SARCOIDOSIS VASCULITIS AND DIFFUSE LUNG DISEASES 2016; 33; 209-215

Role of pulmonary evaluation in diagnosis of neurosarcoidosis

Pascal Kingah[1], Muhammad Alam[2], Karan Chugh[2], John Kamholz[3], Lobelia Samavati[2]

[1] Department of Internal Medicine, Division of Pulmonary, Critical Care and Sleep Medicine, Univerisity of Texas Health Science Center;
[2] Department of Internal Medicine, Division of Pulmonary, Critical Care and Sleep Medicine, Wayne State University School of Medicine;
[3] Department of Neurology, Wayne State University School of Medicine, Detroit Medical Center, Detroit, USA

Abstract. *Background:* Neurosarcoidosis is a serious extra pulmonary manifestation of sarcoidosis. Its presentation ranges from peripheral or cranial neuropathy to central nervous system dysfunction. It can mimic stroke or multiple sclerosis. Due to the variation in clinical presentation, diagnosis is difficult and often delayed. *Objective:* Determine the proportion of patients with neurosarcoidosis who have positive findings on chest CT, lung biopsy or lymph node biopsy. *Methods:* Retrospective study at the Sarcoidosis and Interstitial Lung Disease Center at Wayne State University–Detroit Medical Center in Detroit, MI. Medical records of 424 patients were reviewed and 69 patients with neurosarcoidosis identified. *Results:* We found that most patients diagnosed with neurosarcoidosis had normal PFT values except for reduction in DLCO. However, we also found that 71% of the patients had abnormal findings on chest CT consistent with sarcoidosis. Additionally, 57% of the patients had non-caseating granuloma on hilar lymph node biopsy. *Conclusion:* Patients with neurosarcoidosis may not have any pulmonary symptoms. However, they are most likely to have abnormal chest CT, hilar lymphadenopathy and reduction in DLCO. These data suggest that pulmonary evaluation is warranted in patients who are suspected to have neurosarcoidosis. *(Sarcoidosis Vasc Diffuse Lung Dis 2016; 33: 209-215)*

Key words: neurosarcoidosis, bronchoscopy, imaging CT/MRI

Introduction

Neurosarcoidosis is a serious form of sarcoidosis that is characterized by granulomatous inflammation of affected nervous system. Sarcoidosis is a systemic inflammatory disease of unknown etiology in which the lungs are almost always affected (1, 2). Data from large series of patients with sarcoidosis report an estimation of 5% of patients having nervous system involvement (3-5). The presentation of disease can range from peripheral or cranial neuropathy to central nervous system dysfunction (3). Due to the variation in clinical presentation, diagnosis is difficult and often delayed especially when there is no apparent systemic involvement. Peripheral facial nerve palsy has been reported to be one of the most common presentations occurring in over 25 to 50% of patients with neurosarcoidosis (3). Optic neuropathy can lead to progressive visual deficit if not addressed early (6-8). Due to symptomatic variation, neurosarcoidosis can also be misdiagnosed as stroke, multiple sclerosis or even as brain neoplasia. Stereotactic brain biopsy has been mainly used to confirm neuroscarcoidosis and it is associated with one to two percent mortality and 5-6% morbidity, due to increased risk of symptomatic hemorrhagic complications and neurologic deficits and one series reported 18% biopsy specimens that were non-diagnostic (9, 10). Compared to stereotactic brain biopsy, in the presence of pulmonary abnormalities, transbronchial biopsy or endo-

Received: 25 February 2015
Accepted after revision: 3 February 2016
Correspondence: Fatma Tokgoz Akyıl,
Sureyyapasa GPascal Kingah and Lobelia Samavati
Division of Pulmonary, Critical Care and Sleep Medicine,
Department of Internal Medicine,
Detroit Medical Center/Harper University Hospital,
3990 John R, 3Hudson, Detroit MI 48201, USA

bronchial ultrasound fine needle aspiration remains a relatively safe minimally invasive procedure with less than 0.05% mortality rate and 0.5% to 0.8% morbidity rate with a 74% diagnostic yield (9, 11, 12).

