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Socio-demographic profile of patients with sarcoidosis vis-à-vis tuberculosis

D. Gupta, N. Vinay, R. Agarwal, A. N. Aggarwal
Department of Pulmonary Medicine, Postgraduate Institute of Medical Education and Research (PGIMER), Chandigarh, India.

Abstract. *Background:* Sarcoidosis and tuberculosis closely resemble each other and *Mycobacterium tuberculosis* has been implicated as a causative agent for sarcoidosis. Herein we explore the socio-demographic features of patients with sarcoidosis vis-a-vis tuberculosis. *Methodology:* In a prospective case-control design, we studied a hundred patients each of newly diagnosed sarcoidosis, bacteriologically confirmed pulmonary tuberculosis and healthy controls. Socio-demographic profile was recorded on a standardized questionnaire. Information about tobacco smoking, exposure to environmental tobacco smoke (ETS) and cooking fuels was also collected. Various parameters were compared among the three groups. *Results:* Compared to tuberculosis, patients with sarcoidosis were elder, had better body mass index (BMI), higher urban residence (OR 2.19, 95% CI: 1.02-4.69), were better educated (ORs 8.50 to 74.25 for different categories), had higher per capita income (OR 13.33; 95% CI: 6.79-26.19) and belonged to better overall socio-economic status (SES) (ORs 8.57-195.0 for different categories). All these differences were also significant when sarcoidosis patients were compared to healthy controls albeit to a lesser degree. Tobacco smoking, ETS exposure and use of fossil/biomass fuels for cooking were more commonly seen in TB patients. In the multivariate analysis, as compared to TB or controls, sarcoidosis patients had higher odds for a better SES after adjusting for age, gender, BMI, religion, smoking, ETS exposure and cooking fuel. *Conclusions:* Patients with sarcoidosis are likely to be better educated and more affluent compared to those with tuberculosis and healthy controls and this can be useful in the clinical differential diagnosis of the two conditions in populations with high prevalence of TB. *(Sarcoidosis Vasc Diffuse Lung Dis 2013; 30: 186-193)*

Key words: Sarcoidosis, tuberculosis, epidemiology, socio-economic status, demographic profile

Introduction

Sarcoidosis and tuberculosis (TB) are so closely interrelated that they are even believed to be two ends of a disease spectrum caused by *Mycobacterium tuberculosis* (MTB).(1-3) Granulomatous inflammation in sarcoidosis is believed to be the host response to continued presentation of a poorly degradable, and yet to be identified antigen. Because sarcoidosis most commonly involves the mediastinal lymph nodes and lung, the search for the etiologic agent has centered on ex-

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Dr. Dheeraj Gupta MD, DM, FRCP, FAMS Professor
Department of Pulmonary Medicine
Postgraduate Institute of Medical Education and Research (PGIMER)
Chandigarh. India. 160012
Phone: +91 172 275 6823 (Work); +91 172 272 7219 (Home)
Fax: +91 172 274 8215; +91 172 274 5959
Emails: dheeraj1910@gmail.com; dheeraj88@hotmail.com

posure to some airborne antigen, with mycobacteria being a strong contender.(4) Nucleic acid amplification techniques have demonstrated MTB DNA in a significant proportions of samples from sarcoidosis patients,(5) and this proportion is higher in studies conducted in countries with high burden of TB.(1, 6) Several studies have also demonstrated immune responses to mycobacterial antigens in a significant proportion of sarcoidosis patients.(7-9) These studies reinforce the possible pathogenic role of mycobacteria in sarcoidosis. In fact different human leukocyte antigen (HLA) alleles have been described in various ethnic populations that predispose to development of either TB or sarcoidosis as well as development of TB during treatment of sarcoidosis with immunosuppressant therapy.(2, 3, 10)

Although the genetic differences have been described, the phenotypic differences among patients of sarcoidosis and tuberculosis are not known. Tuberculosis has been extensively studied in India and its socio-demographic profiles are well described. (11, 12) Though increasingly being diagnosed and treated, there is limited data on epidemiological features of sarcoidosis from developing countries. (13, 14) The ACCESS study is the largest case-control epidemiological study on sarcoidosis till date, and it has provided important information on genetic, familial and environmental risk factors for sarcoidosis from the developed world.(15) However, no comparisons with tuberculosis were made in the ACCESS study.

