain duration; this would tend to blur the evidence for a fixed latent period, since it is as likely to shorten as to lengthen the apparent latent period.

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References

1 Parkes SA, Baker SB de C, Bourdillon RE, Murray CRH, Rakshit M. Epidemiology of sarcoidosis in the Isle of Man—1: A case controlled study. *Thorax* 1987; **42**:420–6.

2 Mitchell DN, Rees RJW. A transmissible agent from sarcoid tissue. *Lancet* 1969;ii:81–4.

3 Taub RN, Siltzbach LE. Introduction of granulomas in mice by injection of human sarcoid and ileitis homogenates. In: Iwai K, Hosoda Y, eds. *Proceedings of the Sixth International Conference on Sarcoidosis and Other Granulomatous Diseases*. Tokyo: University Park Press, 1974:20–1.

4 Parkes SA, Baker SB de C, Bourdillon RE, *et al*. Incidence of sarcoidosis in the Isle of Man. *Thorax* 1985;**40**:284–7.

5 Gupta SK, Mitra K, Chatterjee S, *et al*. Sarcoidosis in India. *Br J Dis Chest* 1985;**79**:275–83.

6 McNicol MW, Luce PJ. Sarcoidosis in a racially mixed community. *J R Coll Physicians Lond* 1985;**19**:179–85.

7 Knox G. Detection of low intensity epidemicity: application to cleft lip and palate. *Br J Prev Soc Med* 1963;**17**:121–7.

8 Knox G. Epidemiology of childhood leukaemia in Northumberland and Durham. *Br J Prev Soc Med* 1964;**18**:17–24.

9 Knox EG. The detection of space-time interactions. *Applied Statistics* 1964;**13**:25–9.

10 Pike MC, Smith PG. A case-control approach to examine diseases for evidence of contagion, including diseases with long latent periods. *Biometrics* 1974;**30**:263–79.

11 Bresnitz EA, Strom BL. Epidemiology of sarcoidosis. *Epidemiol Rev* 1983;**5**:124–56.