ILD Collaborative

Project ECHO

Sarcoidosis: Overview, Diagnosis, and Monitoring

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Sarcoidosis

- Epidemiology
- Etiology
- Pathophysiology
- Organ System Involvement
- Clinical and Laboratory Findings
- Radiology
- Diagnosis

Sarcoidosis

- Generalized granulomatous disease primarily affecting the lung and lymphatic system
- Frequently involves multiple organ systems (extra-pulmonary sarcoid)

Sarcoid - Epidemiology

- Both sexes, but women > men
- All races
- Usually < 40 yo, peaks ages 20-29
- Scandinavian countries and Japan – another peak incidence in women > 50 yo
- World: prevalence is highest in Swedes, Danes, and US blacks
- Rare in Spain, Portugal, India, Saudi Arabia, South America

USA – Racial Disparity

Sarcoidosis incidence estimates reported in the literature

References	Country	Sex, race/ethnicity	Time period	Incidence per 100,000	Data source
Baughman et al. (4)	USA	Male and female, multiracial	2010–2013	Black: 17.8 White: 8.1 Hispanic: 4.3 Asian: 3.2	Optum Health Care Database
Cozier et al. (6)	USA	Female, black	1995–2007	71	Black Women's Health Study, self-reported sarcoidosis
Dumas et al. (8)	USA	Female, multiracial	1989–2011	Overall: 11 Black: 43 White: 11	Nurses' Health Study II, self-reported
Rybicki et al. (10)	USA, Detroit, MI	Male and female, multiracial	1990–1994	Black: 35.5 White: 10.9	Health Alliance Plan HMO

Hena, KM Front Immunol. 2020; 11: 537382.

Sarcoidosis – Racial Disparity

- In US: lifetime risk whites 0.85%, blacks 2.4%
- Black patients have more extrapulmonary sarcoid
- Whites – calcium dysmetabolism
- Pulmonary involvement is the only organ involvement independent of age, sex, race

Sarcoidosis – Severity at Dx

- Lower income
- Absence of private/Medicare insurance
- Black race
- Female sex

Sarcoidosis

- Whites
  - more benign asymptomatic disease
- Blacks
  - more chronic w/uveitis, lupus pernio
- Europeans
  - more erythema nodosum
- Japan
  - more cardiac and ocular sarcoid

Sarcoidosis - Mortality

- Overall mortality 1-5%
- Black females: 10 per million
- Black males: 3 per million
- White males & females: 1 per million

Environmental Exposures

- Isle of Man study – 18.8% pts were health care workers v. 4.2% controls
- Firefighters – increased incidence and prevalence compared with health care workers and historical controls
- WTC – increased incidence of sarcoid or sarcoid-like granulomatous pulmonary disease in 5 yrs after 9/11 compared with 15 yrs before
- US Navy aircraft carrier – increased risk of sarcoid

Infectious Etiology

- Transmissible agent – 1964 sarcoid reported in recipients of transplants from sarcoid pts and vice versa
- Bacteria: Proprionibacterium acnes, mycobacteria, Mycoplasma, Borrelia Burgdorferi
- Implicated viruses: HSV, EBV, CMV, retrovirus, coxsackie B

Genetic Etiology: ACCESS

- 706 sarcoid case-control prs: 10K first degree relatives & 17K second degree relatives

- Odds ratio that an individual has a sarcoidosis history and is a relative of a case / OR that an individual has no sarcoidosis history and is a relative of a control

Genetic Etiology

- OR of relative with history of sarcoid being related to case: $\geq$ 4 in 1st and 2nd degree relatives
- Highest OR was for sibs with h/o sarcoid being related to a case
- No positive association for non-blood relatives, close contacts, or spouses of patient with sarcoid

Genetic Etiology

- HLA-B7 significantly increased in AA
- Löfgren's syndrome (acute disease) strongly associated with HLA-DR3, good prognosis
- HLA-DRB1*1501/DQB1*0602 haplotype is associated with chronic course and severe pulmonary sarcoidosis
- HLA allele DQB1*0602 confers increased susceptibility in black families, and risk of radiographic progression

Immunology

- Sarcoid granulomas form in response to a persistent and poorly degradable antigenic stimulus
- Cytokine and chemokine release seen in sarcoid is c/w antigen triggering

Granuloma Formation

- Redistribution of cytokines from peripheral blood to lung
- *In situ* proliferation mediated by IL-2
- Th0 cells differentiate into Th1 cells
- IFN-γ is elevated

Immunology

- CD4+ helper cells > CD8+ T cells
- CD4+ cells release INF-γ and IL-2
- Alveolar macs release TNF-α, IL-12, IL-15, and growth factors

Sarcoidosis - Histology

- Compact, noncaseating epithelioid granuloma (epithelioid cells, giant cells, lymphs)
- Central portion: CD4 + lymphs
- Periphery: CD8+ lymphs
- Fibrosis begins peripherally and spreads centrally
- Occasional necrosis
- 75% are close to or in the connective tissue sheath of the bronchioles
- Nodules -subpleural or perilymphatic distribution

