Epidemiology of sarcoidosis

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Sarcoidosis is a systemic granulomatous disorder of unknown cause characterised by frequent pulmonary involvement. The disease occurs throughout the world, affecting both sexes, and all races and ages. The incidence and prevalence have been extensively studied, but difficulties arise when ascertaining the real extent of sarcoidosis in a community [1]. First, descriptions of sarcoidosis differ widely among various populations in the world and are usually based on data from different studies without standardisation of the diagnostic criteria [2]. Secondly, the clinical presentation of sarcoidosis is highly variable. Involvement of the lungs or intrathoracic lymph nodes becomes clinically evident in 90% of symptomatic patients during their disease and up to 30% have spontaneous remission [3]. However, a large percentage of sarcoidosis-affected individuals may never manifest clinical disease. In a historical cohort of >1 million USA Navy recruits screened with chest radiographs, of the 134 cases of sarcoidosis detected, 48.5% were asymptomatic on examination [4]. Thirdly, studies use different methods of case detection in different selected population cohorts, possibly resulting in selection bias (*e.g.* community-based radiographic screening programmes *versus* retrospective reviews of histologically proven sarcoidosis cases in a tertiary hospital setting), lack sensitive and specific diagnostic tests to detect the disease, resulting in under-recognition and misdiagnosis of the disease, and lack systematic epidemiological investigations of the cause [5]. The aim of this review is to present the available data of the global incidence and prevalence, the possible risk factors and prognosis, and the survival of subjects with sarcoidosis.

Search strategy, definitions and conditions for study design

Search strategy

To identify the published data on epidemiology of sarcoidosis, a search was carried out in PubMed from 1966 to December 1, 2004 and articles were selected that included the combination of keywords "sarcoidosis", "epidemiology", "incidence" and "prevalence". The search was restricted to articles in English, Dutch, German, French, Italian and Spanish and included review articles and original research publications. Recent reviews found by this strategy were also used to identify additional articles. Letters to the editor, commentaries, and case reports were excluded. Publications from nonpeer-reviewed sources and personal correspondence were not included.

Definitions

The term epidemiology is used to define the distribution of disease, factors that cause disease, and the attributes of disease in defined populations. It also includes incidence, frequency, prevalence, endemic and epidemic outbreaks. Moreover, it incorporates surveys and estimates of morbidity in geographical areas and in specified populations. The term incidence is defined as the number of new cases of a given disease during a given period of time in a specified population. It is differentiated from prevalence, which refers to all cases, new or old, in the population at a given period of time.

Conditions for study design

One of the best ways to ascertain the incidence and natural history of a disease is the cohort study design. This type of study can be carried out by going ahead in time from the present (prospective cohort study) or, alternatively, by going back in time to comprise the cohorts and following them up to the present (retrospective cohort study). A survival analysis is a variation in the design (*i.e.* time-to-event cohort study) and is useful when lengths of follow-up vary substantially or when participants enter a study at different times. Selection bias and bias by lost to follow-up are important limitations, and are a challenge for the presentation of incidence and prevalence indices [6]. As sarcoidosis is a rare disease, selection bias is one of the most important issues to manage.

Case-control study design is a statistical method to identify risk groups and risk factors in sarcoidosis. Unlike cohort studies, case-control studies cannot yield incidence rates. Instead they provide an odds ratio (OR), derived from the proportion of individuals exposed in each of the cases and control groups. When the incidence rate of a particular outcome in the population of interest is low (usually <5% in both the exposed and unexposed groups), the OR from a case-control study is a good estimate of relative risk (RR) [7]. Epidemiologists often praise case-control studies as the most efficient design in terms of time, money and effort, but many methodological issues affect the validity of the results of case-control studies, and two factors, *i.e.* choosing a control group and obtaining exposure history, can greatly affect a study's vulnerability to bias [7]. Most of the research in defining risk factors for sarcoidosis is still in the early stages; only few robust case-control studies exist, of which the ACCESS study (A Case Control Etiologic Study of Sarcoidosis) attracted the most attention [8].