Although possibilities to reach a diagnosis are available there have been no clear guidelines on how to diagnose neurosarcoidosis and whether such patients will benefit from pulmonary evaluation when there is suspicion of neurosarcoidosis. We hypothesized that computerized tomography (CT) scan of the chest along with bronchoscopy are invaluable to establish the diagnosis of neurosarcoidosis even in patients without pulmonary symptoms. We set forth to determine the demographics of patients with neurosarcoidosis, comparing pulmonary function testing (PFT) and chest X-ray features between patients with neurosarcoidosis and those with other forms of sarcoidosis. Lastly we determine what percentage of patients with neurosarcoidosis had positive findings on chest CT, positive lung biopsy or positive lymph node biopsy.

Materials and methods

Study design

Retrospective study at the Sarcoidosis and Interstitial Lung Disease Center at Wayne State University, Detroit Medical Center in Detroit, MI, a referral center for patients with sarcoidosis and other interstitial lung disease. There are over 424 patients treated in this center for Sarcoidosis. We have reviewed the demographic radiographic, pulmonary and pathology data of 69 patients who were diagnosed with neurosarcoidosis from January 2000 to January 2014. Over eighty percent of these patients were initially referred to our center from either a neurologist (n=32) or ophthalmologist (n=28). Approval for data use was obtained from the Institutional Review Board of Wayne State University.

Methods

Criteria used in the diagnosis of sarcoidosis, chest radiography and pulmonary function tests have previously been described (13, 14). The diagnosis of neurosarcoidosis was confirmed in patients who had biopsy proven non-caseating granulomas in the central nervous system, or any other organ involved with the presence of clinical neurologic deficits or magnetic resonance imaging changes consistent with sarcoidosis. Chest radiography interpretation was from stage 0-4 (13, 14). PFT data were reviewed and collected on most patients. PFTs were performed in patients in a licensed laboratory, a part of the Harper University laboratory, following American Thoracic Society guidelines (15, 16). Magnetic resonance imaging studies, computerized tomography scans of chest, as well as head, orbits and spine were reviewed. Results of lung biopsy and hilar lymph node biopsies were also reviewed. Patients were classified based on diagnostic criteria proposed by Zajicek et al., class 1 for definite neurosarcoidosis, class 2 for probable and class 3 for possible neurosarcoidosis (17).

Statistical analysis

Data was collected in an excel spreadsheet. Categorical variables were presented as frequencies and percentages while continuous variables were presented as mean ± standard deviation. Paired t-tests were used to compare continuous variables and the Chi-squared test for comparing categorical variables. For all analyses, two-tailed p-values <0.05 were considered significant. Data was analyzed using Stata (Version 12), College Station, Texas.

Results

Demographic data for the subjects is presented in Table 1. As shown there were a total of 69 patients who were considered as having neurosarcoidosis. Most of these patients (greater than 80%) were referred to our clinic by a neurologist or ophthalmologist for signs and symptoms unrelated to pulmonary dysfunction. The mean age was 48 years. Nearly 90% of our patients were African American. Patients were predominantly African American females, 64 (92.7%). There were only 16 males (23.2%). A majority of the patients were on immunomodulatory drugs in combination with corticosteroids (66/95%). Only 3 patients were not receiving medications for sarcoidosis at the time of the study. The majority of the patients were either former or current smokers, whereas only 27% of our patients were non-smokers.

