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Bronchial reactivity in patients with recent pulmonary sarcoidosis

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ABSTRACT Non-specific bronchial reactivity was assessed in 17 consecutive non-smoking and non-steroid treated patients with recently diagnosed pulmonary sarcoidosis, 11 with stage I disease and six with stage II disease. Bronchial reactivity was measured by recording the FEV_1 after increasing doses of methacholine. Three subjects with asthma were hyperreactive. The 14 subjects with no asthma had a mean FEV_1 of 96% predicted. Only one was hyperreactive, with a fall in FEV_1 of over 15% after 0·1% methacholine. The median provocative concentration causing a 15% fall in FEV_1 did not differ from that in a normal population studied previously. It is concluded that sarcoidosis seldom induces airway hyperreactivity within one year of diagnosis in patients with normal spirometric values.

Inflammatory reactions in the bronchial mucosa may increase airway reactivity to irritant agents—for example, in patients with farmer's lung.[1 2] In early sarcoidosis gallium scintigrams and bronchoalveolar lavage indicate an alveolitis with activated macrophages and T lymphocytes,[3] and this could cause inflammatory reactions in the lower airways and thereby an increase in airway reactivity. Many patients with pulmonary sarcoidosis have airways obstruction due to granulomatous infiltrates in the bronchial mucosa, while others show reversible airways obstruction.[4 5] A transient increase in non-specific bronchial reactivity in sarcoidosis was thought to be due to changes in the airway epithelium.[6] To assess whether non-smokers with early non-treated sarcoidosis have hyperreactive airways, we studied airway reactivity in 17 consecutive patients referred to the department of lung medicine of the University of Lund.

Methods

We studied 10 women and seven men admitted consecutively with recently diagnosed sarcoidosis. They had a mean age of 32 (range 22–48) years and an average height of 172 (153–184) cm and weight of 64 (49–86) kg. Fourteen had no history of asthma; one had had asthma for eight years as a child; one had current asthma and one rhinitis, conjunctivitis, and asthma. These three patients were excluded from our evaluation.

The table shows data from the 14 patients studied, of whom nine had a history of acute sarcoidosis. Ten had a chest radiograph compatible with stage I disease and four with stage II. Epitheloid cell granulomas were found in nine of the 10 subjects who had a biopsy. The Mantoux reaction of 2 tuberculin units PPD was negative in nine subjects, and 10 and 11 mm in the other two in whom it was measured. The mean time from the start of symptoms or from a positive radiograph to the study of bronchial reactivity was 4·7 (range 2–10) months.

Five patients had a family history of asthma and atopic diseases but the total IgE concentration (< 15 kU/l) or blood eosinophil count (0·1–0·26 × 10^9/l) (or both) was within normal limits in all cases.

Mean FEV_1 and FVC as percentage of predicted were 96% (range 79–123%) and 93% (range 78–112%) (table). A methacholine provocation test was performed by a standardised method and used to construct a methacholine dose – FEV_1 response curve.[8]

The results from a previous study of normal subjects using the same technique were used for comparison with the results from the present subjects. We have taken a reduction of 15% or more of the control FEV_1 as a positive reaction, on the basis of our earlier studies ($PC_{15\ FEV_1}$ being the provocative concentration of methacholine producing a 15% fall

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Stage, diagnosis, and duration of sarcoidosis; family history of pulmonary disease; and spirometric values in 14 non-allergic, non-smoking untreated patients

Patient No	Stage	Histological diagnosis*	Family history	Duration of symptoms or radiological abnormality† (months)	FEV_1 % predicted	FVC % predicted
1	I	Kveim +	No	3	98	98
2	I	0‡	No	9	93	86
3	I§	0	Asthma	4	96	100
4	II	Subcutaneous nodule +	Asthma-Excema	4	79	78
5	I	0	No	2	90	88
6	I	Kveim +	Sarcoidosis	4	111	107
7	I§	0	No	5	100	112
8	II	Kveim +	No	5	109	100
9	I	Mediastinoscopy +	No	2	83	80
10	I§	Kveim −	No	3	123	109
11	II	Kveim +	No	3	100	93
12	I	Kveim +	Asthma	6	85	85
13	II	Kveim +	Asthma	6	91	87
14	I	Kveim +	Asthma	10	88	83

*Histopathological studies showed epitheloid cells and granulomas in different types of biopsy samples (Kveim test, mediastinoscopy, subcutaneous nodules).
†Time from start of symptoms or positive chest radiograph to test of reactivity.
‡No biopsy was performed as the patient had classical signs and rapid regression.
§Acute sarcoidosis.

in FEV_1). In the 32 non-smoking normal subjects tested with an identical technique only one had a PC_{15} FEV_1 of 0·1% methacholine or less. All subjects had been free from chest infections for six weeks and had not taken any drugs since at least the evening before; all had given informed consent to the procedure.

Results

The mean (SD) baseline FEV_1 (% predicted) was 96% (12%) (table). After 0·001%, 0·01%, 0·1%, and 1% methacholine the mean (SD) FEV_1 was 96% (2·9%), 95% (2·9%), 89% (5·8%), and 82% (12·4%) of control values respectively, the FEV_1 returning to 95% (7·5%) after terbutaline. Only one subject (No 12) showed a positive response—that is, a fall of over 15% of FEV_1 after 0·1% mechacholine.

