

SARCOIDOSIS

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ABSTRACT

Sarcoidosis is a systemic granulomatous inflammatory disorder that affects multiple organs – lungs, skin, heart, kidneys, liver, eyes, and nervous system, among others. The clinical course of sarcoidosis ranges from spontaneous resolution to chronic progressive disease which can be life-threatening. Most often, patients suffer from cough, shortness of breath, chest pain, and severe fatigue. In more severe cases, there is pulmonary fibrosis and/or irreversible damage to the organs affected by granulomas. Recent studies demonstrate innovative research in the field of sarcoidosis, thus significantly improved our knowledge of epidemiology and causative origins of the disease. Despite numerous studies, the aetiology of sarcoidosis is still not fully understood. It is proposed that the disease is caused by an unknown antigen (antigens) in humans with abnormal immune response, and a genetic predisposition. Here, we overview the current advances in sarcoidosis research.

Keywords: *sarcoidosis, epidemiology, aetiology*

HISTORY AND DEFINITION OF SARCOIDOSIS

The initial description of sarcoidosis is credited to an English physician, Jonathon Hutchinson, who reported the cutaneous form of sarcoidosis in 1875. Caesar Boeck described the skin lesions histologically in 1899. Because they resembled sarcoma but had benign histopathologic and clinical features, Boeck named the lesions 'sarcoid'. Jorgen Schaumann was the first to report systemic sarcoidosis, calling it Lymphogranulomatosis benigna. Sven Löfgren a Swedish physician, was the first to link erythema

nodosum with sarcoidosis. The association is now called Löfgren's syndrome. Since then, many scientists have contributed to the current understanding of sarcoidosis as a systemic disease with diverse clinical manifestations (1,2).

An agreed descriptive definition of sarcoidosis was given by the American Thoracic Society, the European Respiratory Society and the World Association for Sarcoidosis and Other Granulomatous Disorders in 1999: "Sarcoidosis is a multisystem disorder of unknown cause. It commonly affects young and middle-aged adults and frequently presents with bilateral hilar adenopathy, pulmonary infiltration, ocular, and skin lesions. The liver, spleen, lymph nodes, salivary glands, heart, nervous system, muscles, bones, and other organs may also be involved. The diagnosis is established when clinicoradiographic findings are supported by histologic evidence of noncaseating epithelioid cell granulomas. Granulomas of unknown causes and local sarcoid reactions must be excluded. Frequently observed immunologic features are suppression of cutaneous delayed-type hypersensitivity and a heightened Th1 immune response at sites of disease. Circulating immune complexes along with signs of B cell hyperactivity may also be found. The course and prognosis may correlate with the mode of the onset, and the extent of the disease. Acute onset with erythema nodosum or asymptomatic bilateral hilar adenopathy usually heralds a self-limiting course, whereas an insidious onset, especially with multiple extrapulmonary lesions, may be followed by relentless, progressive fibrosis of the lungs and other organs" (3).

EPIDEMIOLOGY

The frequency and prevalence of sarcoidosis, as well as the clinical manifestation of the disease, vary widely according to geographical location, gender, age, and ethnicity (4). The incidence of the disease is highest in the Scandinavian countries (11-24 cases per 100,000 per year) (5-7), and among African Americans (18-71 cases per 100,000 per year), (8-10). It is lowest in Asian countries (1 case per 100,000 per year), (11,12).

Currently, Bulgaria has no reliable epidemiological data available. The incidence calculated around 1980 was 8.7 cases per 100,000 people per year. It was

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calculated using data from all over the country (13).

The average age of diagnosed patients with sarcoidosis is 40-55 years. In men, the peak occurs slightly earlier (30-50 years) than in women (50-60 years). But women get sick more often (14).

The clinical manifestations of sarcoidosis vary greatly between races. For example, African-Americans have more severe symptoms, as the disease affects larger lung areas and multiple organs than individuals in other ethnicities (4,15).

Löfgren's syndrome is an acute form of sarcoidosis with a characteristic clinical manifestation - fever, bilateral hilar lymphadenopathy, erythema nodosum of the shank (predominant in women), and/or migratory polyarthritits (predominant in men) (16). Löfgren's syndrome is more common in the white population. It is rarely diagnosed in African Americans and Asians. In Sweden, Löfgren syndrome comprises about one-third of all sarcoidosis cases. Patients usually have the HLADRB1*03 (HLA- DR3) allele and have a good prognosis, with remission in 70–80% of these cases (17).

