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Role of Serum Angiotensin Converting Enzyme in Sarcoidosis

Pages with reference to book, From 131 To 133

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Abstract

This study was conducted to determine the role of Serum Angiotensin Converting Enzyme (SACE) as a marker in the differential diagnosis of pulmonary diseases and prognosis of sarcoidosis. A retrospective analysis of 113 medical records of patients at The Aga Khan University Hospital, with laboratory investigation for SACE was performed. Among 113 patients, 51 cases were found to have sarcoidosis, 44 of them had SACE levels greater than 52 IU/L (mean ACE 104.44). SACE levels were also found elevated in other clinical conditions like tuberculosis (mean 58.64 IU/L), but the enzyme level were less ($p < 0.04$) than those found in sarcoidosis (mean 92-97 IU/L). SACE activity was found to be considerably lower in other chronic lung diseases such as, fibrosing alveolitis (mean 43.98 IU/L), interstitial lung disease (mean 42.11 IU/L) and chronic obstructive lung disease (mean 40.85 IU/L). Twenty patients of sarcoidosis, who received steroid treatment subsequently showed a decline in the SACE levels. SACE is a useful marker in differential diagnosis as 37.2% cases of sarcoidosis compared to only 9.09% of tuberculosis had SACE levels greater than 100 IU/L. In addition, our data also suggest that serum ACE is useful for the diagnosis as well as monitoring prognosis in sarcoidosis (JPM 48:131,1998).

Introduction

Sarcoidosis is a chronic, multisystem disorder of unknown cause with variable clinical manifestations that can involve any part of the body. Usually, a self-limiting condition; the disease in some cases may follow a chronic progressive course resulting in severe morbidity. Diagnosis of sarcoidosis is dependent upon the pathologic demonstration of non-caseating granulomas, usually by lymph node or liver biopsy and absence of tuberculosis or fungal infection or evidence of malignancy. Diagnosis often necessitates an invasive diagnostic procedure like broncho-alveolar lavage and transbronchial or open lung biopsy. During a study of the angiotensin converting enzyme in human serum, Liberman discovered increased enzyme activity in the blood of patients with sarcoidosis and later reported elevated SACE levels in 70% of a total of 390 cases of sarcoidosis and in 90% of those considered to have active disease^{1,2}.

Unfortunately, elevated SACE levels are not absolutely specific for sarcoidosis and raised levels have also been noted in diseases more likely to be confused with sarcoidosis, especially tuberculosis. The distinction between sarcoidosis and tuberculosis is particularly important in South East Asia, including Pakistan where tuberculosis is common and may have similar clinical presentation as that of sarcoidosis, but requires specific and more prolonged therapy.

Reported results of SACE levels in tuberculosis have been discrepant with some observers reporting normal values² while others report elevated levels in 3.5% to 87.5% of patients with millary tuberculosis³. The main source of the SACE in normal subjects is the endothelial cells of the pulmonary vascular bed. It is suggested that raised enzyme levels in sarcoidosis are due to increased enzyme synthesis by the granuloma epithelioid cells⁴ and the serum levels of this enzyme may reflect the granuloma load of the body.

Interest in SACE centers on the potential of the measurement for providing a non-invasive means of

establishing a diagnosis of sarcoidosis and assessing the degree of disease activity and monitoring the effect of therapy^{5,6}. On the basis of this background information, the current study was carried out to assess the sensitivity and specificity of this test in differential diagnosis of pulmonary pathologies, in an environment where tuberculosis is common. In addition, it also addresses the utility of SACE activity in following the course of patients with sarcoidosis.

Material and Method

A retrospective analysis was performed, based on medical records of 113 patients (51 cases of sarcoidosis, 33 cases of pulmonary tuberculosis, 29 cases with other pulmonary pathologies), registered at The Aga Khan University Hospital between 1990-1994, who had laboratory investigation for SACE levels. The diagnosis of sarcoidosis was based on clinical, radiographic and histologic features. Clinical activity of sarcoidosis was judged using the criteria commonly applied in the out-patient department, i.e. an overall assessment based on symptoms (e.g. presence or absence of cough, dyspnoea etc), evidence of extra-thoracic activity (in skin, lymph nodes, upper respiratory tract, joint, eye or nervous system changes), chest radiograph and SACE activity.

Patients with tuberculosis included those diagnosed on symptomatology and by the demonstration of acid fast bacilli either in secretions or biopsy specimens. Diagnosis of other lung diseases such as fibrosing alveolitis, interstitial lung disease, etc. was made on the basis of characteristic clinical features with supportive histology. The procedure used for measurement of SACE levels is a rapid, convenient spectrophotometric method⁷, utilizing the synthetic tripeptide substrate N- α -[2-(2-fuoyl)acryloyl]-L-phenylalanyl-glycylglycine (FAPGG) from Sigma Chemical Company, St Louis, USA and analyzed on Clinicon 4010 of Boehringer Mannheim⁸.

The following reaction is catalyzed by ACE: FAPGG > FAP+glycylglycine

FAPGG is hydrolyzed to fuoylphenylalanine (FAP) and glycylglycine. Hydrolysis of FAPGG results in a decrease in absorbance at 340 nm. The ACE activity in the sample is determined by comparing the sample reaction rate to that obtained with ACE calibrator.

The normal range of SACE activity is defined as mean value $\pm 2SD$. The mean value obtained for 56 clinically healthy adult males and females, by the described method was 30 I.U/L (SD=1) and the reference range was 8-52 I.U/L⁸.