Clinical Symptoms

- Non-specific constitutional symptoms 1/3 (fever, fatigue, malaise)
- Dyspnea, dry cough, chest pain 1/3-1/2
- May involve the sinuses, larynx, trachea, bronchi
- Peripheral Lymphadenopathy 1/3
- Cardiac Sarcoid 5% (25% at autopsy)
- Liver in 50-80% on biopsy

Extrapulmonary Organs

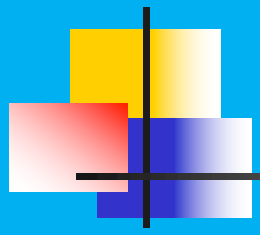
- Skin in 25% (erythema nodosum & lupus pernio)
- Ocular lesions 26%
- Neurosarcoid < 10% (4.6% ACCESS)
- Musculoskeletal system: joints (25-39%), myopathy
- GI tract <1%; Liver (12% abn lft, 96% +bx)
- Bone marrow: anemia, leukopenia (40%)
- Parotid glands (Heerfordt's syndrome)
- Hypercalcemia (6%), renal failure 42%, hypercalciuria (5-15%)
- Kidneys (interstitial nephritis) – 7%
- Endocrine organs – DI, hypo/hyperthyroid
- Reproductive organs

Laboratory Findings

- Leukopenia 5-10%
- Eosinophilia 25%
- Anemia – uncommon
- Thrombocytopenia – rare
- ESR elevation
- Hypercalciuria > hypercalcemia
- Hypergammaglobulinemia 30-80%
- Decreased skin test reactivity
- Alk phos, LFT abnormalities
- ACE +75%; False positive rate <5%

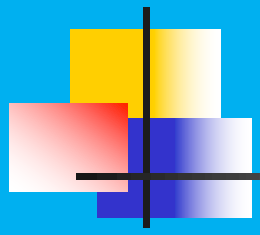
Sarcoidosis: Mechanisms of Hypercalcemia

- Over-production of 1,25-dihydroxyvitamin D3 (calcitriol) by activated macrophages and sarcoid granulomas
- 1,25-OH-Vit D increases the intestinal absorption of calcium
- Hypercalcemia– 5-11%
- Hypercalciuria (absorptive, resorptive, osteoclast activating factor) - 30%
- PTH level is normal or suppressed



PFTs

- Restriction with low DLCO
- Normal
- Obstruction (endobronchial sarcoid in 40% Stage I, 70% Stage II-III)
- Airway hyperresponsiveness – 20%



Diagnosis

- Compatible clinical and radiographic manifestations
- **Exclusion of other diseases** which cause a similar histologic or radiologic picture
- **Histologic evidence** of noncaseating granulomas
- **Systemic**: Evidence of more than one organ involvement

Diagnosis

- In many series, the yield of EBUS-TBNA is > 70%
- Diagnostic accuracy of EBUS-TBNA in 643 patients was 84%, which increased to 89% with the addition of standard techniques such as TBLB and EBBX

Initial Evaluation

- CXR or Chest CT
- Full PFTs
- Eye exam – baseline (v. low quality evidence)
- Creatinine, LFT, CBC with diff
- Calcium & Vit D (25OH & 1,25 OH)
- U/A
- EKG
- PPD

Screening for Cardiac Disease

- HRS Expert Consensus Statement on the Diagnosis and Management of Arrhythmias Associated With Cardiac Sarcoidosis 2014

Screening for CS Recommendations

- Class I “is recommended” for a class I consensus recommendation;
- Class IIa “can be useful”
- Class IIb “may be considered”
- Class III “should not” or “is not recommended”

Screening for CS Recommendations

Expert Consensus Recommendations on Screening for Cardiac Involvement in Patients With Biopsy-Proven Extracardiac Sarcoidosis

Class I	1. It **is recommended** that patients with biopsy-proven extracardiac sarcoidosis **should be** asked about unexplained syncope/presyncope/significant palpitations*
	2. It **is recommended** that patients with biopsy-proven extracardiac sarcoidosis **should be** screened for cardiac involvement with a 12-lead electrocardiogram (ECG).
Class IIa	1. Screening for cardiac involvement with an echocardiogram **can be useful** in patients with biopsy-proven extracardiac sarcoidosis.
	2. Advanced cardiac imaging, CMR or FDG-PET, at a center with experience in CS imaging protocols **can be useful** in patients with one or more abnormalities detected on initial screening by symptoms/ECG/echocardiogram.
Class III	1. Advanced cardiac imaging, CMR or FDG-PET, **is not recommended** for patients without abnormalities on initial screening by symptoms/ECG/echocardiogram.