It is assumed that sarcoidosis development is influenced by various environmental factors, as well as some behavioral and physiological characteristics. For example, smoking is associated with a 50% lower risk of developing sarcoidosis, suggesting an immunomodulatory effect of nicotine or another component of cigarette smoke (18). Cigarette smoking stimulates the release of cytokines favoring a Th-2 immune response (interleukin 13) (19), as opposed to the Th-1 immune response typical of sarcoidosis. These findings support the opinion that the host's immune status is a critical determinant of sarcoidosis.

Overweight and obesity increase the risk of sarcoidosis. This has been proven by two large studies involving women from the United States. In the first, monitoring the health of African-American women in America (n = 59,000), obesity was associated with a 40% increased risk of developing sarcoidosis (20). In the other, involving predominantly white women (n = 116439), obesity was associated with a 70% increased risk (21). Both of these studies reported a relationship between a higher body mass index (BMI) at 18 years and increased sarcoidosis incidence in later life.

Markers of higher endogenous estrogen (a consequence of later menopause, later first pregnancy, or recent birth) were associated with a

decreased risk of sarcoidosis. The observation that women are more often diagnosed with sarcoidosis later in life (50–60 years of age) than men may be due to hormonal changes around the time of menopause (22).

HISTOLOGY OF SARCOID GRANULOMAS AND IMMUNOPATHOGENESIS OF THE DISEASE

Despite the type of organs affected by sarcoidosis, the histology image is similar and shows the presence of non-caseating, epithelioid granulomas. They are composed of a compact core of macrophages, some of which fuse to form giant multinucleated cells. Another part of the activated macrophages differentiates into epithelioid cells that surround the granuloma core. Scattered CD4+ T-helper cells are present in the granuloma, and significantly fewer CD8+ T-helper cells, fibroblasts, and B-lymphocytes can be found in its periphery. Different structures, such as asteroid bodies, Schaumann's bodies, and Hamazaki-Wesenberg bodies, are often observed in granulomas (23,24). A distinctive feature of sarcoid granulomas is the lack of necrosis, which discriminates them from tuberculous granulomas (25).

It is hypothesized that granulomas form around not completely degraded antigens to restrict and prevent its spread. Candidates for such an antigen are both environmental agents and microbial remnants (23,24).

Immunopathogenesis of sarcoidosis has been studied mainly by respiratory investigations.

Bronchoalveolar lavage studies have shown an increased number of CD4 + T-helper cells in sarcoid patients (24). Granuloma formation is associated with the activation of T-helper cells. There is a predominant proliferation of the Th1 cell populations, which changes the balance of Th1 and Th2 lymphocytes. This results in increased expression of the following cytokines: interleukin 2 (IL-2), interleukin 12 (IL-12), tumor necrosis factor-alpha (TNF- α), and gamma-interferon (IFN- γ), resulting in a slow but persistent inflammatory response in the affected tissues (26). IL-2 is a potent inducer of T cell proliferation and IFN- γ production. IL-2 plays a major role in the immune response in sarcoidosis. IL-12 directs the differentiation of naive T helper cells (Th0) to Th1 cell population and also activates the proliferation of cytotoxic and T cells in general (27). IL-12 plays a major role in the immune response against intracellular

pathogens, including *Mycobacterium tuberculosis* (28). In people with a genetic defect in the genes for IL-12 and/or for the receptor for this cytokine, the chance for granuloma formation is reduced. These individuals develop an atypical mycobacterial infection (29). Other commonly expressed T-helper populations in sarcoidosis patients are Th17.1 effector cells secreting INF γ and Th17 cells producing IL-17. The exact role of Th17 cells is not entirely clear but there is an increase in their abundance in patients with Löfgren's syndrome, which can be used as a diagnostic marker (30).

AETIOLOGY OF SARCOIDOSIS

The aetiology of sarcoidosis has remained a medical mystery for more than 120 years. It is proposed that the disease is caused by an unknown antigen (antigens) in humans with abnormal immune response, and a genetic predisposition (23,25).