Global incidence and prevalence

Incidence and prevalence

Several studies tried to calculate the incidence and prevalence of sarcoidosis in different settings and by different study designs and, therefore, are at risk for possible bias. A population-based study that was conducted among residents of Rochester, Minnesota, USA from 1935–1984 found that occurrence of asymptomatic sarcoidosis was elevated in immigrants and health professionals because of more routine use of screening chest radiographs or access to chest radiographs. They concluded that the selection of the population by diagnostic access include a possible bias [9], which is intrinsic to cohort studies [6]. The incidence and/or prevalence of sarcoidosis will be discussed by the method of population selection, including: 1) mass chest radiography screening; 2) use of national registries or databases; 3) use of (nationwide) surveys or questionnaires; and 4) reviewing data from autopsy registries.

Mass chest radiography for screening purposes is one of the first methods used to ascertain the occurrence of sarcoidosis, taking into account that up to 90% of the clinically detected cases have chest radiograph abnormalities [10]. In these studies the prevalence of sarcoidosis varied from 0.2 in Portugal to 64 per 100,000 screened individuals in Sweden. In Finland, a prevalence of sarcoidosis was found of 28.2 per 100,000 inhabitants, with an incidence of 11.4 per 100,000 [11].

Another method is the use of national registries or databases to identify sarcoidosis cases. Using a database of a large health maintenance organisation (1967–1987), the incidence of clinically identified sarcoidosis (*i.e.* ascertained either because of symptoms or an incidental chest radiograph) in a northwest USA population was calculated to be 4.8 per 100,000 (95% confidence interval (CI)=1.7–7.9) [12]. A Danish study identified patients with sarcoidosis by using the Danish National Patient Registry (1980–1994), which contained information about presence of disease, sex, age and residence [13]. The overall incidence was 7.2 per 100,000, but decreased over a period of time with an incidence of 8.1 per 100,000 in 1980–1984 to 6.4 per 100,000 in 1990–1994. Furthermore, they reported a difference in incidence from the eastern region compared with the western region, with an incidence increasing from 5.7 to 8.4 per 100,000, respectively [13].

Three studies in Flanders (Belgium) [14], Japan [15], and Korea [16] used a standardised questionnaire, with specific diagnostic criteria for sarcoidosis sent to the (respiratory) physicians in their country. The Belgian study was intended to evaluate the occurrence of different forms of interstitial lung diseases and was compared with two other European registries of interstitial lung diseases [17]. In Flanders (Belgium), a prevalence of 1.33 per 100,000 and an incidence of 0.17 per 100,000 for sarcoidosis was found. YAMAGUCHI *et al.* [15] conducted their survey in 1972 and 1984, and compared the trends over time in prevalence and incidence. They found a prevalence of 3.0 per 100,000 population in 1972 and 3.8 in 1984 in males, and of 3.3 and 5.6 in females, respectively. In contrast, the incidence of 1.2 per 100,000 in males and 1.4 in females had not changed. The nationwide survey of >80-bed size hospitals in Korea found an incidence of 0.03 per 100,000 in 1993 and of 0.13 per 100,000 in 1998 [16]. Interestingly, they reported that not a single case of sarcoidosis was detected among a population of 190,029 that participated in a screening for tuberculosis with mass chest radiography in 1980–1995.

The use of registries of serial autopsy reports of a specific population is another method to report the occurrence of sarcoidosis. In 1964, HÄGERSTRAND and LINELL [18] described 43 cases of sarcoidosis among 6,706 autopsies (*i.e.* 60% of the population who died) in 1957–1962 in Malmö (Sweden), and calculated a prevalence of 640 per 100,000. A review of 9,324 adult autopsy files from Cuyahoga County (USA) over a period of 7 yrs revealed that 31 cases had sarcoidosis and calculated a prevalence of 320 per 100,000 [19].

