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Review article

Clinical epidemiology of familial sarcoidosis: A systematic literature review

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ABSTRACT

Introduction: Although the presence of familial sarcoidosis has been confirmed, clinical and epidemiological data on its characteristics are scattered and sometimes paradoxical. The objective of this review is to assess what is known on the clinical epidemiology of familial sarcoidosis, by combining data from early case reports with recent population based data; aiming to support in clinical decision making and providing information to patients.

Method: A systematic review of the literature in PubMed was done and 27 studies with clinical or epidemiological data on familial sarcoidosis, published between 1947 and 2017, were included.

Results: The pooled prevalence proportion of familial sarcoidosis, based on twelve study populations, was 9.5% (CI 4.6–16.1), highest in French, African American, Dutch and Irish patients. A heritability of 60–70% was estimated in diverse studies. Relative types and relationships most often reported in familial sarcoidosis were siblings and mother-child relationships. Familial risk is heterogeneous. In African Americans specific environmental factors have been associated with familial sarcoidosis (OR between 1.5 and 3.2). European American and African American subjects had different relative risks for first degree familial relationships (OR of 16.6 vs 3.1) and relative risk differed between relative types. Clinical findings in familial sarcoidosis are still obscure.

Conclusions: Prevalence of familial sarcoidosis is high in specific study populations from countries worldwide. The estimated heritability of 60–70%, suggests a shared determinant, and the heterogeneous familial risk, associated with both genetic and environmental factors. Familial relative risks and clinical phenotypes may differ between ethnic groups and relative types, but require further study.

1. Introduction

Sarcoidosis is a disease of unknown etiology. It is characterized by the presence of non-caseating granulomas in one or multiple organs of the patients [1]. The aggregation of sarcoidosis in families has been described since the early 20th century. It was first confirmed by Rybicki and colleagues in the multicenter 'A Case–Control Etiology Study of Sarcoidosis' (ACCESS) study, from 1996 to 1999 [2]. In addition to measuring familial relative risks, an extensive clinical characterization of the sarcoidosis cases was done. A major strength of the study is the large sample size (706 case–control pairs) with subjects from various areas in the United States. Recently, studies on familial aggregation of disease have regained interest, because findings are potentially useful in the clinic and important to patients [3]. Familial occurrence of a disease is commonly linked to shared genetic or environmental exposures. However, in sarcoidosis there is little evidence for a strong determining role of any of these. Furthermore, clinical and epidemiological data on the characteristics of familial sarcoidosis are scattered and sometimes paradoxical. By means of a literature review on the clinical epidemiology of familial sarcoidosis, we sought for information on familial sarcoidosis that is useful to inform patients and might aid in clinical decision making. We describe epidemiological and clinical findings on familial sarcoidosis from early case reports together with more recent population based findings, including estimates for prevalence and heritability, familial risks with associated factors, relative risks for different relative types and clinical findings.

2. Method

To identify studies a systematic literature search was done in PubMed in collaboration with a clinical librarian from St. Antonius hospital Nieuwegein. Included were original clinical or epidemiological studies on familial sarcoidosis, with abstracts available in PubMed. Language was restricted to English. No further limits were applied, nor

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were specific types of records excluded. The search was run on March 20, 2017 and contained the following terms: (neuro)sarcoidosis, genetic predisposition to disease, familial/family/families, proband, relatives, sibling and ancestry. Articles reporting Blau syndrome or only genetic associations with familial disease were outside the scope of this review.

The full search: ("Sarcoidosis"[Mesh] OR sarcoidos*[tiab] OR neurosarcoidos*[tiab]) AND ("Genetic Predisposition to Disease"[Majr] OR familial[tiab] OR family[tiab] OR families[tiab] OR proband*[tiab] OR relatives[tiab] OR sibling*[tiab] OR ancestry[tiab]) AND (english[la]).

Identified articles were screened by title and abstract reading first, followed by full text reading of the remaining articles. Eligible articles contained original clinical or epidemiological data on familial sarcoidosis. Familial sarcoidosis was defined as presence or history of sarcoidosis in one or more family members of index patients with sarcoidosis. We present the pooled prevalence proportion among the included studies for the appropriate model (based on the results of a heterogeneity test), together with the forest plot. Statistical analyses were performed using MedCalc for Windows, version 18.6 (MedCalc Software, Ostend, Belgium). For all measures, the estimation and the 95% confidence interval (CI) are presented.