Given the fact that both TB and sarcoidosis are prevalent in India, it would be interesting to study the socio-demographic similarities/differences between the two diseases that can be useful in adding few more pieces to the TB-sarcoid jigsaw.

Methodology

Setting and design: This was a prospective case control study (1:1:1 design) carried out in the Chest Clinic of a tertiary care academic hospital located in North India, between January 2010 and June 2011. The study was approved by the Ethics Review and a written informed consent was taken from all participants.

Study population: The study included 300 subjects (100 consecutive newly diagnosed adult subjects EACH of sarcoidosis, pulmonary tuberculosis (PTB) and healthy controls). Pulmonary sarcoidosis was defined by the presence of all the following criteria: (1) clinical features of pulmonary involvement (dyspnea, dry cough, chest pain, fever, fatigue or crackles); (2) consistent radiological findings on chest radiograph and high-resolution CT of the chest; (3) compact non-caseating granulomas on bronchoscopic lung biopsy, which were negative for fungal smears or acid-fast bacilli (AFB) with broncho-alveolar lavage negative for mycobacterial culture and, (4) good clinical response to therapy with oral steroids. PTB was diagnosed based on demonstration of AFB on sputum microscopy, and/or sputum cultures positive for MTB. The controls were healthy volunteers defined as asymptomatic individuals without any diagnosed illness and normal on detailed physical examination. The controls were recruited from the healthy attendants accompanying other patients attending the outpatient departments of our institute. These subjects had no clinical symptoms or previous history suggestive of tuberculosis or sarcoidosis. No immediate family members of a study subject were recruited in any of the three groups. Patients who refused consent were excluded.

Study procedures: Each subject was interviewed as per a structured questionnaire that recorded clinical data including radiological findings, the socio-economic scale (as discussed below), information on tobacco smoking (both active and passive) and indoor exposure to cooking fuels. All the subjects were interviewed by the same person (VN).

Socio-economic scale: The socio-economic scale used for defining socio-economic strata (SES) for this study has been designed specifically for rural and urban Indian population and has been found to be reliable and valid.(16) Briefly the scale has questions on seven domains that include housing, material possessions, education, occupation, monthly income, land possession and social profiles (includes understanding and participation in social activities). All seven profiles are equally weighted, and have subcategories with scores ranging from 0-10. The scores are based on the value assigned to each subcategory, which is different for rural and urban areas. The housing categorization is based on the land area and type of construction. Material possession profile is assessed on value of household gadgets and conveyance facility. Education is categorized into different levels of educational qualifications e.g., '0' for illiterate and '10' for higher studies (Ph.D., M.D., M.S., etc.). The occupational domain is categorized according

to the primary occupation (major source of livelihood) of the individual, with a score of '0' for unemployed and '10' for professionals or equivalent (graduate/post graduate teachers, high profile farmers and businessmen, political leaders, etc.). Monthly income is based on per capita income calculated by dividing the total family income from all sources by total number of family members (highest category being >10,000 Rupees for rural and >15,000 Rupees for urban population). Land possession domain is based on the cost of land owned or cultivated by the family. The social understanding and participation is categorized according to the knowledge of social issues (religious-cultural, developmental, educational, health promotional, and political) and involvement in social activities. The scale is easy to administer and takes about 10 minutes. The developers have given detailed instructions on the use and administration of the scale, which maintains uniformity and eliminates interviewer and reporting bias. The scale divides the subjects into five possible SES: upper, upper middle, middle, lower middle and lower based on the total score (0-70).

Tobacco smoking and indoor exposures: Tobacco smoking (current or former), environmental tobacco smoke (ETS) exposure (passive smoking) at home from spouse or other members living in same house, type of cooking fuel used at home and exposure to cooking fumes was also recorded as previously described by us.(17)

Statistical Analysis: Data was analyzed using commercial statistical package SPSS (Version 10, SPSS Inc., Chicago, IL) for MS-Windows. Data is presented in a descriptive fashion as numbers (all numbers are out of 100) or mean (standard deviation). Categorical variables were compared using chi-square test and continuous variables using Mann-Whitney U test. A logistic regression analysis was performed to determine the association of various socio-demographic factors, indoor exposures and overall SES with sarcoidosis compared to tuberculosis as well as healthy controls.