Age and sex variations

The study by BYG *et al.* [13], which used the Danish National Patient Registry, found a difference in sex and age at diagnosis with a peak incidence in males aged 30–34 yrs of 14.8 per 100,000. Females displayed two peak incidences at 25–29 yrs of age (10.5 per 100,000) and at 65–69 yrs of age (11.0 per 100,000). The median age in males was 38 yrs and in females it was 45 yrs, with an overall male to female ratio of 1.06 [13].

The ACCESS study, a USA based, multicentre case-control study on the aetiology of sarcoidosis, determined organ involvement for the whole group of 736 patients with sarcoidosis within 6 months and differentiated them into subgroups by sex, race, and age (<40 yrs or ≥40 yrs). The study population was heterogeneous in terms of race (53% White, 44% Black), sex (64% female, 36% male), and age (46% <40 yrs). Females were

more likely to have eye and neurological involvement (Chi-squared test=4.74 (p<0.05) and 4.60 (p<0.05), respectively), erythema nodosum (7.28; p<0.01), and more often were ≥40 yrs (6.07; p<0.02), whereas males were more often suffering from hypercalceamia (7.38; p<0.01). The ACCESS investigators concluded that the initial presentation of sarcoidosis was related to sex, race and age [2].

Sarcoidosis in children

Sarcoidosis is uncommon in children, although little epidemiological data exist. A Danish study describes the incidence of sarcoidosis in children ≤15 yrs of age from data obtained from a nationwide patient registry from 1979–1994. They found an incidence of 0.29 per 100,000 person-yrs. The incidence was 0.06 in children aged ≤4 yrs and increased gradually with age to 1.02 in children aged 14–15 yrs. General malaise, fever, weight loss, abdominal discomfort, respiratory symptoms, lymphadenopathy and central nervous system symptoms were common; a total of 31% of patients had erythema nodosum, 12.5% had sarcoid skin lesions, 25% had uveitis/iridocyclitis and 4.2% had sarcoid arthritis [20]. The same authors confirmed the incidence in another Copenhagen-based registry and calculated that the approximate incidence of clinically recognised sarcoidosis in Danish children aged <15 yrs was 0.22–0.27 per 100,000 children per yr, corresponding to approximately three new cases in Denmark each year. In children aged <5 yrs, the disease is characterised by involvement of the skin, eyes and joints, whereas in older children involvement of lungs, lymph nodes and eyes predominate. The long-term prognosis is not well established, but it seems to be poorer in children aged <5 yrs. Older children appear to have a prognosis as favourable as in young adults [21].

Prognosis and risk of death

Sarcoidosis is a benign disorder. A substantial percentage of sarcoidosis-affected individuals may never manifest clinical disease and up to 30% have spontaneous remission [3]. A chronic course occurs in 10–30% of patients, at times resulting in significant impairment of lung function [22]. Mortality rates of 1–6% have been reported [23–25]. The presence of fibrosis on chest radiograph and a vital capacity of <1.5 L seems predictive for dying from respiratory failure because of their sarcoidosis [26, 27].

Comparing the mortality of different forms of interstitial lung disease in a tertiary hospital setting, sarcoidosis had the best prognosis with a 5-yr survival of 91.6% in sarcoidosis compared with 85.5% in idiopathic interstitial pneumonia (nonspecific interstitial pneumonia, desquamative interstitial pneumonia), 84.1% in hypersensitivity pneumonitis, 69.7% in lung fibrosis due to connective tissue disease, 69.5% in undefined forms of lung fibrosis, and 35.4% in idiopathic pulmonary fibrosis [27]. Patients with advanced sarcoidosis awaiting lung transplantation have a high mortality rate with a median survival of <2 yrs [22]. The survival rate of listed patients was 66% at 1 yr, 40% at 2 yrs, and 31% at 3 yrs. Survival after transplantation was 62% at both 1 and 2 yrs, and 50% at 3 yrs. SHORR et al. [28] calculated that patients with sarcoidosis are at as high a risk for mortality as patients with idiopathic pulmonary fibrosis while awaiting transplantation. They also found in another study that race, pulmonary hypertension and oxygen use are important factors indicative of mortality in sarcoidosis patients on the waiting list for lung transplantation [29].

