Relationship of Environmental Exposures to the Clinical Phenotype of Sarcoidosis*

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Study objectives: **Sarcoidosis is a granulomatous disorder with heterogeneous clinical manifestations, which are potentially reflective of a syndrome with different etiologies leading to similar histologic findings. We examined the relationship between environmental and occupational exposures, and the clinical phenotype of sarcoidosis.**

Design: **We performed a cross-sectional study of incident sarcoidosis cases that had been identified by A Case Control Etiologic Study of Sarcoidosis. Subjects were categorized into the following two groups: (1) pulmonary-only disease; and (2) systemic disease (with or without pulmonary involvement). Logistic regression was used to examine the associations of candidate exposures with clinical phenotype.**

Setting: **Ten academic medical centers across the United States.**

Patients: **The current study included 718 subjects in whom sarcoidosis had been diagnosed within 6 months of study enrollment. Patients met the following criteria prior to enrollment: (1) tissue confirmation of noncaseating granulomas on tissue biopsy on one or more organs within 6 months of study enrollment with negative stains for acid-fast bacilli and fungus; (2) clinical signs or symptoms that were consistent with sarcoidosis; (3) no other obvious explanation for the granulomatous disease; and (4) age > 18 years.**

Measurements and results: **Several exposures were associated with significantly less likelihood of having extrapulmonary disease in multivariate analysis, including agricultural organic dusts and wood burning. The effects of many of these exposures were significantly different in patients of different self-defined race.**

Conclusions: **The differentiation of sarcoidosis subjects on the basis of clinical phenotypes suggests that these subgroups may have unique environmental exposure associations. Self-defined race may play a role in the determination of the effect of certain exposures on disease phenotypes.**

(CHEST 2005; 128:207–215)

Key words: environmental exposures; epidemiology; organic dust; race; wood smoke

Abbreviations: ACCESS = A Case Controlled Study of Sarcoidosis; CHP = chronic hypersensitivity pneumonitis; CI = confidence interval; OR = odds ratio

Sarcoidosis is a multisystem granulomatous disease of unknown etiology. The lungs are the most commonly affected organs, but sarcoidosis can also involve the eyes, skin, liver, lymph nodes, spleen, heart, nervous system, muscles, bones, and other organs.[1] Clinical outcomes range from asymptomatic spontaneous remission without treatment to disease progression with multisystem organ failure and death. Despite aggressive treatment, up to 5% of affected patients die from the disease.[2] The heterogeneous nature of the disease has led researchers to believe that sarcoidosis has more than one etiology, which may in turn lead to different patterns of disease.[1]

Patients with systemic disease may be more likely

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Dr. Kreider was supported by grant T32 HL07891 from the National Institutes of Health. The ACCESS study was supported by contracts NO1-HR-56065 through NO1-HR-556075 from the National Heart, Lung and Blood Institute.

Manuscript received September 9, 2004; revision accepted December 24, 2004.

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to have an exposure to systemic infection or to small, absorbable particles that allow for a wider distribution of the causative agent throughout the body, with the subsequent development of significant granulomas in multiple organs.[3] Alternatively, subjects with disease limited to the lungs may be more likely to have been exposed to substances that may not readily disseminate systemically due to an inability to penetrate the blood or lymphatic systems (*ie*, due to particle size or solubility). Therefore, we hypothesized that there are separate and unique environmental risk factors for different clinical presentations of sarcoidosis. The National Heart, Lung, and Blood Institute funded the A Case Control Etiologic Study of Sarcoidosis (ACCESS) study, which is a 10-center study that was designed to examine the etiology and initial clinical course of patients with newly diagnosed sarcoidosis. This report assesses the association between environmental exposures and systemic (with or without pulmonary involvement) vs pulmonary-only involvement in the ACCESS study.

Materials and Methods

Details of the ACCESS study design have been published elsewhere.[4] Briefly, incident cases of sarcoidosis were collected at 10 academic medical centers across the United States. Patients met the following criteria prior to enrollment: (1) tissue confirmation of noncaseating granulomas on tissue biopsy on one or more organs within 6 months of study enrollment with stains that were negative for acid-fast bacilli and fungus; (2) clinical signs or symptoms consistent with sarcoidosis; (3) no other obvious explanation for the granulomatous disease; and (4) age > 18 years. Subjects were characterized in a number of ways including physical examinations, spirometry, radiographs, laboratory measurements, medical history, extensive occupational and environmental exposure histories, and various psychosocial measurements.

Outcome Definition

The primary outcome for this study was the pattern of organ involvement of sarcoidosis at the time of presentation. Organ involvement was determined with the use of a tool that was developed by the ACCESS group that combined information from physical examinations, laboratory values, and medical history.[5] The probability of organ involvement based on this evaluation was categorized as follows: (1) definite; (2) probable; (3) possible; and (4) not involved. For example, the eyes were considered to be definitely involved in patients with biopsy-confirmed sarcoidosis when there was lacrimal gland swelling, uveitis, or optic neuritis. The eyes were designated as probably involved when blindness was found. The eyes were designated as possibly involved when glaucoma or cataracts were found. Subjects were divided into the following two categories: those with "pulmonary-only" disease; and those with "systemic" involvement (*ie*, one or more nonlung organs). For the purposes of the current analysis, patients were characterized as having systemic involvement if at least one nonlung organ had either definite or probable involvement, as determined by this tool. For the systemic category, patients may also have had pulmonary involvement, providing that another organ was also affected.

Classification of Exposure

A list of candidate environmental and occupational exposure categories was derived from an *a priori* list of candidate exposures that was used in the case-control analysis and was further limited to those appropriate for the current hypothesis (Table 1).

The ACCESS study[4,6] obtained information on environmental and occupational exposures through the use of interviewer-

Table 1—*Candidate Environmental/Occupational Exposures*

Exposure	Proposed Mechanism of Exposure	Proposed Clinical Phenotype
Metal dust*	Inhalational	Pulmonary-only
Agricultural organic dust†	Inhalational	Pulmonary-only
Industrial organic dusts‡	Inhalational	Pulmonary-only
Wood dust§	Inhalational	Pulmonary-only
Wood burning‖	Inhalational	Pulmonary-only
Silicates¶	Inhalational	Pulmonary-only
Child care	Systemic	Systemic
Health-care occupations#	Systemic	Systemic
Radiation exposure	Systemic	Systemic
Mold/microbial bioaerosols**	Either	Pulmonary-only if trigger was inhalational; systemic if trigger was systemic
Military	Either	Pulmonary-only if trigger was inhalational; systemic if trigger was systemic
Insecticides/pesticides††	Either	Pulmonary-only if trigger was inhalational; systemic if trigger was systemic

*For instance, auto repair person, assembly worker, electrical worker, welder, and machinist.
†For instance, farming, working with animals, exposure to vegetable dust, and raising birds.
‡For instance, carpentry, cork factory work, cotton ginning, saw mill work, and pulp mill work.
§For instance, carpentry, saw mill work, and pulp mill work.
‖For instance, from using a wood stove or fireplace at home.
¶For instance, from glass making, mining, pottery making, quarry work, sandblasting.
#For instance, a physician, nurse, technologist, or dentist.
**From a self-report of mold/musty odor at home or at work.
††From a self-report of use.