Compared to our 32 non-smoking normal subjects of a similar age the FEV_1 in the sarcoidosis group was lower ($p < 0·05$), but the PC_{15} FEV_1 was not significantly different. (Wilcoxon's rank sum test.)

Discussion

Our aim was to assess whether the recent onset of pulmonary sarcoidosis increased airway reactivity. We excluded factors known to affect the responsiveness of the airways, such as smoking and steroid treatment. Among the first 10 consecutive patients we unexpectedly found four hyperreactive patients. Three of these had a history of asthma, which may be unconnected with the sarcoidosis. After exclusion of these three subjects the remaining subjects had normal spirometric values.

We have found only two previous publications on airway reactivity in sarcoidosis. Bechtel *et al* report increased airway reactivity in 20 patients with pulmonary sarcoidosis compared with 13 normal controls.[9] Their hyperreactive patients with sarcoidosis tended to have more airways obstruction, a lower vital capacity, and more symptoms of wheezing and cough than the normal subjects, although the differences were not significant. The subjects included smokers and non-smokers, patients treated with corticosteroids, and patients who had been ill for up to 12·5 years. In another study Magalif[10] gave acetylcholine aerosol to 65 patients with sarcoidosis. One of the 46 patients with stage I or II disease and two of the 19 with stage III disease had a "positive" result (that is, a fall of FEV_1 or vital capacity of greater than 20% in response to 0·1 or 1·0% acetylcholine).

Konietzko and Kraft[11] found no significant difference in airway reactivity to inhaled carbachol between 39 patients with sarcoidosis and 27 normal subjects.

In our selected subjects, with recent and often acute sarcoidosis, the only patient showing hyperreactivity had stage I disease. The patient had a positive Kveim reaction, a negative tuberculin reaction, and a positive family history of asthma. Methacholine challenge was performed six months after the start of symptoms; serum angiotensin converting enzyme activity was normal (26) when determined 21 months later.

The finding in early sarcoidosis of positive results of gallium scintigraphy and the increase of lymphocytes obtained at bronchoalveolar lavage suggests that inflammatory reactions are likely to be present in the airways. There was, however, no correlation between activity mirrored as increased serum angiotensin converting enzyme activity and the number of lymphocytes obtained at bronchoalveolar lavage.[12]

At present we have no data for man on the relationship between the cells found in bronchoalveolar lavage fluid and the occurrence of clinically relevant bronchial hyperreactivity. Lymphocytes collecting in the lungs in early pulmonary sarcoidosis may not generally release the type or the amount of mediators necessary to cause bronchial inflammation.

References

1 Mönkäre S, Haahtela T, Ikonen M, Laitinen LA. Bronchial hyperreactivity to inhaled histamine in patients with farmer's lung. *Lung* 1981;**159**:145–51.

2 Freedman PM, Ault B. Bronchial hyperreactivity to methacholine in farmer's lung disease. *J Allergy Clin Immunol* 1981;**67**:59–63.

3 Line BR, Hunninghacke GW, Keogh BA, Jones AE, Johnston GS, Crystal RG. Gallium-67 scanning to stage the alveolitis of sarcoidosis: Correlation with clinical studies, pulmonary function studies, and bronchoalveolar lavage. *Am Rev Respir Dis* 1981;**123**:440–6.

4 Levinson RS, Metzger LF, Stanley NN, Kelsen SG, Altose MD, Cherniack IS. Airway function in sarcoidosis. *Am J Med* 1977;**62**:51–9.

5 Renzi GD, Renzi PM, Lopez-Majano V, Dutton RE. Airway function in sarcoidosis: Effect of short-term steroid therapy. *Respiration* 1981;**42**:98–104.

6 Laitinen LA, Haahtela T, Kaava T, Laitinen A. Nonspecific bronchial reactivity and ultra structure of the airway epithelium in patients with sarcoidosis and allergic alveolitis. In: Simonsson BG, ed. *Airway hyperreactivity*. (Symposium, Stockholm 1982.) *Eur J Respir Dis* 1983;**64,** suppl 131:267–84.

7 Berglund E, Birath G, Bjurö T *et al*. Spirometric studies in normal subjects. 1—Forced expirograms in subjects between 7 and 70 years of age. *Acta Med Scand* 1963;**173**:185–92.

8 Kabiraj MU, Simonsson BG, Groth S, Björklund A, Bülow K, Lindell S-E. Bronchial reactivity, smoking, and alpha$_1$-antitrypsin. A population-based study of middle-aged men. *Am Rev Respir Dis* 1982;**126**: 864–9.

9 Bechtel JJ, Starr T III, Dantzker DR, Bower JS. Airway hyperreactivity in patients with sarcoidosis. *Am Rev Respir Dis* 1981;**124**:759–61.

10 Magalif NI. Cholinergischen Bronchialreagibilität bei Sarkoidosekranken. *Allergie Immunol* 1976;**22**:363–6.

11 Konietzko N, Kraft J. Airway hyperreactivity in patients with sarcoidosis. *Am Rev Respir Dis* 1982;**126**:943(letter).

12 Leclerc P, Baumann Ch, Orvoen-Frija E, Blais J, Ameille J, Rochemaure J. Place du dosage sérique de l'enzyme de conversion de l'angiotensine dans la sarcoïdose. A propos de soixante-dix observations. *Sem Hôp Paris* 1982;**58**:1291–4.