3. Results

3.1. Familial reports

Pubmed database searching identified 459 articles. Title and abstract screening resulted in 118 articles with possibly relevant information, that were assessed for eligibility. After full text reading 91 articles were excluded, because they did not contain clinical or epidemiological data on familial sarcoidosis. Finally, 27 studies were included in qualitative synthesis. The study selection process is summarized in the PRISMA flow diagram (Fig. 1).

3.2. Prevalence of familial sarcoidosis among sarcoidosis patients

Since the beginning of the 20th century, there are mainly case reports and surveys on the familial aggregation of sarcoidosis [4–19]. In 2001, Rybicki and colleagues were the first to confirm the familial aggregation of sarcoidosis in the ACCESS study, including 355 European American and 291 African American case-control pairs [2]. Prevalence of familial sarcoidosis, defined as presence or history of sarcoidosis in one or more family members of index patients with sarcoidosis, has been reported or can be obtained from different study populations from nine countries, of which seven European [5,8,14–17,19–21]. Two studies were done in het United States, the first in an African American study population [5], the second in a study population of both African American and European American patients [14]. The diagnosis of sarcoidosis in patients and relatives is mostly either biopsy proven or confirmed by medical record information. In some studies, the diagnosis of sarcoidosis in family members is only self-reported [16,17,21]. It should be noted that the time (span) of inclusion of sarcoidosis index patients differs substantially between studies, varying from a prevalence over 1 year [17] to prevalence over 40 years [14]. Taken the preceding into account, the prevalence of familial sarcoidosis among sarcoidosis patients is highest in French (44.7%), African American (35.0%), Dutch (16.5%) and Irish (9.6%) patients. The I^2 statistic, as a measure for heterogeneity among the studies, was 98.30% (CI 97.81–98.68); $P < 0.0001$. Therefore the pooled prevalence proportion with 95% CI was calculated for the random effects model (9.5%; CI 4.6–16.1). Table 1 and Fig. 2 present the results of these analyses together with the forest plot (results for the fixed model are also shown).

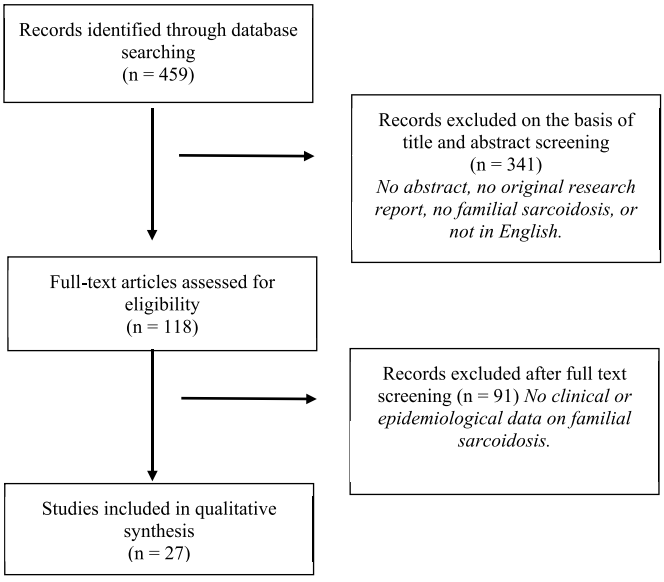

Fig. 1. Flow diagram of study selection.

3.3. Heritability estimates for sarcoidosis

In one of the early studies on familial sarcoidosis, heritability of sarcoidosis was estimated to be between 60 and 70% (SE ± 11–18), based on female probands from a study population of 80 African American sarcoidosis patients [5]. The findings were mainly limited by a small sample size [5]. Later on, Sverrild and colleagues estimated a heritability of sarcoidosis of 66% (CI 45-80), by means of etiological model fitting, in a Danish and Finnish population of 210 twin pairs with at least one proband diagnosed with sarcoidosis. The authors used their national twin registries, that are known as some of the oldest and most well characterized twin registries in the world [22]. There were many differences between these heritability studies, for example the study population, the sample size, the time period at which the studies were conducted, and the method used to estimate heritability. It is then striking that both heritability estimates were in between 60 and 70%. These results do suggest the presence of a shared determinant in familial sarcoidosis, as McGrath and colleagues concluded earlier in their study with an ethnically diverse study population from London [19].

