

HEREDITY IN SARCOIDOSIS

– A REGISTRY-BASED TWIN STUDY

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Abstract

Background

Sarcoidosis is a multiorgan, granulomatous, inflammatory disease with unknown aetiology. Familial clustering of cases and ethnic variation in the epidemiology suggests a genetic influence on the disease susceptibility.

Aim

This paper reports twin concordance and heritability estimates of sarcoidosis in order to assess the overall contribution of genetic factors to the disease susceptibility.

Methods

Monozygotic and dizygotic twins enrolled in either the Danish or the Finnish population-based, national Twin Cohorts (61,662 pairs in total) were linked to diagnostic information on sarcoidosis obtained from the Danish National Patient Registry or the Social Insurance Institution, Finland, registry of re-imbursed medication using the 8th and 10th editions of the International Classification of Diseases. Fisher's exact test was used to compare probandwise concordance rates in different zygosity groups. Heritability was estimated based on a multifactorial threshold liability model.

Results

A total of 210 twin pairs with at least one proband with a diagnosis of sarcoidosis were identified. The probandwise concordance rate was higher in monozygotic than in dizygotic twins, 0.148 vs. 0.012. Compared to the general population we found an 80-fold increased risk of developing sarcoidosis in co-twins of affected monozygotic brothers or sisters. The increased risk in dizygotic twins was on the other hand only 7-fold. Aetiological model fitting gave a heritability of sarcoidosis of 0.66, 95% CI (0.45-0.80).

Conclusions

This study suggests that genetic factors play an important role in the susceptibility to sarcoidosis. This result should encourage the search for molecular genetic markers of the susceptibility to disease.

Keywords

aetiology; epidemiology; genetics; sarcoidosis; twins

Introduction

Sarcoidosis is a rare, multiorgan, immune-mediated disease with unknown aetiology, characterized by the formation of non-caseating granulomas. Ninety percent of the patients are affected in the lungs or intrathoracic lymph nodes however, large differences in organ-involvement are found between ethnic groups and in different parts of the world [1-4].

The prognosis and course of the disease depends on the severity and phenotypic characteristics. Overall, 30% undergo spontaneous remission whereas another 30% progress with chronic manifestations. In addition, a significant number of asymptomatic cases with sarcoidosis have been identified in mass-screenings using chest radiographs [2,3,6]. Mortality rates in patients with sarcoidosis have been reported to be 1 to 6% [2,3,6].

The occurrence of sarcoidosis in the general population remains difficult to establish due to the wide spectrum of phenotypes, differing diagnostic criteria, and the variable choices of study designs [1,2,5]. Incidence rates in Denmark and Finland are 7.2 and 11.4 per 100,000 person-years respectively [6,7]. Prevalence and incidence are conditional on age, sex, and ethnicity [1,2,8-10].

The present understanding of the disease pathogenesis is that sarcoidosis is triggered by an abnormal immune response to an environmental agent in a genetically predisposed individual [1]. Genetic factors are considered to contribute to the development of sarcoidosis due to mainly two reasons [1,2,5,10]; First, epidemiological studies have identified ethnicity as an important risk factor. Secondly, familial clustering of cases has been observed frequently over the last decades. A previous study has suggested an up to 5.7-fold increased risk of developing sarcoidosis in siblings of affected individuals [9]. However, the fact that families do not only share genes but also environment makes it difficult to determine the relative contribution of genetic versus environmental factors to the susceptibility to the disease.

Susceptibility loci have been mapped to the human leukocyte antigen (HLA) gene complex located on the short arm of chromosome 6, whereas a number of non-HLA candidate genes map to other locations in the genome [10-12]. This suggests the influence of a large number of interacting genes. The specific gene findings, however, account for only a minor fraction of the variance in risk to disease.

This study is the first to use the classical twin method to systematically describe the occurrence of sarcoidosis in Danish and Finnish twins in order to address the overall contribution of genetic factors to the susceptibility to the disease.

Methods

The twin method is a classic approach to study the heredity of a disease. Besides sharing their upbringing and early environment, monozygotic twins have all their genes in common whereas dizygotic twins only share genes like normal siblings. Therefore, if a disease is more correlated in monozygotic than in dizygotic twins, it provides evidence for genetic factors contributing to the aetiology of the disease [13].

The Danish and Finnish twin cohorts

The Scandinavian countries have some of the oldest and most well-characterised twin registries in the world making collaboration between countries advantageous when studying rare diseases like sarcoidosis [14, 15]. The Danish study population included all twins, enrolled in the nationwide Danish Twin Registry, who were alive at some point between 1977 and 2004 [16]. This comprises a total number of 60,756 pairs. The Old Finnish Twin Cohort consists of 13,888 pairs of known zygosity, comprising all same-sex twins born before 1958 with both twins alive in 1975. In both

registries zygosity has been determined using questions of similarity and mistaken identity [17]. This method is widely accepted and assigns zygosity correctly in more than 96% of the cases [18].

