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Diagnostic Utility of Angiotensin Converting Enzyme in Sarcoidosis: A Population-Based Study

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Abstract

Purpose—Sarcoidosis is a disease with heterogenous clinical presentations. Diagnosis of sarcoidosis is often challenging with the lack of gold standard tests. In this study, we investigated the diagnostic utility of Angiotensin-converting enzyme (ACE) for diagnosis of sarcoidosis.

Methods—A cohort of Olmsted County, Minnesota residents who were diagnosed with sarcoidosis between January 1, 1984 and December 31, 2013 was identified based on individual medical record review. ACE levels recorded in the medical records of all subjects at the time of diagnosis were extracted. Comparator subjects were residents of Olmsted County, Minnesota who had ACE levels tested the same time period but did not have a diagnosis of sarcoidosis. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and the c-statistic of high vs low/normal ACE to diagnose sarcoidosis were calculated.

Results—A total of 3,277 Olmsted County residents age ≥18 years had at least one ACE test in 1984-2013. The sarcoidosis incidence cohort contained 295 Olmsted County residents diagnosed with sarcoidosis in 1984-2013. Of these, ACE tests were obtained in 251. The sensitivity and specificity of high ACE for diagnosis of sarcoidosis were 41.4% (95% CI, 35.3%-47.8%) and 89.9% (95% CI, 88.8%-91.0%), respectively. The PPV and NPV in this population were 25.4% (95% CI, 21.3% -29.9%) and 94.9% (95% CI, 85.0%-87.4%).

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Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Conclusions—This study demonstrated a poor sensitivity and insufficient specificity of high ACE for diagnosis of sarcoidosis suggesting a limited role of ACE in clinical practice.

Keywords

Sarcoidosis; autoimmune disease; clinical epidemiology; diagnostic testing

Introduction

Sarcoidosis is a multi-system disease of unclear etiology characterized by the presence of non-caseating granuloma. The disease generally has a benign course even though progressive organ dysfunction with significant morbidity and mortality can be seen a minority of patients [1]. The reported annual incidence varies from 0.73 per 100,000 to 71 per 100,000 depending on the studied populations [2, 3].

There are no universally-accepted gold standard diagnostic tests for sarcoidosis. In clinical practice, the diagnosis usually relies on the presence of non-caseating granuloma for the biopsy specimen, compatible clinical presentation, and exclusion of other granulomatous diseases with the exception of stage I pulmonary sarcoidosis that usually requires only radiographic evidence of symmetric bilateral hilar adenopathy [4].

Angiotensin-converting enzyme (ACE) is an integral membrane bound protein that is strongly expressed in many endothelial cells, especially the capillary endothelial cells of the lung. It plays a pivotal role in the renin-angiotensin system to maintain the normal blood pressure and electrolyte balance by converting angiotensin I to angiotensin II and degrade bradykinin [5].

The first report of elevation of serum ACE levels among patients with active sarcoidosis appeared in 1975 [6]. Subsequent studies reported elevated ACE levels in other granulomatous pulmonary diseases such as histoplasmosis, silicosis and tuberculosis [7, 8]. The increased level is thought to be secondary to increased ACE expression by the epithelioid cells present in the granulomas [9].

The utility of ACE levels for the diagnosis of sarcoidosis has been investigated in several studies [6, 10-16]. Most of these used sarcoidosis cohorts from tertiary care centers, which might not represent the true spectrum of sarcoidosis. The current study was conducted using a population-based cohort of patients with sarcoidosis to evaluate the sensitivity and specificity of ACE levels.

Materials and methods

Data source and study population

Through the resources of the Rochester Epidemiology Project (REP), the population of Olmsted County, Minnesota is well suited for epidemiologic study of sarcoidosis because of the availability of comprehensive and complete medical records for all residents seeking medical care for over six decades. A record linkage system allows comprehensive access to the medical records from all health care providers for the local population, including the

Mayo Clinic, the Olmsted Medical Center and their affiliated hospitals, local nursing homes, and the few private practitioners. The application of this record linkage system for use in population-based studies has previously been described [17, 18]. With this resource all clinically recognized cases of sarcoidosis among the residents of Olmsted County, Minnesota were captured.

The study was approved by the Mayo Clinic and Olmsted Medical Center institutional review boards. The need for informed consent was waived.

