

# Systemic Sarcoidosis: Sociodemographic and Genetic Characteristics in a Tunisian Population

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## Research Article

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# Abstract

Sarcoidosis is a multi-systemic granulomatosis of unknown cause, characterized by a clinical polymorphism. It results from interplay of environmental and genetic factors. The aim of our study was to describe sociodemographic and genetic characteristics in Tunisian patients with sarcoidosis. We conducted a retrospective study of patients with sarcoidosis followed in the internal medicine and neurology departments at the Military Hospital of Tunis. We collected epidemiological characteristics. Genetic study concerned only patients who accepted to participate. DNA extraction was performed from whole blood. HLA class II typing and gene mutation testing of the ACE gene were also performed.

Our study concerned 50 patients. The mediastino-pulmonary involvement was the most frequent (72.3%), followed by neurological involvement (58.5%), cutaneous involvement (50.8%) and ophthalmological involvement (40%). Genetic analysis showed a high frequency of the HLA DRB1 \* 1501 allele (38%), DD genotype (30%) and D allele (54%) of the ACE gene. Treatment with corticosteroids was most often used 73.85%. The evolution was favorable in 13 cases (26.15%), and stable in 63% of cases. In conclusion, sociodemographic and genetic characteristic are variable from one ethnic to another. Advances in genotyping and statistical analysis are helping to elucidate the genetics of sarcoidosis.

## Introduction

Sarcoidosis or Besnier Boeck Schaumann's disease is a multi-systemic granulomatosis. It is characterized by the presence of epithelioid and gigantic cellular granulomas without caseous necrosis [1, 2]. It results from a diffuse chronic inflammatory response whose exact mechanism is still unknown [3]. The etiology of sarcoidosis remains unknown. In line with the most recent studies, not only environmental factors, but also genetic factors are involved. We therefore aim to analyze the epidemiological profile of sarcoidosis, and to identify the clinical and genetic characteristics of this pathology in our population.

## Material And Methods

We conducted a descriptive and prospective single-center study of 50 patients with sarcoidosis, followed in the internal medicine and neurology departments at the Military Hospital of Tunis over a period of 3 years (January 2016- January 2019). We included all patients with confirmed diagnosis of sarcoidosis who were hospitalized in our department during the study period. And all patients with clinical features suggestive of sarcoidosis associated with radiological and biological manifestations, and confirmed by biopsy with a non-caseating granuloma. We collected epidemiological, clinical, therapeutic and evolutionary data using an individual file. Genetic study concerned all patients who accepted to participate in the genetic study. DNA extraction was performed from whole blood. HLA class II typing and gene mutation testing of the ACE gene was done by amplification of the target sequence of the DNA by a polymerase chain reaction (PCR) followed by gel electrophoresis of agarose and then visualization of the DNA bands under UV.

## Results

The mean age of onset of the disease is at  $46.68 \pm 11.13$  years with a median equal to 50 years and extremes of age ranging from 21 to 64 years. The most affected age group was between 51 and 60 years of age, accounting for 43.1% of the population. 29.2% of the patients were under 40 years old. 23.1% of the patients were between 41 and 50 years old and in 4.6% of the cases age over 60 was found. A female predominance was noted. Among the 50 patients, we found 39 women (78%) for 11 men (22%), a sex ratio (female / male) equal to 3.54. In our study, the mean age at diagnosis of men and women does not differ statistically ( $p = 0.42$ ). In women, the average age was 47.33 years  $\pm 10.81$  with extreme ages of 21 to 64 years. In men, the mean age was 44.69 years  $\pm 12.2$  with extreme ages of 22 to 60 years. The baseline sociodemographic characteristics of the study population are presented in table 1.

The discovery of the disease was fortuitous in 27.7% of the cases. General signs such as fever, asthenia and weight loss were found in 15.3% of patients. Respiratory manifestations were inaugural in 20% of cases). Neurological signs revealed the disease in 14% of patients. In our series 23% of the cases initially presented ophthalmological, cutaneous, rheumatologic symptoms. The various cases of sarcoidosis are summarized in Table 2, pulmonary involvement is the most common (72.3%) followed by neurological involvement (58.5%), cutaneous involvement (50.8%) and Ophthalmological impairment 30.8% and other disorders are present at lower frequencies.

Biological assessment showed: The angiotensin converting enzyme (ACE) assay concerned 50 patients, it was increased in 53.44% of the cases, serum calcium and phosphore were increased in 14 patients.

In genetic study, DNA extraction was performed to determine the frequencies of the HLA alleles and genotypes of the ACE gene. The analysis of HLA typing allowed us to estimate the different frequencies of alleles in patients. The calculation of the allelic frequency found that the most frequent alleles are HLA-DRB1 \* 1501 alleles with a frequency of 38% and HLA-DRB1 \* 0301 of 28% (table 3).

