

Epidemiology of Sarcoidosis

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Sarcoidosis is a multisystemic disease in which lung involvement is common. Its incidence and prevalence have been extensively studied, but with contradictory results because of the lack of standard diagnostic criteria, variations in the methods for detecting cases, and the low sensitivity and specificity of diagnostic tests. Prognosis is generally favorable. Many of those affected remain asymptomatic and remission often occurs spontaneously, although between 10% and 30% of the patients have chronic disease and permanent deterioration in lung function. Sarcoidosis is caused by an external agent that triggers a characteristic immune response in genetically susceptible individuals. Environmental, occupational, and genetic factors have all been implicated, but research is still in the early stages. Case-control studies, as well as advances in molecular biology, will help to identify genetic susceptibility factors and to understand the different phenotypes of sarcoidosis.

Key words: *Sarcoidosis. Epidemiology. Etiology.*

Epidemiología de la sarcoidosis

La sarcoidosis es una enfermedad multisistémica que afecta frecuentemente al pulmón. Su incidencia y prevalencia han sido ampliamente estudiadas, pero la falta de estandarización del diagnóstico, los diferentes métodos de detección de casos y la escasa sensibilidad y especificidad de las pruebas diagnósticas explican los datos discordantes. El pronóstico es generalmente favorable. Gran parte de las personas afectadas no manifestarán nunca síntomas y muchas tienen remisión espontánea. El curso es crónico en el 10-30% de los casos, con un deterioro permanente de la función pulmonar. La enfermedad es el resultado de la acción de un agente externo que desencadena la respuesta inmunitaria característica en individuos genéticamente susceptibles. Se han implicado factores ambientales, ocupacionales y genéticos, pero las investigaciones están todavía en los inicios. Estudios de casos y controles, así como los avances en biología molecular, ayudarán a definir los factores de susceptibilidad genética y a entender los distintos fenotipos de la sarcoidosis.

Palabras clave: *Sarcoidosis. Epidemiología. Etiología.*

Introduction

Ever since the dermatologist and surgeon Jonathan Hutchinson first reported a case of sarcoidosis in London in 1877 as a dermatological disease, sarcoidosis has intrigued clinicians and investigators. For decades, clinical knowledge of the disease has advanced and findings based on pathological investigations have accumulated, but little is known of the epidemiology of the disease and the factors that contribute to its development and form of expression. Suitable treatment has yet to be well defined for all patients, and more importantly, the cause remains unknown.¹

Sarcoidosis is characterized by an initial immune response of type 1 T-helper cells, leading to the

multisystemic development of noncaseating granulomas. The most commonly affected organs are the lungs (90%), the skin, and the eyes. Within 2 to 5 years of onset of symptoms, more than 60% of the patients make a full recovery, but in almost 30%, the disease follows a chronic course, leading eventually to pulmonary fibrosis with permanent respiratory symptoms in some cases. A multidisciplinary approach to the disease is often necessary given its complexity and the broad range of symptoms a patient may suffer.

A disease state can usually be classified according to the activity or severity of that disease but, in the case of sarcoidosis, activity does not necessarily indicate a progressive course, fatal prognosis, or the need for treatment. This represents a challenge for the clinician, who faces many difficulties when attempting to classify a given sarcoidosis patient.

Recognition of race as an important risk factor for developing the disease is a clear indication that individuals

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may be genetically predisposed.² Recent research has therefore aimed to identify genetic risk factors and clarify how the patient's genotype determines the presentation and course—that is, the phenotype—of the disease. This research has shown that sarcoidosis is a complex disease whose genetic predisposition is not governed by a single gene.³

Why Has the Etiologic Agent Not Yet Been Determined?

Sarcoidosis is a systemic granulomatous disease that occurs throughout the world and that affects men and women of all ages and races. Why then has no causative agent been found?