Only one case-control study suggests a possible increased risk of malignant lymphomas, lung cancer as well as cancer, in other organs frequently involved in sarcoidosis [30]. Two groups of 474 patients from an incidence study (1966–1980) and 8,541 patients identified in the Swedish Inpatient Register (1964–1994) were tested. They

found an elevated RR for cancer in both cohorts, (RR 1.3; 95% CI 1.2–1.4). An elevated risks were found for melanoma (RR=1.6; 95% CI=1.0–2.3) and nonmelanoma skin cancer (RR=2.8; 95% CI=2.0–3.8). An increased risk was also found for liver cancer (RR=1.4; 95% CI=0.8–2.2). However, this study was not confirmed by a long-term follow-up study of 555 Danish sarcoidosis patients. No increased risk of lung cancer or malignant lymphoma (OR=0.23, 95% CI=0.00–1.25 and OR=1.25, 95% CI=0.02–6.95, respectively) was found. Neither age at diagnosis of sarcoidosis nor clinical sarcoidosis features were indicators of later occurrence of malignancy [31].

Prognosis is linked to sarcoidosis severity [26]. RABIN et al. [32] examined the socioeconomic and insurance characteristics of Black and White patients in municipal and private hospital sarcoidosis clinics and their relationship to severity, and the disease's functional and social significance. They concluded that: 1) sarcoidosis severity is associated with socioeconomic status and insurance indicators; 2) no/public insurance and low income are associated with functional limitations; and 3) the lack of private insurance may inhibit the use of medical care, contributing to disease severity and impairment [32].

Risk factors

Environmental and occupational risk factors

An epidemiological investigation using a cluster analysis on the Isle of Man, UK in 1987 found a time–space association with sarcoidosis incidence. This case-control study of residents of the Isle of Man observed that 39.6% of sarcoidosis cases reported prior contact with a person known to have the disease, compared with 1–2% of controls. These contacts included members of the same household, colleagues at work, and close friends. A possible 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 [33] through the presence of a shared environmental or infectious exposure. However, this has never been proved.

Some studies have observed a seasonal clustering of sarcoidosis cases in winter and early spring [34]. The peak incidence appeared to be between March and May in London, March to April in Athens, January to June in Finland [35], and between May and August in Japan [34]. YAMAGUCHI et al. [15] found that the prevalence of sarcoidosis was higher in the Northern part of Japan with cold winters and cool summers, in contrast with the Southern part characterised by mild winters and warm summers.

Geographical and spatial clusters of disease have also been described, although problems with disease misclassification, with differences in racial distributions in these regions and with study design, hamper interpretation. In the 1940s an increased disease prevalence in the rural south-eastern and middle Atlantic USA led to studies that examined potential aetiological factors in meteorology and soil, beryllium in clay, plants, pine, pollen, proximity to forests, water supply, use of firewood, proximity to lumbering and wood milling, and exposure to farm animals and pets. Neither animal experiments nor human studies have yet proven these hypotheses [3]. Also intriguing is the inverse relationship between the presence of sarcoidosis and smoking tobacco. This relationship has never been thoroughly examined, and is possibly biased by the fact patients discontinue smoking on onset of symptoms [3].

The most robust study that investigated the association between environmental and occupational exposures and sarcoidosis is the ACCESS study [8]. In this study 10 centres

recruited 706 newly diagnosed patients with sarcoidosis and an equal number of age-, race-, and sex-matched control subjects. Interviewers administered questionnaires containing questions regarding occupational and nonoccupational exposures. They observed positive associations between sarcoidosis and specific occupations (*e.g.* agricultural employment, OR=1.46, 95% CI=1.13–1.89), exposures (*e.g.* insecticides at work, OR=1.52, 95% CI=1.14–2.04, and work environments with mould and mildew exposures (environments with possible exposures to microbial bioaerosols), OR=1.61, 95% CI=1.13–2.31). A history of ever-smoking cigarettes was less frequent among cases than control subjects (OR=0.62, 95% CI=0.50–0.77). In multivariable modelling, an elevated OR for work in areas with musty odours (OR=1.62, 95% CI=1.24–2.11) and with occupational exposure to insecticides (OR=1.61, 95% CI=1.13–2.28), and a decreased OR related to ever-smoking cigarettes (OR=0.65, 95% CI=0.51–0.82) were observed. The study did not identify a single, predominant cause of sarcoidosis.