Results

Prevalence of Elevated SACE Level (more than 52 IU/L) in Patients with Various disease States:

Forty four (38.9%) subjects with sarcoidosis had elevated SACE levels (i.e. >52 IU/L). The second group that had raised enzyme activity comprised of 18 cases of tuberculosis (15.9%). In addition, in subjects with other types of lung diseases (n=29) for e.g., fibrosing alveolitis (n=8), interstitial lung disease (n=7), C.O.P.D. (n=4), pneumonia (n=4), lung fibrosis (n=3), lung atelectasis (n=1), silicosis (n=1) and bronchiectasis (n=1) all of which are important lung diseases in the differential diagnosis, had SACE levels elevated in 6 cases (5.3%) only.

Role in Sarcoidosis

Comparison of mean ACE levels in various lung diseases show that highest levels are found in Sarcoidosis (mean 97.27 IU/L), which was significantly higher (p < 0.05) than other lung diseases. **Role in Differential Diagnosis**

Table I. Role of SACE levels in differential diagnosis.

ACE levels IU/L	Tuberculosis (n=33)		Sarcoidosis (n=51)		Other pulm. conditions (n=29)		p value
	No.	%	No.	%	No.	%	
<51.9	15	45	7	13.7	23	79.3	<0.05
52-74.9	9	27	13	25	1	3.4	0.03
75-99.9	6	18	12	23.5	4	13.8	0.6
100-149.9	3	9	12	23.5	1	3.4	0.03
150-199.9	-	-	5	9.8	-	-	-
>200	-	-	2	3.9	-	-	-

Table I compares the predictive value of SACE as a marker in the differential diagnosis of pulmonary pathologies. SACE levels were found to be within normal limits (<52 IU/L), in 23 cases (79.3%) of patients with other pulmonary pathologies besides tuberculosis and sarcoidosis, in which 15 cases (45%) and 7 cases (13.7%) were found respectively. In addition, this difference is statistically significant for patients with other lung conditions if SACE value is below 52 IU/L. Serum ACE levels were elevated in tuberculosis, n=18 (54.5%), sarcoidosis, n=44 (86.27%) and other pulmonary conditions, n=6 (20.68%). The degree of elevation of the enzyme is more marked in sarcoidosis in contrast to tuberculosis and other pulmonary conditions. Nineteen cases of sarcoidosis (37.2%) had SACE values greater than 100 IU/L in comparison to only 3 cases (9.09%) of tuberculosis and 1 case (3.4%) with other pulmonary conditions. The distinction between the two i.e. sarcoidosis and tuberculosis becomes difficult when the SACE levels are between 75-100 IU/L (p=0.06).

Table II. Evaluation of ACE in screening of sarcoidosis

	ACE >52 (IU/L)	ACE >100 IU/L
Sensitivity	86.27	37.2
Specificity	61.29	93.4
Positive predictive value	64.70	82.6
Negative predictive value	84.44	64.44

Response of SACE to Treatment

Twenty cases of sarcoidosis were treated with steroids and their SACE levels were measured after treatment. A significant decline ($p=0.01$) in the enzyme activity (mean 42.535 IU/L) was observed following treatment, in contrast to the mean ACE (104 IU/L) found at the time of diagnosis.

Discussion

Activity of Serum Angiotensin Converting Enzyme (SACE) was found to be a useful tool in predicting the diagnosis of sarcoidosis. Enzyme activity was markedly increased in patients with sarcoidosis in contrast to normal or slightly elevated levels in patients with other types of chronic lung diseases and moderately raised levels in patients of tuberculosis. In addition, the assay is easily performed and offers better precision and freedom from interference than a fluorimetric assay⁷. One of the major reasons for studying this enzyme was in the differential diagnosis of lung diseases, especially tuberculosis. Sarcoidosis and tuberculosis have many common features, which includes both the clinical and radiological presentation. This poses a dilemma for the physician especially in an area of high prevalence of tuberculosis.

The data also shows that the patients with a diagnosis of sarcoidosis had significantly higher SACE activity (>100 IU/L) than either the subjects with tuberculosis or subjects with other type of lung diseases, i.e., the incidence of false positive cases of other diseases decreases with more marked elevation of the enzyme (Table II). Diagnosis of sarcoidosis cannot be made with certainty, when the SACE value is between 52-100 IU/L and carries a risk of missing the cases of tuberculosis. In this situation, we advised to consider other criteria for instance, biopsy in the context of the history and if available gallium 67 scan and bronchoalveolar lavage^{9,10}.

In addition to its value in the diagnosis of patients with suspected sarcoidosis, SACE estimation has found to be much useful in assessing therapeutic response. However, there remains 13.7% of patients of sarcoidosis who despite other clear indication of activity have normal SACE measurement (Table I).

De Ramee and Rohrbach⁴ found normal SACE levels in 17% of patients with newly diagnosed sarcoidosis and noted that normal levels correlated with a relatively good prognosis.

- In our patients also, only 1 case required treatment with steroids while the rest showed spontaneous recovery.

Based on our study, it is recommended that a SACE is useful differential diagnostic marker at levels above 100 IU/L or less than 52 IU/L in the diagnosis of sarcoidosis, but it is not suitable, when considered alone for differential diagnosis in pulmonary pathologies, if SACE levels are between 75-100 IU/L. In that case confirmatory diagnosis requires additional investigations. In addition, it is a reliable guide for monitoring the effectiveness of therapy in sarcoidosis.

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