Even though investigators have spent decades trying to isolate a possible microbiological agent, success has been limited for a number of reasons. First, we may still not know the optimal conditions for isolating the possible causative microorganism. Alternatively, the disease might not be triggered by infection. Finally, this nosologic entity labeled sarcoidosis might actually be the sum of more than one disease each with a different etiology.⁴

In addition to these reasons, others related to the design of the studies done to investigate this disease may also explain why the etiologic agent of sarcoidosis has yet to be discovered. For example, a careful review of the medical literature⁵ shows that investigators have used a broad, imprecise, and varied case definition. The possible influence of this limitation has, however, diminished since the publication of guidelines for the disease.¹ Another difficulty is the variety of approaches used for recruiting patients in the studies published in the literature, thus hindering a comparison of findings.

Given the heterogeneity of the disease itself, which presents with a wide range of clinical patterns, we may not even be dealing with a single disease. Rather, different etiologic agents may be involved or a single agent may be responsible for different effects according to individual susceptibility determined by genetic factors.⁶

Worldwide Incidence and Prevalence

Epidemiology identifies the distribution of the disease, the factors that cause it, and its characteristics in a given population. Epidemiology also covers incidence, frequency, prevalence, endemic, and epidemic patterns, and includes studies and estimates of morbidity and mortality in specific regions and populations.

Many investigators have attempted to calculate the incidence and prevalence of sarcoidosis in different populations through a variety of approaches such as detection of diseased lymph nodes with simple chest radiography, national registries, databases or questionnaires, and reviews of autopsies. The data available are therefore discordant and difficult to extrapolate to the rest of the population.

Up until recently, the disease was thought to be more frequent in adults under 40 years old, with the incidence peaking in patients aged between 20 and 29 years. In

Scandinavian countries and Japan, a second peak in the incidence is observed in women over 50 years old. Most studies point to a slight predominance among women and, according to population studies done in the United States of America, the risk of suffering sarcoidosis is 0.85% for whites and 2.4% for blacks,² with an annual age-adjusted incidence rate in that country of 35.5 cases per 100 000 blacks and 10.9 cases per 100 000 whites.⁷

The published annual incidence rates are lower in Spain. In the study done in a health care district of the province of Leon, an incidence of 1.37 per 100 000 inhabitants was reported,⁸ and for the whole country, the overall annual incidence rate was estimated to be 1.36 per 100 000 inhabitants.⁹ According to the Spanish registry of the incidence of diffuse interstitial lung disease for October 2000 to September 2001, with data from 37 centers, sarcoidosis was the second cause of interstitial disease in Spain behind idiopathic pulmonary fibrosis, with 76 cases recorded, corresponding to 14.9% of all cases of diffuse interstitial lung disease.¹⁰

Studies of prevalence also report contradictory results, with rates ranging from 1 to 40 cases per 100 000 inhabitants per year. Swedes, Danes, and African Americans appear to have the highest prevalence rates in the world population.¹¹

The largest and best designed study to date is the ACCESS study (A Case Control Etiologic Study of Sarcoidosis¹²), which has shed light on different epidemiological and etiologic aspects of sarcoidosis. That multicenter study was designed to determine the etiology of the disease. Ten investigators in the USA participated from 1997 to 1999. The importance of the study lies in the selection criteria and case definition, which attempted to overcome the imprecision of previous studies. Case definition required histologic confirmation of noncaseating granulomas, even though these were not pathognomonic, and biopsies had to be interpreted as indicative of the diagnosis of sarcoidosis, with other possible causes ruled out (Table). All histologic samples were analyzed in a central laboratory and were reviewed by the same pathologists designated for the study.¹³ With case definition clearly established, all centers participating in the ACCESS study followed a strict protocol for diagnosis with clear and well-defined criteria for determining organ involvement and for recruitment of the control group.¹⁴

In addition to investigating the possible etiology of the disease, this study examined the psychosocial characteristics¹⁵ and clinical course of 736 patients enrolled in the first 6 months after histologic diagnosis of sarcoidosis and compared them with control subjects paired by age, sex, and race. A follow-up study of the first 215 cases was undertaken 2 years after enrollment.¹⁶ Despite its importance, this study is subject to limitations. For example, it may overestimate lung involvement (found in 95% of the cases) because the investigators were pulmonologists. Also, with a follow-up period of 2 years, patients with chronic sarcoidosis, that is, those who probably had the most severe form of the disease, were not included. We must wait longer