Genotyping of the ACE gene: Genotyping of the polymorphism of the angiotensin converting enzyme (ACE) involved 50 patients. Genotypic frequencies (II, ID and DD) and allele frequencies (I and D) were estimated in order to evaluate the frequencies of each genotype and the 2 alleles for this pathology. The genotypic and allelic frequency results are summarized in Table 4. Our results show a higher DD genotype than genotype II (30% vs. 22%), and the D allele is 54%.

The evolution under treatment was favorable in 13 cases (26.15%), and stable in 63% of cases.

## Discussion

Our study highlighted the different sociodemographic, clinical, paraclinical, genetic, diagnostic and therapeutic features of sarcoidosis. Some epidemiological parameters have never been taken into consideration in Tunisia (eg geographical variation or seasons of the onset of the disease). However a

larger number of patients could have increased the reliability and the significance of our results. This was due to the exclusion of outpatients, or from other structures, which is a selection bias.

Sarcoidosis can occur at any age but is typical of young adults with a peak between 20 to 34 years old, and a second peak of the disease was noted 45–65 years old. It is very rare before the age of 20 and after the age of 65 [4]. In our study, the age of our patients was between 21 and 64 years old with an average of  $46.68 \pm 11.13$  years, the most affected age group is between 51 and 60 years old, with a percentage of 43.1%. Our results concord with those reported in the literature, indeed in a study conducted in Singapore the average age of patients was 41 years [5]. A recent study by Ungprasert et al. including 448 patients stipulated that the average age is 44.2 years [6]. In Tunisia, in the series of Ben Jannet et al. in 28 cases the mean age was 45.5 years [7]. Gender-specific incidence varies by series, with some not taking into account female or male predominance, while others note that female dominance is regularly found. In our series we found 49 women (75.4%) and 16 men (24.6%). Other studies are close to our results, with a female predominance of 52% [9]. In Tunisia, the study of Khaled et al. showed female predominance with a sex ratio of 4F / 1H [8]. Regarding environmental exposure, the ACCESS study conducted by Newman et al. analyzed the association between occupational and environmental exposure with sarcoidosis. He found a positive association between certain trades (agriculture, poultry farming, clothing, education, health), exposure to certain potentially toxic agents (insecticide and organic dust in the environment) and work in atmospheres contaminated by strong odors. Several studies suggest a possible relationship with product exposure (woodburning, non-organic particles, insecticides, molds or tree pollens [9, 10, 11]). The ACCESS study identified a modest risk of sarcoidosis in subjects with agricultural occupations exposed to molds or pesticides [12]. But none of these hypotheses has been definitively confirmed or excluded so far, and no specific agent has been identified. Our results did not show any significant difference for this parameter. Sarcoidosis appears as the result of the interaction of certain environmental factors (higher-risk occupations, geographical or seasonal variations in incidence). Some recent studies have reported a geographical variation of sarcoidosis. High prevalence has been noted in the northern regions of some countries, these gradients may be related to environmental and / or occupational exposures [13, 14, 15]. Our study showed the existence of a North-South gradient, in fact, 56.9% of our patients are from the north of the country, 26.2% from the center, and 16.9% from the south. Our study showed also that the disease appears mainly in winter (40%) (between January and March) and in summer (29.2%) between July and September. Few studies have examined this parameter. An American study conducted between 1976 and 2013 by Ungprasert et al. where 345 cases were found to have the highest incidence of sarcoidosis in winter (January) and summer (July) [16]. For tobacco use, although tobacco is the leading cause of death in industrialized countries, and is directly involved in the occurrence of cardiovascular, respiratory, and bronchopulmonary cancers, we have not found an association with sarcoidosis (23.1% smokers vs. 76.9% non-smokers). In the literature also, no significant association of tobacco with the disease has been demonstrated [6, 9].

Sarcoidosis can affect any organ; its clinical presentation is highly variable, including nonspecific symptoms of a general nature and symptoms related to organs affected by the disease [17]. The discovery of the disease is fortuitous in more than one third of cases when performing a chest X-ray in an

asymptomatic patient. In two-thirds of cases patients are symptomatic. Since sarcoidosis is more than 80% intrathoracic. It can also be demonstrated during the exploration of quite specific extra-thoracic clinical manifestations (ophthalmological, cutaneous, ganglionic, and neurological). In our study, the circumstances of discovery varied between general signs 15.3%, respiratory signs 20%, neurological signs 14%. The manifestations of sarcoidosis may be diffuse or affect only an organ. Mediastino-pulmonary disorders is the most frequent organ involvement (85 to 90% of cases), in our series, pulmonary involvement involved 47 patients (72.3%).