Occupational clusters, with presumptive toxic or infectious exposures, have been reported for sarcoidosis in healthcare workers [33, 36, 37], USA Navy enlisted males serving on aircraft carriers, lumbar or wood millers, post office workers and mechanics [3], and fire fighters [38]. Perhaps this increased incidence is only reflecting increased detection rates arising from more frequent use of routine chest radiographs in these occupations [3, 38]. This argument is probably not true for fire fighters, an occupation more at risk for toxic exposures. A case-control study was performed in the New York City Fire Department, New York, NY, USA with >11,000 fire fighters as cases and nearly 3,000 emergency medical services healthcare workers as the controls. The investigators found an annual incidence of biopsy-proven sarcoidosis in fire fighters ranging from 0–43.6 per 100,000, and averaged 12.9 per 100,000. This study, although being a case-control design, did not calculate the OR of the risk factor (being a fire fighter of the New York City Fire Department), probably because controls are not selected in the same time period as for the case group and, therefore, are not comparable.

A case-control study performed among 10,161 USA military personnel suggests the association between sarcoidosis-like disease and environmental factors. They found, after adjusting for age, ship assignment and length of service, a decreased risk for sarcoidosis diagnoses among males who worked only on "clean ships" (OR=0.37, 95% CI=0.13–0.84) [39]. They calculated that being Black (OR=8.6, 95% CI=7.5–10.0), entered in the USA Navy before 1985 (OR=4.7, 95% CI=3.6–6.3), length of service (OR per yr=1.1, 95% CI=1.1–1.1) and age at entry (OR=1.4, 95% CI=1.3–1.7) were increased risk factors. In the study, they could not assign which single factor was attributable to the decreased risk.

Infectious agents as risk factor

Environmental exposures to infectious agents have been from time to time appointed as the (exclusive) causative agent for sarcoidosis. The characteristic lesion of sarcoid granulomas is a discrete, compact, noncaseating epithelioid cell granuloma and can only be differentiated with an infectious cause by microbiological studies and cultures [5]. Also, the granulomatous nature of inflammatory response in sarcoidosis suggests that infection may play a possible role in the pathogenesis of this disease [3].

Mycobacteria have, since the search of the aetiology of sarcoidosis, always be one of the most important suspects. Several studies identified DNA of mycobacteria by PCR [40, 41]. The study of SABOOR *et al.* [41] included 104 patients (62 referred for possible tuberculosis and 20 for possible sarcoidosis, and 22 control patients) and analysed bronchial washings, and tissue specimens (one from each patient) underwent assay by PCR. They found *Mycobacterium tuberculosis* DNA was found in half the sarcoidosis

patients, and nontuberculosis mycobacterial DNA in a further 20%, suggesting that *M. tuberculosis* complex may play an aetiological role in sarcoidosis [41]. However, isolation or culture of mycobacteria in the specimens has until now never been shown, which is an important criteria for establishing an infectious agent as a cause of sarcoidosis.

On April 11, 2002 the Swedish newspaper "Aftonbladet" printed on its front-page "Bakterien finns hos var sjätte fasting", as if the cause of sarcoidosis was defined. Many sarcoidosis patients and their representative support groups were informed, as they had to be treated by antibiotics and many physicians had to temper their thoughts. This news was derived from an article published by NILSSON *et al.* [42]. They found genetic material from *Rickettsia helvetica* by PCR in samples obtained from autopsy of two patients with sarcoidosis. However, in a recent study, sera from 20 well-characterised sarcoidosis patients did not display detectable titres of anti-rickettsia immunoglobulin G antibodies. Therefore, the association between Rickettsia and sarcoidosis could not be confirmed [43].