Table 1. Baseline characteristics for patients with neurosarcoidosis

Variable	Mean, n (%)
Age (years)	47.9±10.5
Race	
African American	64 (92.7)
White	3 (4.3)
Other	2 (3)
Sex	
Male	16 (23.2)
Female	53 (76.8)
BMI	32.6±8.5
Medication	
None	3 (4.3)
Steroids	58 (84)
IMD	66 (95.7)
Smoking status	
Current smoker	20 (29)
Never smoker	27 (39.1)
Ex-smoker	22 (31.9)

Radiographic staging of the patients was distributed across the numerical scale. As shown in Figure 1A, the main site of central nervous system (CNS) involvement in our patients was brain white matter 33%, followed by optic nerve involvement in 28% of cases. Using Zajicek criteria 81% of patients were considered in diagnostic class 2 (Figure 1B) (17). When comparing pulmonary function of patients with neurosarcoidosis with those of patients with other forms of sarcoidosis, the percentage predicted forced vital capacity (FVC%) was higher in patients with neurosarcoidosis 88% compared to 79%, p=0.0007 (Table 2).

Similarly, the forced expiratory volume in 1s (FEV1%) was significantly higher in the patients with neurosarcoidosis, 87% compared to 76.5%, p=0.0002. Additionally, we found that the FEV1/FVC (Forced vital capacity) ratio was higher in patients with neurosarcoidosis compared to other forms of sarcoidosis, 79% compared to 76%, p=0.018. There was no statistically significant difference in total lung capacity (TLC) and diffusion lung capacity for carbon monoxide (DLCO). The DLCO in both groups was low, 16.4 with percentage predicted of 64.35 in patients with neurosarcoidosis and 15.6 with percentage predicted of 61.76 in patients with other forms of sarcoidosis. Patients with all other forms of sarcoidosis had more advanced disease on chest X-ray compared to those with neurosarcoidosis, and there were more patients with staggering stages more than stage 0 in those with other forms of sarcoidosis than neurosarcoidosis, 81.2% compared to 75%, p=0.002. The only abnormality revealed on the PFT of patients with neurosarcoidosis was a reduction in DLCO, 16.65 with a percentage prediction of 64.36.

In addition, we evaluated both chest CT and pulmonary tissue biopsies in patients with neurosarcoidosis. We found that 71% of patients with neurosarcoidosis had positive CT findings as shown on table 3. Some of these individuals also underwent tissue biopsy based on these abnormal CT findings. Interestingly, about 57% of these patients had non-caseating granuloma on hilar lymph node or airway biopsies (Figure 1C).

Since there were only minimal changes in DLCO as well as subtle changes on the chest CTs in patients with neurosarcoidosis as compared to those with primary pulmonary sarcoidosis, we compared the brain magnetic resonance images (MRI), chest CT and bronchoscopy results of patients with

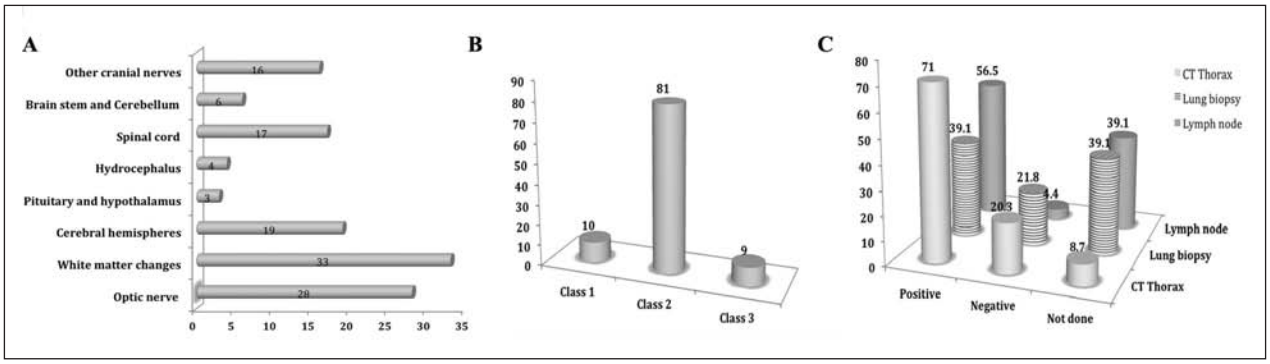

Fig. 1. A, Sites of central nervous system involvement. **B**, Zajicek Classification (percentage of neurosarcoidosis patients). **C**, Percentage of neurosarcoidosis patients with positive findings on chest CT, lung biopsy or hilar lymph nodes