Granulomatous Diseases and Possible Etiologies of Sarcoidosis

Type of disease	
Infectious disease	
Fungi	<i>Histoplasma</i> species, <i>Aspergillus</i> species, <i>Coccidioides</i> species
Protozoa	<i>Toxoplasma</i> species, <i>Leishmania</i> species
Metazoa	<i>Schistosoma</i> species
Spirochetes	<i>Treponema pallidum</i>
Mycobacteria	<i>Mycobacterium tuberculosis</i> complex, <i>Mycobacterium leprae</i> , nontuberculous mycobacteria
Bacteria	<i>Yersinia</i> species, <i>Brucella</i> species, <i>Borrelia</i> species, <i>Propionibacterium</i> species
Virus	Epstein-Barr virus, herpesvirus, cytomegalovirus, <i>Coxsackie</i> virus
Neoplastic disease	Carcinomas, sarcomas
Metals	Beryllium, aluminum, titanium, zirconium
Inorganic dusts	Silica, talc, silicone, glass fiber
Organic dusts	Hypersensitivity pneumonitis
Autoimmune diseases	Crohn disease, primary biliary cirrhosis, giant cell arteritis, common variable immunodeficiency, hypogammaglobulinemia
Vasculitis	Wegener disease, Churg–Strauss disease, lymphomatoid granulomatosis, polyarteritis nodosa, bronchocentric granulomatosis
Others	Leukocyte oxidase deficiency, Blau syndrome

for the findings from this study on the course and prognosis of the disease.

Nevertheless, the results of the ACCESS study are surprising in many ways. First, the age of the patients at onset of the disease was over 40 years, particularly among women. The investigators were unable to find a reason for this “delay” with respect to previous studies. Second, the investigators concluded that lung involvement was the only form of the disease independent of age, sex, or race, whereas other clinical presentations of the disease appeared linked to these factors.¹⁷ Each of these aspects will be discussed at length in the present review.

Variations According to Age, Sex, and Race

Epidemiological information on sarcoidosis is based principally on studies done more than 30 years ago. These early studies already pointed to a greater prevalence among blacks compared to whites and women compared to men.¹⁸ These findings were the basis for subsequent studies that confirmed certain interesting associations but that failed to find such clear differences according to race and sex as suggested initially. Indeed, the risk of sarcoidosis among the African American population is 3 to 4 times greater than among Caucasians in the USA. Women have a higher relative risk than men, but this relative risk does not exceed 2. Familial clustering was also found, indicating a certain genetic susceptibility. Familial sarcoidosis is more frequent among African Americans (17%) than among Caucasians (6%).¹⁹ The epidemiological evidence from these studies indicates that both environmental and genetic risk factors for sarcoidosis should be considered because the disease is likely to be caused by an interaction of these 2 types of factor.²⁰

A recent population study in Denmark using the national patient registry found differences in age and sex at diagnosis. For men, the incidence of the disease peaks in

patients aged between 30 years and 34 years old at 14.8 cases per 100 000 inhabitants, whereas women show 2 peaks, one for patients aged between 25 years and 29 years old (10.5/100 000 inhabitants) and the other for those aged between 65 years and 69 years old (11.0/100 000 inhabitants).²¹ The mean age at onset was 38 years for men and 45 years for women, with a slight predominance among women of 1.06.

In the ACCESS study, the study population was heterogeneous in terms of race (53% were white and 44% black), sex (64% were women and 36% men), and age (46% were under 40 years of age), but the differential characteristics are interesting. Women presented more often with neurological or ocular involvement, erythema nodosum, and age over 40 years, whereas in men, abnormal calcium metabolism was reported more frequently. In black patients, skin involvement other than erythema nodosum, ocular, hepatic, and bone-marrow involvement, and lymph node disease outside the thorax were reported more often.¹⁷ The biggest differences in this study were reported in relation to the race of the patients.