Genetic risk factors

The familial predisposition dates back to 1920s when the first cases of acute sarcoidosis in siblings were reported. There have been a number of reports of the prevalence of familial clustering in sarcoidosis, ranging from 1.7% (UK), 4.3% (Japan), 4.7% (Finland), 9.6% (Ireland) to 17% (African-Americans) [44].

The ACCESS study estimated sarcoidosis familial RR using data on disease occurrence in 10,862 first- and 17,047 second-degree relatives of 706 age-, sex-, race- and geographically-matched cases and controls. They concluded that a significant elevated risk of sarcoidosis was observed among first- and second-degree relatives of sarcoidosis cases compared with relatives of matched control subjects. Siblings had the highest RR (OR=5.8, 95% CI=2.1–15.9), followed by avuncular relationships (OR=5.7, 95% CI=1.6–20.7), grandparents (OR=5.2, 95% CI=1.5–18.0), and then parents (OR=3.8, 95% CI=1.2–11.3). In a multivariate model fit to the parents and siblings data, the familial relative risk adjusted for age, sex, relative class, and shared environment was 4.7 (95% CI=2.3–9.7). White cases had a markedly higher familial RR compared with African-American cases (18.0 *versus* 2.8; p=0.098) [45]. Another study, in which 179 African-American families were ascertained through an index sarcoidosis case diagnosed at Henry Ford Hospital in Detroit, Michigan, USA, found that in African Americans, siblings and parents of sarcoidosis cases have about a 2.5-fold increased risk for sarcoidosis [46].

A study performed in the UK in 2000, based on a questionnaire and answered by 268 sarcoidosis patients, revealed that 5.91% were found to have at least one other relative (first, second or third degree) with biopsy-proven sarcoidosis. They calculated that the prevalence of sarcoidosis in siblings of an affected person/population prevalence for the disease (*i.e.* RR ratio to siblings of sarcoidosis) was 38–73 (95% CI=21–145) [44]. Interestingly, they found an absence of a significant difference in ethnic distribution between familial and index sarcoidosis patients, which is in contrast to the findings of RYBICKI *et al.* [46].

Conclusion

The global incidence and prevalence of sarcoidosis have been extensively studied, but difficulties arise when ascertaining the real extent of sarcoidosis in a community. In the

different studies presented, the prevalence varies between 0.03–640 per 100,000. The lack of standardisation of the diagnostic criteria, the different methods of case detection in different selected population cohorts used and the lack of sensitive and specific diagnostic tests to detect the disease are different causes of this variation in prevalence. The prognosis of sarcoidosis is favourable. A large percentage of affected individuals may never manifest clinical disease and up to 30% have spontaneous remission. A chronic course occurs in 10–30% of the patients, at times resulting in significant impairment of lung function. Mortality rates of 1–6% have been reported. Studies that defined possible environmental, occupational and genetic risk factors as cause of sarcoidosis are promising, but most of the research in defining risk factors for sarcoidosis is still in the early stage. These case-control studies, together with recent advances in molecular genotyping, will hopefully help to define in the future the genetic factors that predispose to sarcoidosis and to the variability in the phenotype of sarcoidosis.

Summary

The global incidence and prevalence of sarcoidosis varies between studies, mostly because of selection bias when ascertaining the actual extent of sarcoidosis in a given community. The prevalence of sarcoidosis varies between 0.03–640 per 100,000 in various studies.

In general, the prognosis of sarcoidosis is favourable. A large percentage of affected individuals may never manifest clinical disease and up to 30% have spontaneous remission. A chronic course occurs in 10–30% of patients, at times resulting in a significant impairment of lung function. Mortality rates of 1–6% have been reported. Studies that defined possible environmental, occupational and genetic risk factors as a cause of sarcoidosis are promising. Most of the research in defining risk factors for sarcoidosis are still in the early stages and only a few robust case-control studies exist, of which A Case Control Etiologic Study of Sarcoidosis (ACCESS) attracted the most attention.

Keywords: Epidemiology, incidence, prevalence, prognosis, risk factors, sarcoidosis.

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