Study design

A cohort of Olmsted County, Minnesota residents who were diagnosed with sarcoidosis between January 1, 1984 and December 31, 2013 was identified. All patients with diagnosis codes related to sarcoid, sarcoidosis, and contextual noncaseating granuloma were screened for inclusion in the cohort based on individual medical record review. Inclusion required physician diagnosis of sarcoidosis supported by the presence of non-caseating granuloma without evidence of acid-fast bacilli or fungi in tissue samples, radiologic features of intrathoracic sarcoidosis and compatible clinical presentation without other known granulomatous diseases. The only exception to the requirement of histopathological confirmation was stage I pulmonary sarcoidosis that required only radiographic evidence of symmetric bilateral hilar adenopathy in the absence of other identifiable causes. Cases of isolated granulomatous disease of a specific organ except for the skin were also included if the patients were physician diagnosed with sarcoidosis, and there was no better alternative diagnosis. Cases with a diagnosis of sarcoidosis prior to residency in Olmsted County (prevalent cases) were not included.

ACE levels recorded in the medical records of all subjects at the time of diagnosis were extracted, and as well all ACE values ordered as part of clinical care at Mayo Clinic were obtained electronically for the time period of 1984-2013. Test values obtained in patients who denied research authorization, were not residents of Olmsted County and those who were age <18 years at the time of ACE testing were excluded. The ACE levels at diagnosis were recorded and categorized as “high” or “low and normal” according the reference range for the specific time the tests were performed. Regardless of provider, all of the ACE tests were done at the same laboratory (Mayo Medical Laboratory). Comparator subjects were residents of Olmsted County, Minnesota who had ACE levels tested but did not have a diagnosis of sarcoidosis. The ACE levels of controls were categorized in the same fashion. If ACE was tested more than once, the first ACE test result in each patient was used for analysis.

Statistical analysis

Descriptive statistics (means, percentages, etc.) were used to summarize the characteristics of patients with and without sarcoidosis. Chi-square and rank sum tests were used to compare characteristics between the groups. Sensitivity, specificity, positive predictive value, negative predictive value and the c-statistic (i.e., area under the receiver operating characteristic curve) of high vs low/normal ACE to diagnose sarcoidosis were calculated. Ninety-five percent confidence intervals (CI) were calculated using exact binomial methods.

Logistic regression models adjusted for age and sex were used to examine the association between ACE and sarcoidosis.

Age- and sex-specific prevalence rates for ACE testing were calculated by using the number of patients with at least one ACE test in each year as the numerator and population estimates for adults (age ≥18 years) based on decennial census counts as the denominator, with linear interpolation used to estimate population size for intercensal years. Prevalence rates were age- and sex-adjusted to the 2010 white population of the United States. Analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA).

Results

A total of 3,277 Olmsted County residents age ≥18 years had at least one ACE test in 1984-2013. The sarcoidosis incidence cohort contained 295 Olmsted Count residents diagnosed with sarcoidosis in 1984-2013. Of these, ACE tests were obtained in 251. Table 1 describes the characteristics of Olmsted County residents with ACE test results in 1984-2013.

Table 2 summarizes the performance of high ACE for diagnosis of sarcoidosis. The sensitivity and specificity of high ACE for diagnosis of sarcoidosis were 41.4% (95% CI, 35.3%-47.8%) and 89.9% (95% CI, 88.8%-91.0%), respectively. The positive predictive value (PPV) and negative predictive value (NPV) in this population were 25.4% (95% CI, 21.3% -29.9%) and 94.9% (95% CI, 94.0%-95.7%). The c-statistic was 0.66 for ACE alone, demonstrating some utility for high ACE over change alone (which corresponds to c=0.5). Similarly, the incremental c-statistic for high ACE after age and sex adjustment was 0.12. High ACE was associated with a 6-fold increased likelihood of sarcoidosis (Odds ratio: 6.31; 95% CI: 4.8 - 8.3, p<0.001). This association persisted after age and sex adjustment (odds ratio: 6.15; 95% CI: 4.7- 8.1, p<0.001).

ACE testing rates were examined to determine trends in clinical use of ACE for diagnosing sarcoidosis. Prevalence of ACE testing increased from 1984-1999 and declined from 2000-2013 in the Olmsted County population (Figure 1). Trends in testing rates over time were similar for both males and females. Correspondingly, the 15% of patients in our cohort who did not have ACE testing at the time of sarcoidosis diagnosis were somewhat more likely to be diagnosed with sarcoidosis in more recent years (p=0.11).