Table 2. Characteristics of patients with neurosarcoidosis compared with all other sarcoidosis patients

Variable	Neurosarcoidosis		All Others		p-value
	Subjects	Mean ± SD	Subjects	Mean ± SD	
FVC (L)	61	2.95±0.81	325	2.81±0.82	0.228
FVC %	61	88.6±19.76	324	79.1±19.26	0.0007
FEV1 (L)	61	2.32±0.63	325	2.22±1.28	0.4692
FEV1 %	61	86.7±18.9	324	76.5±19.94	0.0002
FEV1/FVC	61	79.18±7.83	322	75.65±11.15	0.018
TLC (L)	57	4.52±1.06	312	4.62±3.76	0.846
TLC %	56	85.14±15.52	313	80.61±17.32	0.068
DLCO	58	16.4±6.06	319	15.6±5.82	0.325
DLCO %	58	64.36±19.59	320	61.76±19.57	0.351
Chest radiograph stage	60	1.13±0.94	320	1.60±1.16	0.002
Percentage with CXR Stage >0	68	75	320	81.2	0.002

Table 3. Number and percentage of neurosarcoidosis patients with positive findings on chest CT, lung biopsy or hilar lymph node biopsy.

Test	Positive findings n (%)	Negative findings n (%)	Not done n (%)
CT Thorax (n=69)	49 (71)	14 (20.3)	6 (8.7)
Lung biopsy (n=69)	27 (39.1)	15 (21.8)	27 (39.1)
Lymph node (n=69)	39 (56.5)	3 (4.4)	27 (39.1)