Little epidemiological data are available for children under 15 years of age,²² although an annual incidence of 0.29 cases per 100 000 inhabitants has been reported for this population, with variations from 0.06 in children under 4 years old and progressive increases up to 1.02 in children aged 14 years to 15 years old. Children have a more favorable prognosis, similar to that of young adults.

Despite contradictory data from the different studies, it seems clear that sarcoidosis tends to develop in early adulthood (the disease is rarely reported in infancy and adolescence or in patients aged over 70 years old²³), leading to the hypothesis that exposure to environmental or infectious agents or antigens might occur during the working life of the patients. The contribution of occupational exposure has therefore

been proposed. The reader is reminded that the proportion of those affected is slightly greater among women. However, in the only US population study of incidence,⁷ the age-adjusted incidence was similar for men (5.9/100 000 inhabitants/year) and women (6.3/100 000 inhabitants/year), but the investigators highlighted the rise in incidence among women between 1946 and 1975. This finding prompted them to suggest that the progressive incorporation of women into the workplace during this period would lead to greater exposure to environmental antigens that might trigger the development of the disease.

All studies show evidence that sarcoidosis is more frequent among blacks than Caucasians but, paradoxically, certain clustering has been documented among descendants of northern Europeans, particularly for the acute forms of the disease, such as Löfgren syndrome.²⁴ Studies done in these patients point to an important genetic determinant that would explain these forms of presentation,²⁵ though consideration needs to be given to many other factors associated with the host and the environment that might influence expression of these genes.

Seasonal and Regional Association

Sarcoidosis tends to develop towards the end of winter and, above all, at the beginning of spring.²⁶⁻²⁸ The period of latency between exposure to the causative agent and developing sarcoidosis symptoms is assumed to be of the order of a few weeks to a few months, in line with experimental animal models. Exposure would therefore often have to occur in the months prior to clinical manifestation. An attractive hypothesis is that sufferers would be in closer contact with the etiologic agent, whether antigenic or infectious, when they spend more time in enclosed areas such as the workplace or at home during the coldest months. We would thus think of sarcoidosis as a "building-related" disease, resulting from sensitization to antigens or germs suspended in the air (bioaerosols), as is the case for other diseases such as hypersensitivity pneumonitis or legionellosis.

Not all studies agree on the spacial distribution of sarcoidosis. Nevertheless, despite the discrepancies in the different methods used, most of the published data point to disease being more common in certain areas. This has led to investigation of meteorological factors, and studies of soil, plants, pollen, closeness to forests, use of water resources, use of logs for fuel, and exposure to household pets or farm animals in the search for possible etiologic agents or risk factors.⁶ The ACCESS study found a positive association between certain occupations (farming), exposure to certain potentially toxic agents (insecticides and organic dust in the environment), and work in contaminated atmospheres with musty smells. That same study documented a greater risk of sarcoidosis among those who had lived in small towns in their childhood, suggesting that a rural environment is a risk factor.²⁹ This association has also been described in Spain.³⁰

In addition to regional associations, sarcoidosis shows a certain tendency to appear in individuals in close physical contact with patients or with close relatives within the same community. A case-control study in the Isle of Man in the United Kingdom revealed that 40% of the 96 confirmed cases had been in close contact with a person previously diagnosed with sarcoidosis, compared to 1% to 2% of the controls.³¹ Of these contacts, 14 occurred in the same house, although only 9 were blood relatives. A further 19 had been in contact with co-workers, 2 with neighbors, and 14 with friends who they were not living with. This spacial association suggests that sarcoidosis may be a communicable disease, but the association could also be due to exposure to a common environmental or occupational agent that induced the same hypersensitivity response.

