

# Sarcoidosis - Angiotensin Converting Enzyme

## Clinical Background

Sarcoidosis is a multisystemic disorder of unknown etiology, characterized by granuloma formation.

### Epidemiology

- Incidence – 10-15/100,000 in U.S.; 40/100,000 in some North European countries and among African Americans
- Age – peak incidence 20-39 years
- Sex – F>M
- Ethnicity – most prevalent in Swedish, Danish and African Americans

### Risk Factors

- Family member with sarcoidosis (5-fold increased risk)

### Pathophysiology

- Result of chronic immunological response associated with a genetic susceptibility and specific infections or environmental factors
- Accumulation of activated T-cells and macrophages at site of disease activity
- Lymphocytes are CD4 type
- Macrophages release cytokines that drive inflammation, granuloma formation and eventual fibrosis

### Disease Stages

- Stage I – isolated thoracic lymphadenopathy
- Stage II – lymphadenopathy plus lung infiltration
- Stage III – lung infiltration
- Stage IV – overt pulmonary fibrosis

### Clinical Presentation

- Asymptomatic (30-50%) diagnosed by routine chest X-ray with abnormalities of hilar adenopathy
- Nonspecific (30%) – fever, weight loss, fatigue
- Pulmonary (30%)
  - Löfgren syndrome – bilateral hilar adenopathy, ankle arthritis, fever, myalgia, weight loss and erythema nodosum
  - Dyspnea, wheezing
- Dermatologic – maculopapular rashes, plaques and nodules (lupus pernio), erythema nodosum and lupus pernio
- Cardiac – rhythm disorders, infiltrative cardiomyopathy and pericarditis
- Ophthalmic – anterior uveitis
- Hepatic/Splenic – granulomas, but dysfunction is rare
- Endocrine – hypercalcemia with nephrolithiasis
- Central nervous system (CNS) – neurosarcoidosis is an uncommon, but serious manifestation of sarcoidosis, affecting about 5-10% of patients
  - The most common manifestations include myelopathy, cranial neuropathy and encephalopathy
  - Untreated patients may develop acute neurologic emergencies, including seizures, cord compression and increased intracranial pressure
  - Heerfordt's syndrome – uveitis, parotid gland enlargement, fever and cranial neuropathy (usually 7th nerve)

## Diagnosis

### Diagnosis

- Indications for testing – lymphadenopathy on chest x-ray or other appropriate clinical signs and symptoms consistent with diagnosis of sarcoidosis
- Laboratory testing
  - Rule out other granulomatous diseases – consider stains and cultures for fungi and tuberculosis (TB test)
  - Chemistry panel – may demonstrate hypercalcemia (~10%), hypercalcuria (~30%) or liver transaminase elevations (~20%)
  - Angiotensin converting enzyme (ACE) – may have elevated level (2x normal) but this is not diagnostic for disease
    - Reflects disease activity and may be useful to follow disease activity
    - Cerebrospinal fluid (CSF) ACE – elevated level supports diagnosis of neurologic sarcoidosis but is not diagnostic
- Histology – presence of noncaseating granulomas
- Fiber optic bronchoscopy with bronchoalveolar lavage, transbronchial biopsy or endobronchial biopsy
  - CD4/CD8 ratio higher than 3.5 is suggestive of sarcoidosis and is further supported if ACE levels are abnormal
  - If criteria above are met and clinical presentation is consistent with sarcoidosis, absence of granulomas on biopsy does not negate the diagnosis of sarcoidosis
- Pulmonary function testing – full function testing with diffusing capacity of the lung for carbon monoxide (DLCO) demonstrates decreased volumes and diffusion capacity
- Imaging studies
  - Pulmonary disease – high resolution CT produces better diagnostic yield than a chest X-ray; classically shows widespread micronodules with perilymphangitic distribution in middle and upper lobes (unnecessary test for most patients)
    - Justified when there are atypical chest X-ray findings or normal chest X-rays but suspicion of disease
    - For detection of complications of lung disease
  - Central nervous system disease
    - Gadolinium-enhanced MRI

### Differential Diagnosis

- Chronic beryllium disease
- Fungal infection
- Hypersensitivity pneumonitis
- Malignancy – lymphoma
- Tuberculosis
- Wegener's granulomatosis

## Lab Tests

### Indications for Ordering

Tests generally appear in the order most useful for common clinical situations. For test-specific information, refer to the test number in the ARUP Laboratory Test Directory on the ARUP Web site at [www.aruplab.com](http://www.aruplab.com).

Test Name and Number	Recommended Use	Limitations	Follow Up
Angiotensin Converting Enzyme, Serum <b>0080001</b> Method: Enzymatic	Support diagnosis of sarcoidosis or neurosarcoidosis via ACE levels in serum  Evaluate response to treatment via ACE	Antihypertensive medications such as ACE inhibitors, ACE receptor blockers and diuretics may interfere with test results  This test is not specific for diagnosis of sarcoidosis  Test is a nonspecific indicator of response to treatment  In neurosarcoidosis, serum ACE concentrations are less likely to be elevated than CSF ACE concentrations. CSF ACE levels are increased in about 55% of patients with neurosarcoidosis, 5% of those with sarcoidosis (without neurologic abnormality) and 13% of those with other neurological diseases	Further tissue biopsy and evaluation for granulomas is necessary to confirm the diagnosis
Angiotensin Converting Enzyme, CSF <b>0098974</b> Method: Spectrophotometry	Support diagnosis of sarcoidosis or neurosarcoidosis via ACE levels in CSF  Evaluate response to treatment via ACE	Antihypertensive medications such as ACE inhibitors, ACE receptor blockers and diuretics may interfere with test results  This test is not specific for sarcoidosis  Test is a nonspecific indicator of response to treatment	

Lymphocyte Subsets Panel 4 - T-Cell Subsets Percents & Ratio, Bronchoalveolar Lavage <b>0093420</b> Method: Flow Cytometry	Assist in the diagnosis of sarcoidosis when biopsy is negative		
Calcium, Serum or Plasma <b>0020027</b> Method: Spectrophotometry			
Aspartate Aminotransferase, Serum or Plasma <b>0020007</b> Method: Enzymatic			
Alanine Aminotransferase, Serum or Plasma <b>0020008</b> Method: Enzymatic			
Alkaline Phosphatase, Serum or Plasma <b>0020005</b> Method: Enzymatic			

**General References**

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**References from the ARUP Institute for Clinical and Experimental Pathology®**

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