Serum Angiotensin-Converting Enzyme Levels in Patients with Pigeon-Breeder’s Disease*

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The serum concentration of angiotensin-converting enzyme is frequently elevated in individuals with active sarcoidosis. The enzyme is presumably actively synthesized by the epithelioid and giant cells of the granuloma. Hypersensitivity pneumonitis, resulting from the inhalation of antigens from pigeons by susceptible individuals, is associated with the development of a granulomatous interstitial and alveolar infiltrate in the pulmonary parenchyma. Because the clinical and pathologic presentation may mimic that of sarcoidosis, we compared the serum levels of angiotensin-converting enzyme in these two diseases. The concentration of angiotensin-converting enzyme is not elevated in individuals with active hypersensitivity pneumonitis, in contrast to its frequent elevation in sarcoidosis. We suggest that the granulomatous response in hypersensitivity pneumonitis may differ at a biochemical level from that of sarcoidosis, since the synthesis of angiotensin-converting enzyme does not appear to be increased.

Pigeon breeder’s disease is a form of hypersensitivity pneumonitis characterized by symptoms of dyspnea, cough, tightness in the chest, and often fever, occurring several hours after exposure to organic antigens present in avian droppings or feathers. The disease is associated with evidence of humoral and cell-mediated immunity to antigens from pigeons and the development of a granulomatous interstitial and alveolar inflammatory response often situated near small airways.1,2 Frequently, the association between exposure and the onset of symptoms is unclear, and the symptomatic individual has dyspnea and a diffuse linear or reticulonodular infiltrate on the chest roentgenogram. In the absence of hilar and mediastinal lymphadenopathy and involvement of other organs, the differentiation between hypersensitivity pneumonitis and sarcoidosis may be difficult, even when a biopsy is obtained. The histopathologic abnormalities of these two lesions are similar, each exhibiting noncaseating granulomas within the interstitium. Although interstitial and alveolar lymphocytic and macrophagic accumulation may be more prominent in hypersensitivity pneumonitis, it has recently been demonstrated that early sarcoidosis may exhibit a considerable interstitial pneumonitis.8 The contrasts are subtle, and biopsy techniques such as the transbronchoscopic approach now favored to aid in the diagnosis of pulmonary sarcoidosis are not likely to yield sufficient tissue to render a definite diagnosis. In addition, the cellular composition of the fluid from pulmonary lavage is similar in these diseases.4,5

Recently, Lieberman et al8 have suggested that serum angiotensin converting enzyme may prove useful in differentiating sarcoidosis from other diffuse pulmonary diseases. The concentration of angiotensin-converting enzyme is elevated in as many as 75 percent of the individuals with active untreated sarcoidosis and is consistently elevated in few other diseases. This group has also reported that the serum level of angiotensin-converting enzyme is normal in farmer's lung and a few other cases of an unspecified form of hypersensitivity pneumonitis.6 We wish to present our experience with the assay of angiotensin-converting enzyme in a group of individuals with proven, clinically active pigeon breeder’s disease.

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Pigeon breeders were identified from the population of patients of the Wood Veterans Administration Hospital and the Medical College of Wisconsin, Milwaukee, and were divided into two groups. Asymptomatic individuals were defined as clinically well, yet evidencing significant exposure to antigens from pigeons by the presence of serum precipitins. Symptomatic pigeon breeders also had evidence of humoral immunity to pigeon antigens but, in addition, exhibited clinical findings consistent with active hypersensitivity pneumonitis and developed symptoms several hours after aerosol exposure to an extract of pigeon serum.7,8

Patients with sarcoidosis all had clinical and radiographic findings consistent with that disease and had undergone biopsy of the lung or lymph node for confirmation. There was no evidence of exposure to antigens known to produce hypersensitivity pneumonitis.

A group of normal volunteers was also studied. None of these individuals had either evidence of pulmonary disease or serum precipitins to extract of pigeon droppings.9

Angiotensin-Converting Enzyme

The assay for angiotensin-converting enzymes was performed according to the method of Lieberman et al.8 Hippuryl-histidyl-leucine (Sigma) was used as the substrate, and activity was expressed conventionally in units per milliliter. One unit represents one nanomole of hippuric acid liberated per minute at 37°C. Differences between groups were assessed using Student’s unpaired t-test.

RESULTS AND DISCUSSION

The control subjects, both normal subjects and asymptomatic individuals with evidence of immunity to pigeon antigens, had levels of angiotensin-converting enzyme in the range reported by Lieberman et al.8 and were not significantly different from each other. Symptomatic patients also had normal serum levels of angiotensin-converting enzyme, and these three groups were significantly different from patients with active untreated sarcoidosis (Fig 1).

Angiotensin-converting enzyme is principally produced by endothelial cells, and it is from this source that serum angiotensin-converting enzyme presumably normally originates.9 In sarcoidosis the alveolar macrophage clearly contains angiotensin-converting enzyme,10 and the enzyme can be demonstrated in granulomatous lymph nodes by immunofluorescence and direct enzymatic assay.11 It has been postulated that something peculiar to the macrophage in sarcoidosis accounts for its capability to secrete the enzyme, but recently alveolar macrophages from normal individuals have been found to contain small amounts of angiotensin-converting enzyme activity.10

Angiotensin-converting enzyme has also been recently localized to sarcoid epithelioid and giant cells using an immunofluorescent technique.12 Therefore, these cells may be another source of angiotensin-converting enzyme in this disease. Other granulomatous diseases may have different subpopulations of epithelioid and giant cells which do not synthesize angiotensin-converting enzyme. Several other inflammatory diseases have been associated with elevated serum concentrations of angiotensin-converting enzyme, but none are likely to be confused with sarcoidosis.5 In contrast, hypersensitivity pneumonitis may mimic sarcoidosis clinically, radiographically, and pathologically.13 Since sarcoidosis is a systemic disease and hypersensitivity pneumonitis is confined to the lungs, the differences in angiotensin-converting enzyme activity may reflect the larger number of granulomas in the former disease. Whatever the mechanism, it appears that the granulomatous inflammatory response accompanying pigeon breeder’s disease does not result in elevations of the serum concentration of angiotensin-converting enzyme; and thus, when increased, this assay may help differentiate between the two diseases.

ACKNOWLEDGMENTS: We are grateful for the excellent secretarial support of Ms. Barbara Hoekman and the technical assistance of Ms. Arlene Kerlin and Mr. Michael Moore.

REFERENCES

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FIGURE 1. Mean serum levels (±SD) of angiotensin-converting enzyme (ACE) for normal control subjects (25.9±4.7 mU/ml), patients with sarcoidosis (44.5±11.4 mU/ml), and pigeon breeders with (symptomatic, 27.1±9.6 mU/ml) and without (asymptomatic, 26.4±5.8 mU/ml) hypersensitivity pneumonitis. Although normal subjects and pigeon breeders are significantly different from patients with sarcoidosis (P < 0.001), there are no significant differences between normal subjects and pigeon breeders.
12 Silverstein E, Pertschuk LP, Friedland J. Immunofluorescent localization of angiotensin converting enzyme in epithelioid and giant cells of sarcoidosis granulomas. Proc Natl Acad Sci USA 1979; 76:6646-48