Prognosis and Mortality

Sarcoidosis is not a malignant process. Many patients never develop clinical manifestations of their disease and remission is spontaneous in more than 30%. The disease follows a chronic course in 10% to 30% of the cases, sometimes leading to significant deterioration in lung function. Mortality rates of 1% to 6% have been reported,³² findings of fibrosis in the chest radiograph and a forced vital capacity below 1.5 L are predictive of death due to respiratory failure caused by sarcoidosis.³³ A recent study found that 40% of sarcoidosis patients with pulmonary hypertension were without stage IV radiographic findings; that is, they did not have fibrosis. When fibrosis and pulmonary hypertension are present at the same time, there is a sharp drop in respiratory function variables (diffusing capacity of lung for carbon monoxide of 30%-35%; forced midexpiratory flow rate $\leq 30\%$; forced expiratory volume in 1 second < 1.2 L). Such findings should alert the clinician to this serious complication.³⁴

In the survival analysis, sarcoidosis has a better prognosis at 5 years (91.6% survival) compared to other diffuse interstitial lung diseases such as nonspecific or desquamative interstitial pneumonia (85.5%), hypersensitivity pneumonitis (84.1%), collagen-related diffuse interstitial lung disease (69.7%), undefined forms of pulmonary fibrosis (69.5%), and idiopathic pulmonary fibrosis (35.4%).³³ Only 1 case-control study points to a possible increased risk for developing neoplastic processes such as lymphomas, lung cancer, or cancer of other organs affected by the disease,³⁵ but these findings have not been confirmed in other studies with long-term follow-up.³⁶ Indeed, those studies concluded that neither the age of the patient nor the clinical manifestations at diagnosis are indicative of subsequent development of neoplastic disease. What is beyond doubt is that the prognosis of sarcoidosis is clearly linked to the severity of the disease.

Risk Factors

Variation in individual susceptibility to sarcoidosis has been clearly established.

Genetic factors are associated with specific patterns of the disease (clinical phenotype), the risk of falling ill, and

the severity and progression of sarcoidosis.³⁷⁻⁴⁰ As a result, even if a specific environmental factor could be identified, the risk of disease is probably determined by the interaction of this environmental factor with genetic factors in the host and with the host's socioeconomic status and health behavior.^{41,42}

There is good reason to think that sarcoidosis is caused by environmental antigens in genetically predisposed individuals. Both the skin and lungs—the organs most frequently involved—are in constant contact with such antigens. Studies of immunopathogenesis in sarcoidosis suggest that the disease is the result of an immune response and that there are many potential environmental antigens that may induce sensitization and subsequent response mediated by the cells responsible for the development of granulomas.⁴³ These environmental factors cause a host of diseases that simulate sarcoidosis (Table). Factors include inhalation of beryllium or other metals (aluminum, titanium, and zirconium), hypersensitivity pneumonitis, and infections such as tuberculosis and atypical mycobacterial and fungal infections, among others. Inorganic fibers and dusts (talc, silica, and glass fiber) are also able to induce immune responses similar to those of sarcoidosis. The list of agents able to induce a granulomatous response in animals is even longer and includes mycobacteria, avian proteins, fungal spores, amebiasis, and eggs of *Schistosoma* species, *Brucella* species, and *Leishmania* species.⁶ In summary, sarcoidosis is currently thought to appear as a result of exposure to one or more environmental agents that interact with individual genetic factors. The challenge lies in identifying these environmental agents and relating them to genetic susceptibility.

Environmental and Occupational Risk Factors

Some of the first epidemiological studies of sarcoidosis raised the possibility of common exposure to antigens inducing granulomatous immune response in the workplace, but until recently, few studies have prospectively and systematically examined the occupational or environmental exposure of sarcoidosis patients.⁴⁴ Recent publications derived from the ACCESS study,⁴⁵ in addition to a study done in South Carolina in the United States⁴⁶ and another one that examined the occupational risk factors in African American families,⁴⁷ have helped establish the importance of this type of risk factor.

In the study by Barnard et al⁴⁵ based on data from the ACCESS study, Standard Industrial Classification and Standard Occupational Classification codes were used to define the occupation of the patients and to investigate the contribution of occupation to the risk of sarcoidosis. The univariate analysis of the results identified a greater risk among workers with industrial exposure to organic powders, particularly among Caucasians, and among those who worked for suppliers of building materials, hardware, and gardening materials. The jobs associated with childcare were negatively associated with sarcoidosis, as was occupational exposure to metal vapors or dust, a trend that was also more evident among Caucasian workers.