Although heritability is high, genetic determinants specific for familial sarcoidosis have not been identified. Articles reporting Blau syndrome or genetic associations with disease were outside the scope of this review. Some findings on this topic are however interesting with respect to our review. Early onset sarcoidosis was shown to be linked to the nucleotide binding oligomerization domain containing 2 (*NOD2*) gene, previously known as *CARD15*, the same gene that harbors mutations causative of Blau syndrome [23]. Several studies have shown that this gene is not involved in risk for familial sarcoidosis [24,25]. The strongest genetic associations that were found for sarcoidosis are located at the human leukocyte antigen (HLA) region. In a study of the HLA-region in a German cohort of familial patients with sarcoidosis, significant excess of marker haplotype sharing was found among affected siblings [26]. In sarcoidosis, a polymorphism in the HLA class III gene *BTNL2* is the strongest risk factor for development of sarcoidosis [27]. Analysis of one family with 5 members through 3 generations with severe sarcoidosis showed that all subjects were homozygous for this risk allele [28], however, analysis of the *BTNL2* variant in French and African American familial cohorts showed that the frequency of the risk allele in familial sarcoidosis was more or less equal to that in sporadic patients with sarcoidosis [21,29]. It may therefore be concluded that, so far, common genetic risk factors for familial sarcoidosis are not different from those observed in sporadic disease and that genetic variants with high penetrance have not been identified in familial sarcoidosis. The heritability is used to quantify the role of genetic factors, however, a significant part of familial occurrence cannot be

Table 1
Prevalence of familial sarcoidosis, defined as presence or history of sarcoidosis in one or more family members of index patients with sarcoidosis.

Study	Country	Sample size	Proportion (%)	95% CI	Weight (%)	
					Fixed	Random
1 Headings (1976)	United States	80	35.0	24.7 to 46.5	1.3	7.8
2 Brennan (1984)	Ireland	114	9.6	4.9 to 16.6	1.8	8.0
3 Rybicki (1996)	United States	809	12.6	10.4 to 15.1	13.0	8.5
4 Wirnsberger (1998)	The Netherlands	1026	16.6	14.3to 19.0	16.5	8.5
5 Fité (1998)	Spain	188	2.1	0.6 to 5.4	3.0	8.2
6 Pietinalho (1999)	Finland	1378	3.6	2.7to 4.8	22.1	8.5
7 Pietinalho (1999)	Japan	208	4.3	2.0 to 8.1	3.4	8.3
8 Pietinalho (1999)	Finland	571	4.7	3.1 to 6.8	9.2	8.5
9 Pietinalho (1999)	Japan	686	2.9	1.8 to 4.5	11.0	8.5
10 McGrath (2000)	United Kingdom	406	5.9	3.8 to 8.7	6.5	8.4
11 Musellim (2009)	Turkey	293	1.0	0.2 to 3.0	4.7	8.4
12 Pacheco (2016)[a]	France	463	44.7	40.1to 49.4	7.4	8.4
Total (fixed effects)		6222	8.8	8.1 to 9.5	100.0	100.0
Total (random effects)		6222	9.5	4.6 to 16.1	100.0	100.0

[a] In this study prevalence of familial sarcoidosis was not estimated, we calculated a prevalence proportion with the available data.

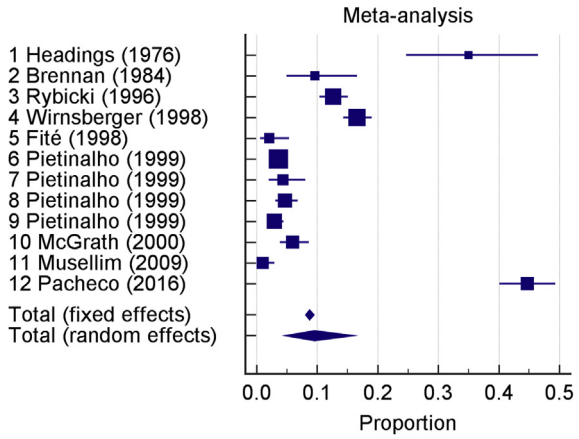

Fig. 2. Pooled prevalence of familial sarcoidosis among sarcoidosis patients.

explained by heritable factors and may be explained by environmental factors.