Case identification

Diagnostic criteria were limited to codes 135.99 and D86.0-D86.9 of the 8th and 10th editions of the International Classification of Diseases. Information on sarcoidosis in the Danish cohort was gathered from the Danish National Patient Registry (DNPR) at the Danish Board of Health on all twins alive between 1977 and 2004. DNPR contains details on all hospitalisations in Denmark including information on all diagnostic coding. Cases in the Finnish cohort included all twins who had applied for medical reimbursement associated with a diagnosis of sarcoidosis in the period from 1976 to 2004 (which included 11,186 twin pairs of working age and not on disability pension in 1975). The Social Insurance Institution, Finland, grants the right to full reimbursement based on a medical certificate from an appropriate medical specialist or hospital unit.

Statistical analysis

Fisher's exact test was used to compare probandwise concordance rates in different zygosity groups. The probandwise concordance rate denotes the probability that one twin has the disease given the co-twin is affected and is estimated as two times the number of concordant affected pairs (both twins are affected) divided by two times the number of concordant affected pairs plus the number of discordant pairs (one twin is affected) [19].

Recurrence risk ratios were calculated by dividing the probandwise concordance rate with the prevalence rate, denoting the increased risk of disease relative to the general population.

The heritability, which is the proportion of variation in susceptibility ascribable to genetic differences, was estimated from the number of unaffected, discordant and concordant pairs. This was based on a multifactorial threshold liability model and computed according to the methods described by Neale and Cardon [20].

Results

Of 61,662 twin pairs with known zygosity a total of 210 twin pairs were identified with at least one diagnosed proband, the distribution of subjects is shown in table 1. The Danish and Finnish cohorts did not significantly differ regarding the prevalence in the two groups of twins; neither did the prevalence in mono- and dizygotic twins compared in each cohort. Pooled analysis of the data showed that the probandwise concordance rate was higher in monozygotic twin pairs than in dizygotic twin pairs (0.148 vs. 0.012, $p=0.012$).

Moreover, a co-twin of an affected identical twin runs an 80-fold increased risk of getting sarcoidosis compared with the general population, whereas the risk was increased 7-fold in a co-twin of an affected dizygotic twin.

We found that an aetiological model including genetic and non-shared environmental effects fitted the data best with a heritability estimate of 0.66, 95% CI (0.45-0.80). The proportion of variance explained by non-shared environmental factors was 0.34, 95% CI (0.20-0.55).

Discussion

Sarcoidosis has been studied in affected families to reveal any possible genetic influence on susceptibility. Since families share not only genes but also environment, aggregation of cases may be due to either inherited factors or environmental exposures. The elevated relative risk of 5.8 in siblings found in the ACCESS study [9], concur well with our equivalent findings in dizygotic twins. However, no studies have partitioned observed familial clustering into genetic and environmental components of variance.

The significantly higher concordance rate in monozygotic twins in this study shows that genetic factors appear to play a substantial role in the susceptibility to sarcoidosis. The heritability reflects the difference between monozygotic and dizygotic twin pairs, which tells us that genetic factors account for two thirds of the variation in the susceptibility to the disease whereas environmental factors account for one third.

Since monozygotic twins are mostly discordant for the disease, we need to emphasize the importance of additional environmental risk factors. The heritability estimate does not reflect the overall risk of getting the disease, merely the variance between the twins. The genetic influence on the overall risk of developing sarcoidosis is reflected in the 7-fold versus 80-fold increased risk in dizygotic and monozygotic twins, respectively. Aggregation of disease in twins has been described in the medical literature before [21], but not with the requisite statistical power to identify any difference or heritability. It now seems evident that a considerable component of the disease accumulation is due to genetic influences on susceptibility.

Still, in spite of a large sample size we were left with relatively few cases to analyse due to the rareness of the disease. By pooling the two cohorts we benefited from a larger number of cases, in particular concordant twin pairs, which also seemed sensible, since the prevalence was similar in the two cohorts. The Finnish data built on reimbursement inclusion criteria, which leave out patients with no need for treatment. An overweight of more severe cases is therefore to be expected. There was no available information on the phenotypic distribution of the cases and therefore it was not possible to distinguish between genetic influences on the overall susceptibility versus genetic influence on varying phenotypes as has been suggested by others [10,11].

Our results support the idea of sarcoidosis as a complex disease triggered by a combination of environmental and genetic risk factors. To get further insight into the interactions causing disease, specific genetic, environmental and infectious risk factors need to be investigated.

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Statement

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Table 1. Occurrence and resemblance between twins for sarcoidosis in 61,662 Danish and Finnish twin pairs.

Zygoty	Pairs (n)	Prevalence, number (%)	Discordant pairs (n)	Concordant pairs (n)	C_{Pr}	RRR (95% CI)
Denmark						
MZ	11,085	41 (0.185)	37	2	0.098	
DZ	39,391	129 (0.164)	127	1	0.016	
Finland						
MZ	3,519	13 (0.185)	9	2	0.038	
DZ	7,667	32 (0.209)	32	0	0	
All MZ	14,604	54 (0.185)	46	4	0.148	80.13 (37.06-173.64)
All DZ	47,058	161 (0.171)	159	1	0.012	7.26 (1.96-26.87)
Total	61,662	215 (0.174)	205	5	0.030	

C_{Pr}, probandwise concordance rate.

RRR, recurrence risk ratio.