Discussion

This study demonstrated a poor sensitivity and insufficient specificity of high ACE for diagnosis of sarcoidosis (with false positive of about 10%). The association between high ACE and sarcoidosis did not significantly change after the adjustment for age and sex.

These results were in line with previous studies, although the sensitivity of ACE for the diagnosis of sarcoidosis was generally lower than other studies which reported sensitivity in the range of 60%-80% [6, 13-16]. It is possible that the current population-based study might capture more milder cases of sarcoidosis compared with those tertiary care center

cohorts. Nonetheless, the specificity of the test was fairly consistent across studies, with the false positive rates ranging from 5% - 15%.

Sarcoidosis is a multi-system disease with heterogenous clinical presentations. Diagnosis of sarcoidosis is often challenging with the lack of universally-accepted gold standard test. Elevated ACE levels have been proposed as useful in sarcoidosis diagnosis. However, the results of this study do not support the role of ACE level to exclude the diagnosis. ACE level might have a limited role in supporting the diagnosis of sarcoidosis in the situation that the pretest probability is high and patients/physicians prefer to avoid more invasive tests. For example, high ACE level might help to support the diagnosis of patients presented with classic bilateral hilar adenopathy who do not want to pursue diagnostic bronchoscopy.

Although the NPV appears to be high, the prevalence of sarcoidosis among the tested subjects was only 9.2%. The NPV may be much lower in different populations or in patients with higher pretest probability.

The major strengths of this study are that it is a population-based study that minimizes referral and selection biases. The comprehensive record-linkage system allows capture of nearly all the cases of sarcoidosis in the community with verification of diagnosis by medical record review. This approach also reduces the likelihood of misclassification, a common concern in coding-based studies. The major limitations are those inherent in the retrospective study design. The ACE levels were not obtained in approximately 15% of cases; it is unknown how if at all clinical presentation and clinician reasoning or secular trends in clinician willingness to obtain ACE levels may have affected the decision to obtain the test. As well, it was not possible to fully extract the data regarding use of ACE inhibitors which could interfere with the serum ACE activity. Furthermore, due to changes in ACE assay over this 20 year time period, we were not able to analyze ACE levels as continuous variables, which limited our ability to examine whether ACE might perform better at different cutoff values. This study also did not attempt to evaluate the performance of ACE as a marker for disease activity. The population of Olmsted County is also predominately of Northern European ancestry with a higher proportion of health-care workers and correspondingly higher education level and socioeconomic status, which may affect the generalizability of the results to other populations.

Conclusion

ACE levels perform poorly as a diagnostic test for sarcoidosis. The results did not support the role of ACE in clinical practice.