Concerning genetic characteristics; an epidemiological study of the ACCESS study (a case control etiologic study for sarcoidosis) has shown that the risk of developing the disease was significantly increased in the first and second degree members of the family [12]. The hereditary mode of transmission of sarcoidosis is however complex, involving multiple genetic factors each having a modest effect [1]. These clinical findings on family forms and ethnic particularities have prompted many teams to search for candidate genes and more recently genome-wide work has been presented [18]. In HLA typing, different studies have reported a combination of sarcoidosis with class II histocompatibility antigens with an increased risk of developing the disease, a number of HLA alleles appear to be associated with sarcoidosis regardless of the ethnicity studied [19]. The class II antigens most commonly encountered are: DRB1 \* 08, DRB1 \* 09, DRB1 \* 11, DRB1 \* 12, DRB1 \* 14, DRB1 \* 15 in Japanese [20]. In the Chinese population the disease has been associated with the DRB1 \* 11 allele while the DRB1 \* 07 allele seems to protect against the disease [21]. The DRB1 \* 11 allele has been reported in relation to the disease in the Indonesian population [22]. In African Americans DRB1 \* 1101 and DRB1 \* 12 increases the risk of susceptibility to the disease, while the DRB1 \* 15 allele is associated with the risk of having persistent sarcoidosis [23]. The DRB1 \* 0302 allele appears to confer protection against the disease in the same population. In the Caucasian population, DRB1 \* 03, DRB1 \* 11, DRB1 \* 12, DRB1 \* 14, and DRB1 \* 15 are related to the risk of susceptibility to the disease, whereas the HLA-DRB1 \* 01 and DRB1 \* 04 alleles appear to confer protection against the disease [24]. Several authors have reported that the DRB1 \* 0301 allele is associated with a favorable evolution up to the resolution of the disease in the Caucasian population; some authors have even proposed that this allele is a marker of good prognosis [24]. Our results showed that the HLA-DRB1 \* 1501 allele is found with the highest frequency 38% followed by the allele DRB1 \* 0301 with 28%. These alleles may confer a risk of susceptibility to the disease.

Genotyping of the polymorphism of angiotensin converting enzyme (ACE): There is an increase in serum angiotensin converting enzyme (ACE) activity in patients with sarcoidosis [25]. The polymorphism of the gene coding for ECA (chromosome 23q), shows either an insertion (I) of a so-called nonsense sequence at the level of intron 16, or a deletion (D), thus giving three genotypes: DD, DI, II. There is a relationship between the D allele and a strong production of angiotensin converting enzyme [26]. Our results showed a higher frequency of the DD genotype than that of the genotype II, and the D allele is present at 54%, these results could be in favor of the implication of DD genotype in the occurrence of the disease. Recent studies have shown that the DD genotype is associated with an increased risk of sarcoidosis in the Caucasian population, however this genotype is not associated with the disease in the Asian population, but the results remain contradictory [27]. Our study also showed that the genotype ID is found in 48% of

cases. A Turkish study reported a genotype ID frequency of 48.6%. A review of literature including 8 bibliographic references reported a genotypic frequency ID of 45.7 and 26.7% for the genotype DD [26].

## **Conclusion**

At the end of this work, we have identified some propositions taking into account the most recent data from the literature. A multicenter epidemiological study of sarcoidosis is necessary to better evaluate the frequency of this pathology in Tunisia. We should look for genetic and environmental predisposing factors through case-control studies in order to establish a clear diagnostic approach, taking into account frequent comorbidities to provide the appropriate therapeutic indication, and regular monitoring of the evolution for better patient management. Finally, recent advances in the pathophysiology and genetics of this disease may have therapeutic implications for the early and radical management of the disease.

## **Declarations**

### **Financial interests:**

The authors declare they have no financial interests

### **Conflict of interest :**

The authors declare that they have no conflict of interest.

### **Author contributions :**

All authors contributed to the study conception and design

### **Ethics approval :**

Approval was obtained from the ethics committee

### **Informed consent**

was obtained from all subjects

The study was approved by ethic committee of military hospital of Tunis

All methods were carried out in accordance with relevant guidelines and regulations in the manuscript file.

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## Tables

Table 1

Sociodemographic characteristics of the study population

<b>Sociodemographic characteristics</b>	
Age (years): Average	46.68± 11.13 years
Gender (%):	
Male	22%
Female	78%
Environmental exposure to toxics	
High exposure:	56.9%
Low exposure:	43.1%
Geographic variation	
North	56.9%
Centre	26.2%
South	16.9%
Smoking:	
Yes (%)	23.1%
No (%)	76.9%

Table 2  
Sarcoidosis localizations

<b>Sarcoidosis localizations</b>	<b>Percentages (%)</b>
Pulmonary involvement	72.3
Neurological involvement	58.5
Cutaneous	50.8
Ophtalmological	40
Lymphadenopathies	30.8
Articular	26.1
Renal	15.4
Liver involvement	15.4
Spleen involvement	13.8
ORL	7.7
Cardiac involvement	3
Bone involvement	3.07
Gastric involvement	1.5

Table 3

HLA type results

HLA type (50 patients)	Number of patients	%
HLA-DRB1*1501	19	38%
HLA-DRB1*0301	14	28%
HLA-DRB1*1106	9	18%
HLA-DRB1*0401	8	16%

Table 4

Genotype results

Genotype	Number of patients	%
II	11	22%
ID	24	48%
DD	15	30%
<b>Allele</b>		
I	46	46%
D	54	54%