3.4. Familial sarcoidosis and environmental factors

In African American siblings, a variety of occupational risk factors have been associated with the occurrence of familial sarcoidosis [30,31]. Some specific occupational exposures were found to associate with familial sarcoidosis, when exposed for more than 1 year, including titanium (OR, 3.15; CI 1.02 to 9.68) and vegetable dust (OR, 1.82; CI 1.01 to 3.27), and indoor exposure to high humidity (OR, 1.51; CI 1.13 to 2.02), water damage (OR, 1.50; CI 1.11 to 2.03), or musty odours (OR, 1.78; CI 1.32 to 2.40) [30]. Photocopier toner dust was considered an unrecognized antigen in the pathophysiology of some familial patients with sarcoidosis [31]. In the study by Sverrild and colleagues on familial sarcoidosis with Scandinavian twins, the etiological model that fitted their data best, included both genetic and non-shared environmental effects. The proportion of variance explained by the environmental factors was 34% (CI 20- 55) [22]. Gene-environment interactions are particularly interesting, because they might explain the high degree of heterogeneity in disease risk between families. Evidence for such interactions has been presented by Rossman and colleagues, who observed suggestive interaction between *HLA DRB1**1101 and exposure to musty odours in the occurrence of pulmonary sarcoidosis in a study population from the ACCESS study, that included the first 474 cases and matched controls [32]. Although in the Scandinavian twin study by Sverrild and colleagues on familial sarcoidosis no specific environmental factors were investigated, they confirmed a combined role of genetic and non-shared environmental factors [22]. The case series described by Piotrowski and colleagues [33] highlights the coincidence of tuberculosis and familial sarcoidosis and shows that an etiologic role for *Mycobacterium tuberculosis* in familial sarcoidosis still cannot be excluded. Current understanding on the etiology of sarcoidosis is that there is a role for exogenous and endogenous triggers and, in part genetically determined, cellular function of both innate as well as adaptive immunity [34]. Interestingly, it is known that successful intracellular pathogens can limit parts of immunity, especially *M. tuberculosis*, that has been found able to evade both innate and adaptive immunity [35].

3.5. Reported relative types in familial sarcoidosis

Familial relationships in sarcoidosis have been assessed for various relative types, that is (grand)parents, siblings, uncles, nieces etc. Most often, first degree relatives, especially siblings and parents, were reported. Sarcoidosis in grandparents was described in few studies and avuncular relationships have been reported in several studies. Articles reporting relative types in familial sarcoidosis are summarized in Table 2. This includes many case reports or small case series of familial cases; the results of individual studies may therefore be biased. Together, however, the results may be more informative (Table 2). In the study by McGrath and colleagues [19] there was an equal distribution of mother-child and father-child pairs. However, together, the results do support that familial sarcoidosis occurs more often in siblings compared to parent-child relationships and more often in mother-child relationships compared to father-child relationships. Although findings can be study population specific. In some studies, familial relationships by marriage are reported [2,15,18]. As expected, in the ACCESS study the relative risk for spouses was not higher (OR 0.2; CI 0.04–1.1; not

Table 2
Reported relative types in familial sarcoidosis.

Familial relationship	Study ref (nr)
First degree relatives	[20]
First, second and third degree relatives	[16]
Siblings	[2,5–11,13–19,22,30,31,33,36,38,41]
Parent-child	[2,14,19,36]
Mother-child	[5,6,12,15–18,33,41,42]
Father-child	[16,17]
Grandparents	[2,5]
Avuncular	[2,4,5,13,15,17,19,41]
Relationships by marriage	[2,15,18]

statistically significant) [2]. Interestingly, in the study by Elford and colleagues [18], two genetically unrelated affected family members shared the same HLA haplotype A11-B7-DR15.