A study carried out by Kajdasz et al⁴⁶ established other associations between black patients admitted to hospital for this disease such as use of wood-burning stoves, fireplaces, consumption of water not from the public mains supply (such as water from wells), or living or working on a farm. This study found that farm work itself was not so important, but rather highlighted the different effects of wood usage in the rural communities of South Carolina.

With a questionnaire derived from the ACCESS study, Kucera et al⁴⁷ found positive associations with certain occupations of African Americans suffering from sarcoidosis compared to healthy siblings. The investigators observed that those who might be exposed to metals at work or who worked in humid places or with musty smells (indicative of an environment rich in microbes) could be at a higher risk. They drew attention to how complex assessment of possible occupational exposure is, making it difficult to identify specific agents based solely on the characteristics of the work. This problem is applicable to most studies of the risk of sarcoidosis due to occupational exposure done to date.

Once again, the ACCESS study is the most consistent one to have investigated the association of environmental and occupational exposure with sarcoidosis. The investigators drew up some questionnaires with specific questions on possible occupational and nonoccupational exposure and its duration. The findings, which have already been mentioned earlier in this review, show a positive association between sarcoidosis and certain occupations such as those related to agriculture, contact with birds, car manufacture, secondary education, and health care. A careful review of the individuals exposed to birds showed that these patients could not be considered as typical cases of hypersensitivity pneumonitis. Additional positive associations with sarcoidosis were also found for the use of insecticides and for work in environments with exposure to fungi or mold, and so the authors investigated the possibility of inhalation of microbial bioaerosols. The multivariate statistical model established high odds ratios (ORs) for areas with musty smells and exposure to insecticides, and a protective effect for smokers and former smokers, although this could be a methodological bias because many of the patients stopped smoking when the symptoms started. In any case, the ACCESS study did not find a single overriding risk factor for sarcoidosis; on the other hand, although the ORs were high for some factors, these associations were generally weak.²⁹

Infectious Agents as Risk Factors

During the last century, the general view was that microbial pathogens caused sarcoidosis. More specifically, mycobacteria were the main suspects, and reports were even published of increased concentrations of these bacteria in blood samples from cases compared to controls, although these findings were not confirmed in a recent study.⁴⁸ Several studies have identified mycobacterial DNA by polymerase chain reaction (PCR) techniques in up to half the patients compared to controls and nontuberculous mycobacteria in more than 20%, which would indicate

that *Mycobacterium tuberculosis* complex could play a part in the etiology of this disease.^{49,50} However, it has not been possible to isolate the germ or cultivate it from patient tissue, a fundamental step in determining the etiology of a process according to the Henle–Koch postulates (isolation of the pathogen in the patient, growth in pure culture, and reproducibility of the disease when inoculated in a susceptible host⁶). In addition, follow-up lasting more than 10 years in sarcoidosis patients positive for *M tuberculosis* has proved insufficient to detect a single case of development of tuberculosis.⁵¹

The Kveim antigen, a protein extract obtained from lymph nodes or spleens, induces an oligoclonal T-cell response in sarcoidosis patients, in addition to producing granulomatous infiltration of the skin. Although the active agent of the Kveim antigen has yet to be identified, this antigen is known not to contain bacterial DNA. A recent study has reported the presence of mycobacterial antigens in sarcoid tissue, as well as antibodies in some patients, once again pointing to the role of mycobacteria in the etiology of this disease.⁵²

This line of investigation is still pursued because, although no infectious agent has been identified in cultures of biopsies from sarcoidosis patients and such agents could not even be consistently detected with ribosomal RNA markers, certain clinical and epidemiological observations point to an infectious origin of this disease. For example, there is evidence of the communicability of sarcoidosis. In fact, “donor-acquired” sarcoidosis has been reported in which the disease develops in the recipient of a tissue or organ transplant from donors with diagnosed or probable sarcoidosis.⁵³ Sarcoidosis has also developed in the transplanted lung of sarcoidosis patients.⁵⁴ Animals implanted with affected tissue from patients have developed sarcoid-like granulomas.⁵⁵ When such human tissue was inoculated into mice, the granulomas took 15 months to develop, but they failed to develop if the tissue sample was autoclaved, frozen to -20°C , or irradiated prior to inoculation.