*Palpitations were defined as "a prominent patient complaint lasting >2 weeks."[25]

Screening for CS Recommendations

Table 2 Prevalence of abnormalities, sensitivity, and specificity of diagnostic criteria

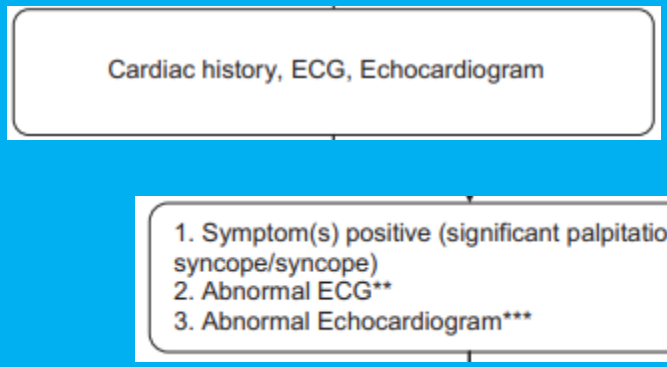
Abnormality on baseline testing	Prevalence*	Sensitivity (95% CI) (%)	Specificity (95% CI) (%)
History of cardiac symptoms	12 (19)	46 (26–27)	95 (82–99)
Electrocradiogram	3 (50)	8 (1–27)	97 (86–100)
Holter	13 (21)	50 (29–71)	97 (86–100)
Echocardiogram	8 (13)	25 (10–47)	95 (82–99)
Any screening variable	29 (47)	100 (88–100)	87 (72–96)
Two or more screening variables	7 (11)	25 (10–47)	97 (86–99)
Three or more screening variables	1 (2)	4 (1–21)	100 (92–100)

CI = confidence interval.

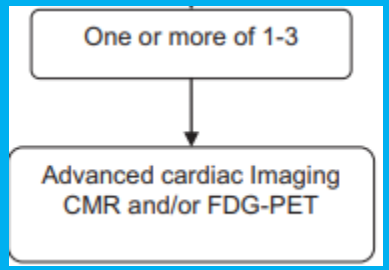
Significant echocardiographic abnormality was defined as LV dysfunction (LVEF $\leq$45%), significant wall motion abnormalities (two or more segments), right ventricular (RV) systolic dysfunction in the absence of pulmonary hypertension, and/or significant diastolic dysfunction inappropriate for the patient's age. Significant abnormal Holter monitor finding was defined as premature ventricular contractions (>10 per hour) and/or nonsustained or sustained ventricular tachycardia (VT) and/or supraventricular tachycardia (SVT) (more than three beats).

*Values are presented as n (%). Adapted with permission from Mehta et al.[25]

Screening for CS Recommendations



* palpitations were defined as "prominent patient complaint lasting > 2 weeks[25]"
** abnormal ECG defined as complete left or right bundle branch block and/or presence of unexplained pathological Q waves in 2 or more leads and/or sustained 2nd or 3rd degree AV block and/or sustained or non-sustained VT[25]
*** abnormal echocardiogram defined as RWMA and/or wall aneurysm and/or basal septum thinning and/or LVEF < 40%*[25]



Screening Continued

- When compared to CMR and FDG PET, echocardiography has low sensitivity for detection of CS, ranging from 25% to 65%
- A negative echocardiogram should not be used to exclude cardiac involvement in patients with known extracardiac or suspected
- The sensitivity (75%−100%) and specificity (76.9%−78%) of LGE-CMR have been reportedly comparable with FDG PET

Advanced cardiovascular imaging for the evaluation of cardiac sarcoidosis J Nucl Cardiol. 2019 February ; 26(1): 188–199

Screening Continued

- Advantages CMR: higher spatial resolution of CMR compared with PET allows for visualization of subcentimeter lesions as well as the distinction between subepicardium, mid-myocardium, and subendocardium involvement
- The presence of LGE appears to be the strongest predictor for mortality and sustained ventricular arrhythmias among individuals with suspected CS; very high negative predictive value for adverse outcomes in general and ventricular arrhythmic events in particular

Screening Continued

- Cardiac FDG PET imaging is aimed at identifying metabolically active sarcoid
- CMR is better at detecting areas of fibrosis
- FDG provides a unique role for assessing the response to anti-inflammatory therapy
- FDG has limitations, as healthy myocardial cells can utilize glucose
- 10%–15% of FDG PET remain nondiagnostic due to incomplete FDG suppression,
- There is growing evidence supporting the combined use of CMR and FDG PET imaging for enhancing both the diagnostic and prognostic performance of evaluating patients with suspected CS

Monitoring

- Most intense first 2 years. Stage I every 6 months, higher stages every 3-6 months
- Monitor vigilantly for minimum of 3 years after treatment is stopped due to high rate of relapse, longer if extrapulmonary sites are involved
- Stage II-IV monitor indefinitely at least annually regardless of treatment or not
- Periodic chest radiographs and spirometry, eye exams, periodic labs

Treatment Indications: Pulmonary Sarcoid

- Worsening symptoms
- Deterioration in pulmonary function on serial testing
  - decline in TLC $\geq$ 10%
  - FVC $\geq$ 15%
  - DLCO $\geq$ 20%, worsening gas exchange
- Progression in radiograph, evidence of fibrosis
- Signs of pulmonary hypertension

Treatment Indications: Extrapulmonary Sarcoid

- Cardiac disease
- Neurologic disease
- Ocular disease refractory to topical therapy
- Severe constitutional symptoms
- Disfiguring skin disease
- Hypercalcemia
- Renal sarcoid