3.6. Measurement of familial aggregation for various relative types

Familial clustering of disease is most commonly measured by two methods that use relative risks [3]. The first method: λ = risk in relative of affected individual/risk in the general population; and the second method: familial risk = risk in relative of affected individual/risk in relative of unaffected individual. In most situations, with these two definitions the familial risk will be roughly equal; the translation between measures is dependent on disease prevalence [3]. A major limitation to the measurement of familial aggregation of sarcoidosis so far, is that the absolute number of (familial) cases is generally low, even in the largest study [2].

In three of the included studies, by Rybicki and McGrath and colleagues [2,19,36], familial aggregation of sarcoidosis was measured with these different methods. In the ACCESS study, a particular statistical method (method of Liang) was used to account for possible family correlation structures. With this method odds ratios and p values were calculated for covariates in all familial aggregation models [2]. The results are presented in Table 3. In the combined ACCESS study sample of both European American and African American case control pairs, it was found that the relative risk in both avuncular relationships (OR 5.7; CI 1.6–20.7) and grandparents (OR 5.2; CI 1.5–18.0) may be higher than in parents (OR 3.8; CI 1.2–11.3) [2]. Relative risks, calculated for first degree familial relationships sibs and parents combined were higher in European American subjects with an OR of 16.6 (CI 2.2–126.1) compared to African American subjects with an OR of 3.1 (CI 1.4–7.1). In another study in 179 African American families, a familial risk ratio (λ) was calculated [36], between 1970 and 1999. The familial risk ratios in family members were more or less similar to the relative risks of African American subjects from the ACCESS study: λ 2.24 (CI 1.16–3.92) versus OR 5.1 (CI 1.6–16.4) for sibs and λ 2.82 (CI 1.41–5.05) versus OR 1.8 (CI 0.5–6.0) for parents. The familial risk ratio for parents and sibs combined was λ 2.49 (CI 1.58–3.73) versus OR 3.1 (CI 1.4–7.1). The extremely high λ of 36–73 in the London cohort [19] was calculated in a different way and the size may be due to bias in comparing the prevalence of familial sarcoidosis with population prevalence estimates [2]. The results primarily show that the subject deserves further investigation, because the high familial relative risk for disease in family members of specific groups of patients with sarcoidosis may be clinically useful.

3.7. Heterogeneity of sarcoidosis familial risk

Studies have shown that African Americans are more commonly and severely affected by sarcoidosis compared with European Americans and that prevalence of a family history of sarcoidosis is also higher in African Americans [14]. Therefore, etiologic heterogeneity has been suspected [14]. Rybicki and colleagues assessed heterogeneity among sarcoidosis families by means of a non-parametric statistical method, in a study population of 361 African American and 197 European American families(14). The results confirmed heterogeneity in disease risk, more pronounced in African American families compared to European American families. Characteristics of the index sarcoidosis patients that were found to be associated with high-risk families were: African American race (OR 3.24; CI 1.71–6.14) and having an affected offspring or second-degree relative with sarcoidosis (OR 6.21; CI 2.85–13.45) [14]. It was thought that in African American families there may be a greater sharing of transmissible disease risk factors among family members [14].

In the ACCESS study [2], sibs and parents of European American patients (OR16.6; CI 2.2–126.1) had a markedly higher familial relative risk compared with those of African-American patients (OR3.1; CI 1.4–7.1). The authors concluded that the disproportionately higher familial relative risk found in European Americans compared with African-Americans suggests genetic factors may exert a more detectable effect in European American families with sarcoidosis [2]. With respect to these findings it should be noted that the variable race or ethnicity is difficult to measure and use in research, because it is composed of various characteristics (such as shared origins or social background; shared culture or tradition; and a common language or religious tradition) that may change over time [37]. Thus, further stratification in future studies, especially of the African American cohort, might be informative with respect to the familial variation in disease risks.

3.8. Clinical findings in familial sarcoidosis

Perhaps most in line with the aim of our review, that is to support in clinical decision making and providing information to patients, we searched for clinical findings in the included studies. Pietinalho and colleagues [17] were the first to make a clinical comparison between sporadic and familial cases of sarcoidosis in Finnish (56 familial/544 non-familial cases) and Japanese (40 familial/646 non-familial cases) patients with sarcoidosis. They found no statistically significant differences between familial and sporadic sarcoidosis in either sarcoidosis patients from Finland or Japan. However, familial patients in both areas had a slightly less favourable prognosis compared with sporadic patients, based on normalization of chest radiography during five-year

Table 3
Measures of familial aggregation of sarcoidosis for various relative types.