Results

Study Population

There were 59 men and 41 women (mean age [SD] 44.4 [11.26] years and 45.43 [10.17] years respectively) in the sarcoidosis group, 74 men and 26 women in the TB group (mean age [SD] 36.37 [16.12] years and 41.38 [14.26] years respectively) and 53 men and 47 women among healthy controls (mean age [SD] 43.11 [14.24] years and 39.31 [17.53] years respectively). The gender differences among the three groups were not significant, however sarcoidosis patients were significantly older (OR 1.06; 95% CI, 1.02-1.09). The mean (± SD) body mass index (BMI) of sarcoidosis patients (25.4 ± 4.3) was significantly higher than that of TB patients (16.8 ± 2.9; P<0.0001) and similar to that of controls (24.7 ± 3.9; p= 0.26)

Clinical Features and socio-economic profile

The clinical details of the sarcoidosis patients are summarized in Table 1. All the patients were newly diagnosed, without any history of past diagnosis or treatment for sarcoidosis. All except two patients of sarcoidosis were symptomatic and extra pulmonary symptoms were quite frequent (observed in 44 patients). Dry cough and dyspnea were the most common pulmonary symptoms while fever, anorexia, weight loss and arthralgia were the most common extra pulmonary symptoms. Eye was the most common extra-pulmonary organ involved and extra thoracic lymphadenopathy was seen in 7 patients. Four patients had erythema nodosum, of which two fitted the description of Lofgren's syndrome.

Spriometry was available for 99 patients and it was normal in 60 of them. Based on chest roentgenogram more than half the patients had Stage 1 disease. Tuberculin skin test (1TU) was negative in a vast majority of patients. All the TB patients were symptomatic with either fever, productive cough, dyspnea or hemoptysis.

The distribution of various study variables among the study populations is presented in Table 2. Compared to TB, sarcoidosis patients were more likely to hail from urban areas, belong to Sikh community, were better educated, and higher monthly per capita income. There was a trend towards a higher category of occupation, however it was not significant. The SES categories were reduced to three for the purpose of analysis since there are very few patients in the top most and the lowest category (these were merged with the upper middle and lower middle category, respectively). Compared to TB, sarcoidosis patients were placed in a much higher SES. All these differences were also significant when sar-

coidosis patients were compared to healthy controls albeit to a lesser degree. (Table 2)

Among the other exposures studied, the use of fossil/biomass fuels like kerosene and coal/wood, tobacco smoking and exposure to environmental tobacco smoke (ETS) were more often seen among TB compared to sarcoidosis or controls. (Table 2)

Multivariate analysis

Multivariate logistic regression analysis was performed to study the association of SES and sarcoidosis. Patients with sarcoidosis were more likely than TB patients to fall in the upper SES (OR 2052.82; 95% CI 37.9-110913.9) or middle SES (OR 144.36; 95% CI 8.46-2463.19) compared to the lower SES after adjusting for age, gender, BMI, religion, smoking, ETS exposure and type of cooking fuel used. In this model BMI was the only other significant factor with higher odds for increasing BMI among sarcoidosis patients (OR 2.07; 95% CI, 1.57-2.72). Compared to healthy controls, sarcoidosis patients were more likely to be placed in higher SES categories; however BMI was not significantly higher. TB patients on the other hand had a lower BMI compared to controls. (Table-3).

Table 1. Clinical details of sarcoidosis patients (N=100)

Parameter	Number positive
Presentation	
Asymptomatic	2
Pulmonary symptoms	18
Extrapulmonary symptoms	36
Both	44
Symptoms	
Dry cough	48
Dyspnea	29
Fever	39
Weight loss	20
Anorexia	19
Arthralgias	34
Fatigue	18
Signs	
Peripheral nodes	7
Hepatomegaly/ Splenomegaly	2
Ocular involvement	14
Erythema nodosum	4
Facial Nerve palsy	3
Gland involvement (Parotid /Salivary/ lacrimal)	3
Spirometry	
Normal	59
Restriction	26
Obstruction	14
Not done	1
Scadding stage (Chest radiograph)	
Normal	1
Stage 1	54
Stage 2	39
Stage 3	5
Stage 4	1
Tuberculin skin test Negative (<10mm)	92

Discussion

In this study, we compared the socio-demographic profile of patients of sarcoidosis with TB and healthy controls and found important differences. In general, sarcoidosis patients were more affluent and better educated than either TB patients or healthy controls, while TB patients were poorer and undernourished.