There are two main hypotheses about the nature of this antigen. According to the first, sarcoidosis is caused by the action of an environmental agent/s. The second, indicates the possible involvement of one or more different microorganisms in the pathogenesis of the disease (25). Multiple environmental and occupational exposures have been reported to confer an increased risk of sarcoidosis, including organic dust, solvents, mold/mildew, pesticides, wood stoves, and others (31,32).

More pieces of evidence are accumulating to support the hypothesis of the infectious nature of sarcoidosis, but the specific etiological agent(s) has not been conclusively proven yet. Various microorganisms have been proposed for candidate pathogens in sarcoidosis. Among them are species of the *Mycobacterium spp*, *Cutibacterium spp*, *Borrelia spp*, *Human Herpes Virus 8 (HHV8)*, *Rickettsia helvetica*, *Chlamydia pneumonia*, and others (33).

Strong evidence for the presence in sarcoid samples and possible involvement in the pathogenesis of sarcoidosis was obtained for *Cutibacterium acnes* (previously known as *Propionibacterium acnes*) and some mycobacteria species (34,35).

C. acnes has been reported as a possible cause of sarcoidosis in many Japanese studies (36-38). It is the only successfully cultured microorganism isolated from sarcoid lesions (39,40). In 2002, a large relevant study was published as a collaboration between Japan, Italy, Germany, and the UK. The

results of this international study suggest an association between *C. acnes* and sarcoidosis in not only Japanese patients (positive signal rate of 89.2%) but also Europeans (positive signal rate of 81.4%) (41). However, more international studies with quantitative PCR are needed to clarify the role of *C. acnes* in sarcoidosis.

European and American research teams propose *M. tuberculosis* or another member of the genus as the most likely etiological agent (42-44). *M. tuberculosis* has been the longest hypothesized and the most investigated microorganism, due to the histological similarity between tuberculosis and sarcoidosis. Cultures and acid-fast stains of sarcoid specimens do not demonstrate the presence of mycobacterial organisms. PCR methods have detected mycobacterial DNA or RNA in different percentages in sarcoid patients (from 0 to 80%) (45). Recent studies have shown the presence of a mycobacterial DNA - the *katG* marker gene, coding for the *KatG Mycobacterium tuberculosis* catalase-peroxidase protein in 38% of the biopsy materials and evidence for circulating IgG to mycobacterial *KatG* in 50% of blood samples from sarcoid patients (46). Lack of mycobacterial DNA or its remnants in many sarcoid probes excludes *Mycobacterium spp*. as the sole etiologic agent in sarcoidosis.

A meta-analysis from 2016 shows the relationship between the most commonly associated with sarcoidosis microorganisms, and the disease itself. It includes 58 scientific case-control studies, published from 1980 to 2015, in which the presence of microorganisms in sarcoid samples was detected by cultural or molecular methods. The results of over 6000 patients were summarized and presented by odds ratio (OR) and 95% confidence intervals (95% CI). The possible etiological link between sarcoidosis and *Cutibacterium acnes* was with an OR of 18.80 (95% CI 12.62, 28.01), between sarcoidosis and mycobacteria, with an OR of 6.8 (95% CI 3.73, 12.39), between sarcoidosis and *Borrelia* - an OR of 4.82 (95% CI 0.98, 23.81), and between sarcoidosis and *HHV-8* with an OR of 1.47 (95% CI 0.02, 110.06). The authors suggest that more than one microbial species could be involved in the pathogenesis of sarcoidosis. The most probable etiological agents are *C. acnes* and members of the *Mycobacterium* and *Borrelia* genus. They also note the possible link between the geographical location and the predominance of

certain microorganisms in samples from patients with sarcoidosis (33).

CONCLUSIONS

Sarcoidosis develops in individuals with an immunogenetic predisposition to the disease. Many occupational and environmental exposures may increase the risk of developing sarcoidosis. The underlying inflammatory process is an antigen-driven, strongly polarized Th1 immune response. Although there has been some progress in understanding sarcoidosis over the past years, much is still unknown. Several important questions remain to be answered: whether one or more than one aetiological agents are leading to the disease; what are the exact geographical or racial impacts on the disease manifestation; what is the role of the genetic factors that increase susceptibility to sarcoidosis?

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