Acknowledgement

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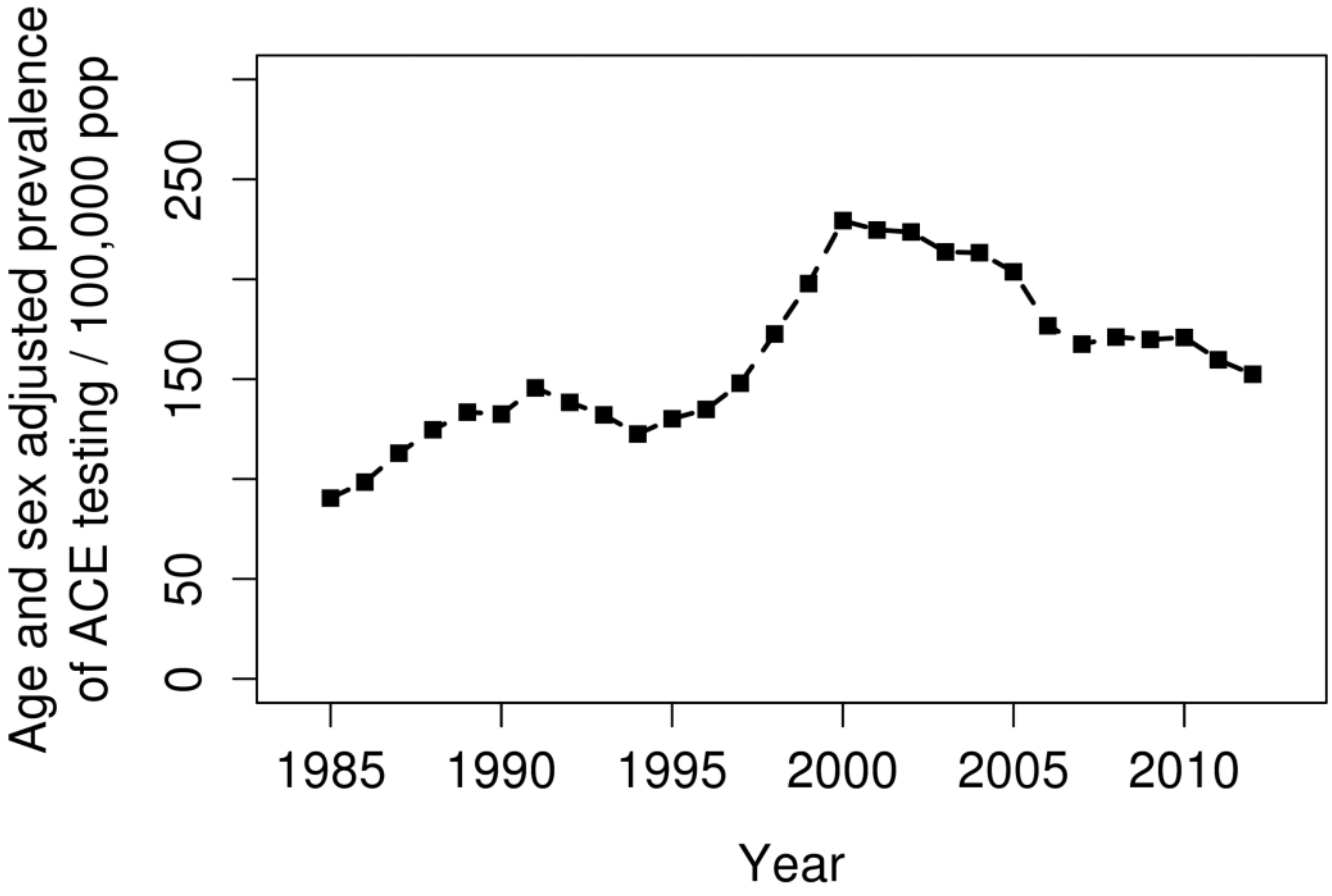

Figure 1.
Prevalence of angiotensin-converting enzyme testing in Olmsted County, Minnesota residents in 1984-2013

Table 1

Characteristics of Olmsted County residents with Angiotensin-converting enzyme test results in 1984-2013.

	Control (N=3026)	Case (N=251)	Total (N=3277)	p value
Age, years				<0.001
Mean (SD)	51.0 (17.4)	45.2 (12.8)	50.6 (17.2)	
Median	50.1	44.8	49.5	
Q1,Q3	36.9, 64.0	34.8, 54.1	36.7, 63.0	
Range	(18.0-97.9)	(20.6-83.3)	(18.0-97.9)	
Sex				0.009
Female	1753 (58%)	124 (49%)	1877 (57%)	
Male	1273 (42%)	127 (51%)	1400 (43%)	
Race				0.590
Caucasian	2429 (80%)	205 (82%)	2634 (80%)	
African-American	130 (4%)	15 (6%)	145 (4%)	
Asian	74 (2%)	3 (1%)	77 (2%)	
Other	85 (3%)	6 (2%)	91 (3%)	
Choose not to disclose	24 (1%)	2 (1%)	26 (1%)	
Unknown	284 (9%)	20 (8%)	304 (9%)	
ACE result				<0.001
Low and Normal	2721 (90%)	147 (59%)	2868 (88%)	
High	305 (10%)	104 (41%)	409 (12%)	

Table 2

Performance of Angiotensin-converting enzyme for diagnosis of sarcoidosis

Characteristic	Calculation	Value	95% confidence interval	
Sensitivity	104/251	41.43	35.27	47.80
Specificity	2721/3026	89.92	88.79	90.97
Positive Predictive Value	104/409	25.43	21.28	29.94
Negative Predictive Value	2721/2868	94.87	94.00	95.65
Accuracy	2825/3277	86.21	84.98	87.37