Examination of the sarcoid granuloma with an electron microscope and immunohistochemical techniques has identified structures similar to organisms such as *Leptospira* species, *Mycoplasma* species, and *Propionibacterium* species.⁶ More research is therefore needed on the nature of the ultrastructural elements that form sarcoid granulomas until a conclusive result is reached.

The epidemiological findings of the ACCESS study clearly point to a link between sarcoidosis risk and environmental conditions conducive to the formation of bioaerosols, whether antigenic or infectious.²⁹ As discussed already, occupations directly related to humid and contaminated atmospheres with musty smells are associated with the risk of sarcoidosis in the multivariate model of the study. During their growth, most fungi exude volatile organic compounds responsible for the characteristic smell associated with fungal contamination. These compounds may reflect the presence of the microorganism even when growth is not visible. Furthermore, in the ACCESS study, cases of sarcoidosis were reported among patients who used air conditioning at home, with and without humidifiers. Many of the microorganisms that have been indicated as

potential etiologic agents of the disease, or that produce clinical signs and symptoms similar to the disease, grow quickly in water. The right conditions for forming aerosols of antigenic particles or infectious agents might lead to the inhalation of these particles, subsequent deposition in the lungs, and induction of the characteristic immune response.

Other microbiological agents that may cause sarcoidosis include herpes virus, retrovirus, *Chlamydia pneumoniae*, *Borrelia burgdorferi*, *Rickettsia helvetica*, and finally *Pneumocystis jiroveci*.⁵⁶ However, none of these pathogens can be considered an etiologic agent of the disease for the same reason that mycobacteria do not meet the Henle–Koch postulates.

Despite great effort to find a possible microbiological agent implicated in the etiology of sarcoidosis, we still lack sufficient scientific evidence to support the hypothesis of an infectious etiology, but nor can it be ruled out. One possibility that has been put forward is that the microorganisms probably act as antigen triggers in genetically predisposed individuals without causing infection, and that these antigens would initiate the granulomatous response of sarcoidosis.⁵⁷ Analysis with PCR techniques could help detect infectious agents in patient tissue, even when cultures fail. With these PCR techniques, it has been possible to identify causative agents of other diseases such as bacillary angiomatosis (*Bartonella henselae*), Whipple disease (*Tropheryma whippelii*), and severe acute respiratory syndrome (new coronavirus).

Genetic Factors

Many studies have focused on familial clusters of sarcoidosis in pairs of parent and offspring of the same sex, mother and son, siblings of the same sex, and monozygotic twins.^{6,19,58} The initial results showed that this familial clustering was more common among blacks than Caucasians.⁵⁹ The figures for prevalence of familial clustering of sarcoidosis range from 1.7% in the United Kingdom, 4.3% in Japan, 4.7% in Finland, and 9.6% in Ireland, to 17% in African American families in the USA.⁶⁰

The ACCESS study investigated familial clustering of sarcoidosis using data from 10 862 first-degree relatives and 17 047 second-degree relatives with 706 pairs of cases and controls matched for age, sex, race, and place of residence. The conclusions were that there is a high risk of developing sarcoidosis for first- and second-degree relatives of patients compared to first- and second-degree relatives of controls. Siblings had the highest relative risk (OR, 5.8; 95% confidence interval [CI], 2.1–15.9), followed by aunts and uncles (OR, 5.7; 95% CI, 1.6–20.7), grandparents (OR, 5.2, 95% CI, 1.5–18), and parents (OR, 3.8; 95% CI, 1.2–11.3). With a multivariate model of the data for parents and siblings, the relative familial risk adjusted for age, sex, social class, and common environmental factors was 4.7 (95% CI, 2.3–9.7), but Caucasian patients had a higher relative familial risk than African American ones (18.0 vs 2.8; $P=0.098$).¹⁹ In another study done in 179 African American families, the same

investigators concluded that the risk of developing the disease was 2.5-fold higher among the siblings and parents of these patients.⁶¹