Few epidemiological studies have explored the relationship between TB and sarcoidosis. Initial studies focused on a history of contact with TB patients prior to diagnosis of sarcoidosis.(18) A study from London demonstrated parallel increase in the prevalence of the two diseases in two time frames between 1958 and 1963.(19) However, based on secular trends in several other studies, it was proposed in that the epidemiological decline of tuberculosis was associated with an increased incidence of sarcoidosis. For example, sarcoidosis in Japan came to be widely recognized in the 1950s when the mortality from TB significantly went down (20, 21). Similarly, significant epidemiological dissimilarities between age, gender and incidence of tuberculosis and sarcoidosis were demonstrated from Croatia, with sarcoidosis occurring more often in women, who were older as compared to TB patients. There were also gross geographic differences in the reported incidence of the two conditions within the study area, thus failing to provide any epidemiological similarity between the two conditions.(22) In India, TB continues to be a major public health problem, but sarcoidosis is also being recognized with increasing

Table 2. Socio-demographic profile of the study population (SA=Sarcoidosis; TB= Tuberculosis; C=Controls; N=100 in each group) with pair-wise univariate analysis among different groups

	SA	TB	C	SA vs. TB		SA Vs. C		TB Vs. C	
	n	n	n	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
Female Gender	41	35	47	1.29 (0.73-2.29)	.382	0.78 (0.45-1.37)	.393	0.62 (0.35-1.09)	.097
Religion									
Hindu	81	91	94	1.00		1.00		1.00	
Muslim	3	3	4	1.12 (0.22-5.72)	.839	0.87 (0.19-4.0)	.858	0.78 (0.17-3.59	.753
Sikh	15	4	2	4.21 (1.34-13.21)	.014	8.7 (1.93-39.2)	.005	2.09 (0.37-11.68)	.402
Others	1	2	0	-		-		-	-
Urban residence	88	77	70	2.19 (1.02-4.69)	.440	3.14 (1.5-6.58)	.002	0.71 (0.38-1.33)	.282
Occupation									
Unemployed	6	4	9	1.00		1.00		1.00	
Student/housewife	34	42	48	0.54 (.14-2.07)	.368	1.06 (0.35-3.27)	.916	1.97 (0.56- 6.86)	.282
Unskilled	12	29	14	0.28 (0.07-1.16)	.078	1.29 (0.35-4.67)	.702	4.66 (1.22-17.79)	.024
Skilled	33	19	17	1.16 (0.29-4.63)	.836	2.91 (0.89-9.54)	.078	2.37 ((0.62-9.09)	.207
Professional	15	6	12	1.67 (0.34-8.09)	.526	1.88 (0.52-6.78)	.336	1.12 (0.24-5.21)	.880
Education									
No formal education	2	22	25	1.00		1.00		1.00	
Primary level	8	32	8	2.75 (0.53-14.2)	.222	12.5 (2.19-71.36)	.004	4.54 (1.73-11.91)	.002
Secondary level	17	22	24	8.5 (1.75-41.26)	.008	8.85 (1.84-42.49)	.006	1.04 (0.46-2.35)	.922
Higher secondary	19	16	19	13.06 (2.65-64.25)	.002	12.5 (2.59-60.35)	.002	0.96 (0.39-2.30)	.922
Graduation and above	54	8	24	74.25 (14.59-377.77)	.000	28.13 (6.16-128.39)	.000	0.36 (0.14- 0.97)	.043
Monthly income ≥ Rs.15000 (urban) or Rs.10,000 (rural)	79	22	65	13.34 (6.79-26.19)	.000	2.03 (1.08-3.81)	.029	0.15 (0.08-0.28)	.000
Socio-economic status									
Middle	62	47	58	8.57 (3.72-19.77)	.000	3.61 (1.52-8.58)	.004	0.41 (0.23-0.76)	.004
Upper Middle	30	1	15	195 (23.25-1635.77)	.000	6.75 (2.48-18.41)	.000	0.03 (0.00-0.28)	.002
Cooking									
Past	11	5	11	2.62 (0.86-7.97)	.090	1.07 (0.43-2.65)	.886	0.41 (0.14-1.26)	.121
Now	31	26	27	1.42 (0.76-2.66)	.275	1.23 (0.66-2.3)	.523	0.88 (0.46-1.66)	.692
Type of Fuel used in house									
LPG	86	45	81	1.00		1.00		1.00	
Kerosene	12	30	13	0.21 (0.10-0.45)	.000	0.87 (0.38-2.02)	.744	4.20 (1.99-8.86)	.000
Coal/wood	2	25	6	0.04 (0.01-0.19)	.042	0.31 (0.06-1.6)	.163	7.59 (2.9-19.88)	.000
Smoking									
No smoking	85	68	79	2.67 (1.34-5.32)	.005	1.51 (0.73-3.13)	.271	0.56 (0.29-1.06)	.073
No ETS exposure	78	53	65	3.08 (1.66-5.7)	.000	1.91 (1.02-3.57)	.043	0.64 (0.36-1.12)	.121