Familial relative risks and familial risk ratios (λ) in various relative types	Study population	Study ref (nr)
Sibs: λ 2.24 (1.16, 3.9*327 siblings* Parents: λ 2.82 (1.41, 5.05) *161 parents*	Family study with 179 African American families ascertained through index sarcoidosis cases diagnosed at Henry Ford Hospital in Detroit, Michigan, between 1970 and 1999.	[36]
Sibs: λ 36-73 *38 siblings of 15 index patients with an affected sibling*	Survey among 406 index patients with sarcoidosis, from a hospital in London (62.2% Caucasian, 37.4% Afro-Caribbean and 11.8% Asian), attending the Royal Brompton Hospital between the years 1990 and 1995	[19]
Sibs OR[a]5.8 (2.1–15.9) *2722 cases/2587 controls* Avuncular OR 5.7 (1.6–20.7) *5884 cases/5435 controls* Grandparents OR 5.2 (1.5–18.0) *2936 cases/2792 controls* Parents OR 3.8 (1.2–11.3) *1468 cases/1396 controls* Children OR 3.3 (0.3–32.2) *1335 cases/1354 controls* Spouses OR 0.2 (0.04–1.1) *702 cases/700 controls*	355 European American and 291 African American case-control pairs, who participated in the multicenter ACCESS (A Case–Control Etiology Study of Sarcoidosis) study from 1996 to 1999.	[2]

*Numbers between brackets represent 95% confidence intervals. In italic the number of individuals used for the calculations.
[a] In the ACCESS study (ACCESS), the method of Liang was used to calculate odds ratios and p values for covariates in all familial aggregation models.

follow-up. There was no trend over time, but the differences were larger for the Japanese patients [17]. In Spain [15], Löfgren syndrome was observed frequently and also occurred more often in the familial cases of sarcoidosis. Notably, most sarcoidosis cases in that study were female [15]. Others reported rare clinical presentations in familial sarcoidosis, including neuro-ophthalmic sarcoidosis occurring in a woman, whose paternal-uncle also had sarcoidosis [4], and sarcoidosis of the lacrimal gland in two sisters [7]. By means of phenotypic expression modeling in African American sibling pairs using logistic regression, increased risks for ocular (OR 3; CI 1.7–5.4) and liver involvement (OR 3.3; CI 1.5–7.4) were found in the affected sibs [38]. Recently, Pacheco and colleagues [21] did a more extensive comparison between patients with familial (207 cases) and sporadic sarcoidosis (256 cases) from France. In this study, the combination of lung and skin involvement at diagnosis [21] and a younger age at diagnosis were more frequently observed in familial sarcoidosis [21]. Because others had not reported differences in age at diagnosis between familial and sporadic patients, it was thought that the observation of a younger age at diagnosis in familial sarcoidosis patients, could reflect earlier establishment of the diagnosis. Furthermore, differences in disease outcome were found by means of the Sarcoid Clinical Activity Classification (SCAC) [39], that is composed of six progression patterns and, whenever possible, a classification of outcome in four categories: 1) recovery within 3 years; 2) recovery between 3 and 5 years; 3) no recovery at 5 years; 4) death [21]. The authors consider a lack of power regarding the classification of outcome. However, familial sarcoidosis patients appeared to receive less treatment and to recover less often between 3 and 5 years [21]. We conclude that limited studies describe clinical findings in familial sarcoidosis and that scarce results show little overlap. Also, there was no standardized assessment of organ involvement across the different studies included in this review, such standardized assessment is currently available and would aid comparison between studies [40]. Even so, several studies described more severe disease and multi-organ involvements in familial patients, which deserves further investigation.

4. Conclusions

Prevalence of familial sarcoidosis is high in specific study populations from countries worldwide. The estimated heritability of 60–70%, suggests a shared determinant, and the heterogeneous familial risk, associated with both genetic and environmental factors. Familial relative risks and clinical phenotypes may differ between ethnic groups and relative types, but require further study. These findings are potentially important in patient care and deserve investigation in the future.

Declarations of interest

None.

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