The study in the United Kingdom, based on a questionnaire answered by 268 sarcoidosis patients, found that 5.91% had at least one first-, second-, or third-degree relative with histologically confirmed sarcoidosis.⁵⁸ The investigators calculated a ratio of prevalence of sarcoidosis in siblings of patients with respect to the prevalence in the rest of the population between 38 and 73 (95% CI, 21-145), with no significant differences according to race, unlike the US study.¹⁹

One of the aims that has occupied investigators most in recent years is the search for the genetic factor responsible for susceptibility to sarcoidosis. The first results were obtained by analyzing the genes of the major histocompatibility complex (MHC), particularly human leukocyte or histocompatibility antigens (HLA). In the pathophysiology of sarcoidosis, antigen recognition, processing, and presentation by the macrophages to the T cells are likely to be affected, according to immunophenotype studies of T cells obtained by bronchoalveolar lavage.⁶² Initial genetic investigation using serologic techniques evaluated possible associations with MHC genes located on the 6p chromosome, specifically, with class I HLA genes. Although no conclusive association was found, the alleles most frequently linked to risk of sarcoidosis were HLA-B8 and HLA-B7. In addition, certain HLA associations have been found in sarcoidosis patients belonging to different ethnic groups.^{59,63}

The most recent studies have used molecular biology techniques to determine associations with class II MHC, specifically, with HLA-DR, which seems to influence susceptibility and disease prognosis more than class I MHC. In recent years, many of these class II alleles have been implicated in certain aspects of the disease. HLA-DR5, HLA-DR6, HLA-DR8, and HLA-DR9 seem to confer risk of falling ill on Japanese patients, although HLA-DR9 protects the Scandinavian population. In German patients, HLA-DR5 is associated with chronic disease and HLA-DR3 with acute forms. Likewise, in Scandinavians, HLA-DR14 and HLA-DR15 are associated with chronic forms and HLA-DR17 with self-limiting ones.⁶⁴ The ACCESS study identified a significant association between HLA-DRB1 alleles (specifically HLA-DRB1*1101) and the development of the disease, both in blacks and Caucasians.⁶⁵ The only class II allele that was distributed differently among different races with respect to the disease was HLA-DRB1*1501, which was associated with controls in blacks and with cases in whites. This would indicate that, in general, alleles similar to class II HLA may be associated with sarcoidosis in both populations.

Similarly, other studies have identified specific alleles of HLA-DQB1 as determining susceptibility to sarcoidosis in the African American population,³⁸⁻⁴⁰ it remains to be shown how these alleles interact with environmental factors and with other genes to determine the disease phenotype.⁶⁶

Ongoing studies will help to confirm whether the genes that confer susceptibility to sarcoidosis are located in this complex region of the 6p chromosome.^{67,68}

Conclusions

We currently have convincing evidence at our disposal that sarcoidosis is triggered by environmental factors that induce effects in genetically susceptible individuals, leading in turn to an excessive immune response with formation of granulomas in the affected organs. Although the disease has been described in almost all populations throughout the world, many variations in incidence and prevalence have been reported among the different clinical phenotypes.

Studies of familial clustering and case-control studies support the hypothesis that immunogenetic predisposition is responsible for the different pattern of affected organs in sarcoidosis. At present, a solid scientific consensus points to the class II MHC location on the 6p chromosome as the site with the strongest genetic associations.

More rigorous definitions of the different clinical phenotypes and the ongoing studies with large patient cohorts that include familial sarcoidosis in combination with recent advances in technology will no doubt extend our understanding of genetic susceptibility to sarcoidosis and its phenotypes.

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