Abbreviations: OR= Odds Ratio; CI= Confidence interval; P= Level of significance; LPG=Liquefied petroleum gas; ETS= Environmental tobacco smoke

frequency, though no incidence or prevalence figures for sarcoidosis are available.

To the best our knowledge this is the first head-to-head comparison of socio-demographic profile of patients with sarcoidosis and TB. Socio-economic factors play an important part in health.(23) By the turn of the 20th century, the concept of SES-health gradient became established, i.e. the relative risk of mortality/ morbidity from a particular disease increases at a relatively constant rate with decreasing SES across the entire SES-spectrum, and tuberculosis is an ideal example.(24, 25) Tuberculosis has been hailed as a disease related to low socioeconomic status, poor living conditions and malnutrition.(11, 12)

Table 3. Pair-wise multivariate logistic regression analysis for socio-demographic factors prevalent in patients of sarcoidosis (SA) , tuberculosis (TB) and healthy controls (C)

	SA Vs. TB		SA Vs. C		TB Vs. C	
	Adjusted OR (95% CI)	P	Adjusted OR (95% CI)	P	Adjusted OR (95% CI)	P
Age in years	1.02 (.97-1.07)	.393	1.02 (.99-1.05)	.090	1.00 (0.97-1.05)	.966
Male gender	3.87 (.82-18.27)	.087	0.72 (.36-1.42)	.339	1.73 (0.43-6.92)	.437
Body mass index (kg/m2)	2.07 (1.57-2.73)	.000	1.02 (.94-1.1)	.596	0.42 (0.32-0.55)	.000
Religion						
Hindu	1.00		1.00		1.00	
Muslim	1.19 (0.0-9095.27)	.970	1.18 (.22-6.23)	.842	0.41 (0.01-15.34)	.627
Christian	-		-		-	
Sikh	0.39 (.05-3.21)	.383	6.47 (1.34-31.38)	.020	41.18 (2.51-676.63)	.009
Others	-		-			
Smoking	0.39 (.05-2.94)	.362	1.24 (.47-3.26)	.669	1.29 (0.26-6.42)	.758
ETS exposure	3.69 (.74-18.54)	.113	1.81 (.85-3.87)	.125	0.52 (0.13-1.2)	.338
Fuel						
LPG	1.00		1.00		1.00	
Kerosene	8.87 (.98-80.04)	.052	2.17 (.67-6.99)	.194	3.37 (0.45-22.83)	.213
Coal/wood	0.61 (.04-8.42)	.710	0.64 (.11-3.76)	.623	10.67(1.17-97.23)	.036
Socioeconomic status						
Lower	1.00		1.00		1.00	
Middle	147.25 (8.66-2503.42)	.001	4.03 (1.4-11.61)	.010	0.57 (0.11-2.98)	.509
Upper middle 0.15 (0.01-3.59)	2085.82 (38.63-112632.12) .239		.000		6.35 (1.86-21.72)	.003

Abbreviations: OR= Odds Ratio; CI= Confidence interval; P= Level of significance; LPG=Liquefied petroleum gas; ETS= Environmental tobacco smoke

Our results once again substantiate this hypothesis when TB patients were compared to healthy controls.

On the other hand, direct relationship of SES with prevalence or outcome of sarcoidosis has not been studied. Several studies including the ACCESS study have systemically examined the role of occupation and environmental exposures in sarcoidosis patients and these can provide indirect clues to the socio-demographic factors. The ACCESS study observed positive associations between sarcoidosis and specific occupations such as agricultural employment, jobs raising birds, jobs in automotive manufacturing, middle/secondary school teaching, and physicians.(26) In another retrospective case control study it was observed that sarcoidosis patients were likely to be professionals or sales workers and less likely to be laborers and also there were ethnic differences (African-Americans vs. others).(27) The results of this study also demonstrates that sarcoidosis patients were more educated, had higher per capita income and belonged to higher SES compared to TB or healthy volunteers.

Higher prevalence of 'white collar jobs' among patients of sarcoidosis has fuelled speculations about the association of indoor environmental exposures and sarcoidosis. We specifically looked at indoor exposure to cooking fuels and ETS, and found sarcoidosis patients were less likely to use coal/wood compared to TB patients. However, this could just be a reflection of higher SES and urban residence in sarcoidosis patients, making costlier fuels like LPG more affordable/available or due to burning of solid fuels being an independent risk factor for TB.

Low socioeconomic status by various factors results in a weaker immune system with poor im-

munological responses (28, 29) which in turn may result in causation of TB, whereas people of high socio economic status with a good immunological response are more likely to veer towards the hyper-immune spectrum of the granulomatous response to the mycobacteria, which in a genetically predisposed individual leads to sarcoidosis. In a recent paper Dubaniewicz concludes, *"There is 100% homology between M. tuberculosis and Mycobacterium bovis BCG heat shock protein. In light of evidences necessary to establish sarcoidosis which is autoimmune in origin, my recently published findings prompted me to raise the hypothesis that, in genetically different individuals, the same antigens (Mtb-hsp) may induce different immune responses, leading to the development of sarcoidosis or TB"*;(30) re-enforcing the often debated hypothesis that analogous to leprosy wherein tuberculoid (paucibacillary) and lepromatous (exuberant bacilli) forms represent different levels of host immune responses to the pathogen; sarcoidosis represent tuberculoid form of the pathological responses to mycobacteria.(2, 3, 10, 31, 32)

Tobacco smoking and ETS exposures are known to have adverse impact on TB.(33, 34) On the contrary tobacco smoking is considered protective for sarcoidosis; however some studies have refuted this notion.(35, 36) In a recent study we found no significant negative association of active smoking and environmental tobacco smoke (ETS) with sarcoidosis. Also, tobacco smoke did not have any effect on the clinical behavior or disease severity in sarcoidosis.(37) Although, prevalence of smoking and ETS exposure was lower in patients with sarcoidosis when compared to TB, the differences were not significant on multivariate analysis. This again negates the notion that smoking may be protective for sarcoidosis.

Whatever be the factors of MTB leading to either TB or sarcoidosis (in some patients), the clinical differentiation of the two conditions remains a challenge for clinicians practicing in countries with high burden of TB.(13) This has been one of the major factors for under recognition of sarcoidosis in these countries. This study can add an important clinical clue in this challenging differential diagnosis.(1)

Limitations of our study include small numbers, and the possibility that all the observations are in fact due to strong inverse relationship of SES to TB rather than a true difference between sarcoidosis and tuberculosis, even though the sarcoidosis patients were socio-economically better than healthy controls also. In a high TB prevalence country there is always a cynicism associated with exclusion of tuberculosis while making a diagnosis of sarcoidosis. However, we have followed all our patients of sarcoidosis for response to corticosteroids that rules out active tuberculosis.

To conclude, in comparison to tuberculosis or healthy controls, sarcoidosis patients were found to be more affluent in terms of their education, income and overall socio-economic status. This information can be useful to clinicians faced with the dilemma of differentiating the two conditions in populations with high burden of TB. Further studies into effects of this affluence on nutrition/immunity coupled with genetic susceptibility can provide vital clues to decipher the complex interactions between sarcoidosis and tuberculosis.

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