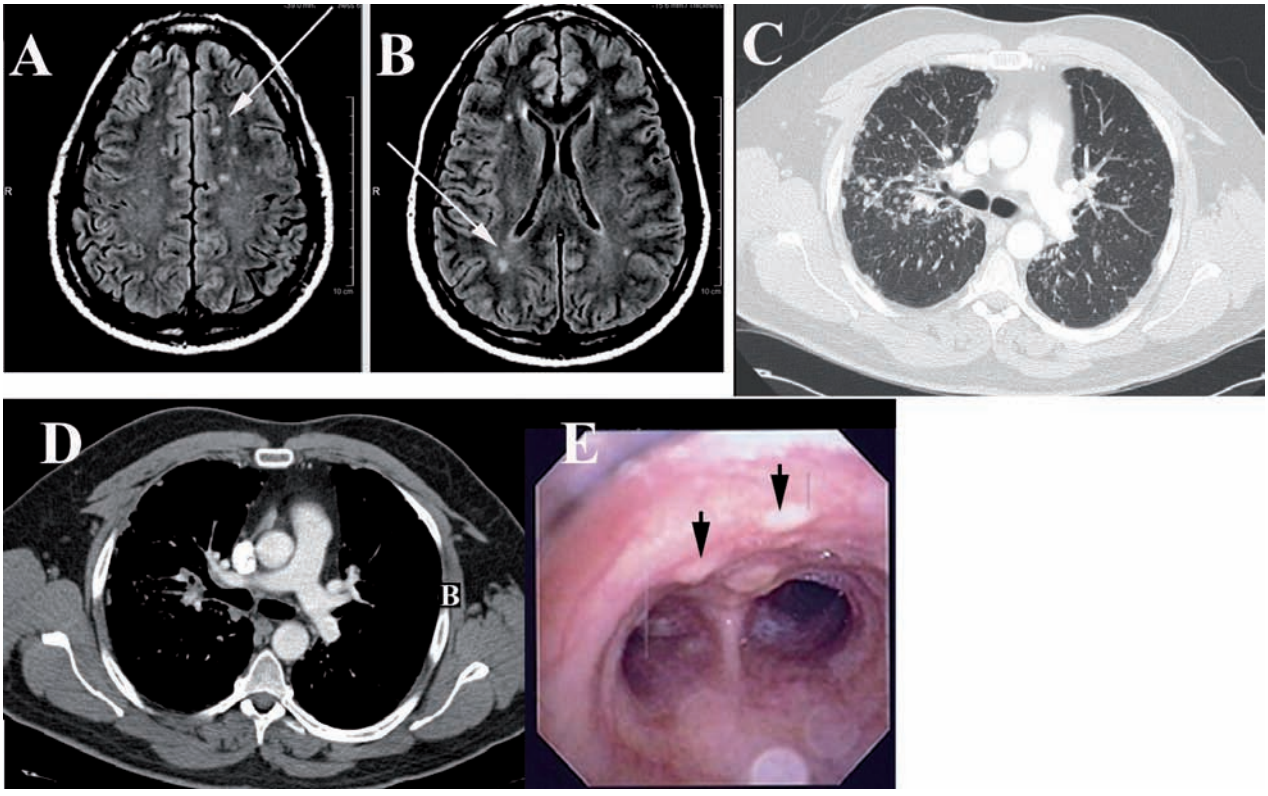

Fig. 2. A and **B**, MRI of the brain of a patient, who initially presented with seizures headaches and confusion. **A**, and **B,** shows numerous small discrete foci in T2/Fluid attenuation inversion recovery (FLAIR) signal scattered throughout cerebral white matter (white arrows). **C**, and **D**, show CT of the chest. (**C**) Lung window shows subtle changes on the lung parenchyma. (**D**) Mediastinal window shows the presence of mediastinal lymph nodes. (**E)** Fiberoptic image of distal trachea during bronchoscopy shows abnormal mucosal lining and subtle endobronchial lesions that revealed non-caseating granulomas following biopsy (Black arrows)

central nervous system biopsy proven sarcoidosis to those with pulmonary sarcoidosis. Interestingly, we found a broader spectrum of radiological abnormalities among patients with neurosarcoidosis, ranging from minimal lymphadenopathy to severe adenopathy and parenchymal changes on the CT scan. Two representative cases are shown in Figures 2 and 3. We expected that more abnormalities found on MRI of the brain would reflect more profound changes in the chest CT of corresponding patients. This was only partly true in some patients. Figure 2A and B shows brain MRI of one of our patients with multiple white matter lesions. Figure 2C and D show the lung and mediastinal windows of the same subject. Interestingly, bronchoscopy showed multiple lesions and cobble stoning of the mucosa in his larger airways with the biopsies of the lesions confirming the presence of well-formed granulomas (Figure 2E). However, we also found some cases, in which a patient with severe abnormalities on brain MRI (Figures 3A and B) had only minimal changes in his chest CT (Figure 3C and D). Despite only subtle changes on his chest CT, bronchoscopy showed an abnormal mucosal membrane with nodular lesions of his airway (Figure 3E) and the presence of non-caseating granuloma on biopsy.

Discussion

The diagnosis of neurosarcoidosis remains a challenge, especially in cases where sarcoidosis minimally involves the lungs or other target organs such as the skin. In our study, the majority of the patients were African Americans, which likely reflects the demographics of the local population. The typical patient was African American female with a mean age at diagnosis of 48 years. This is comparable to the study by Carlson et al. in which the mean age was 46.7 years in a predominantly Caucasian population (18). Earlier studies by Zajicek et al. and Joseph et al. found mean ages of 38.9 and 40 years respectively (6,17). The main sites of involvement in our patients were the brain characterized by hyperdense white matter lesions followed by optic neuropathy. Pawate et al. reported 13 (24%) of their patients pre-

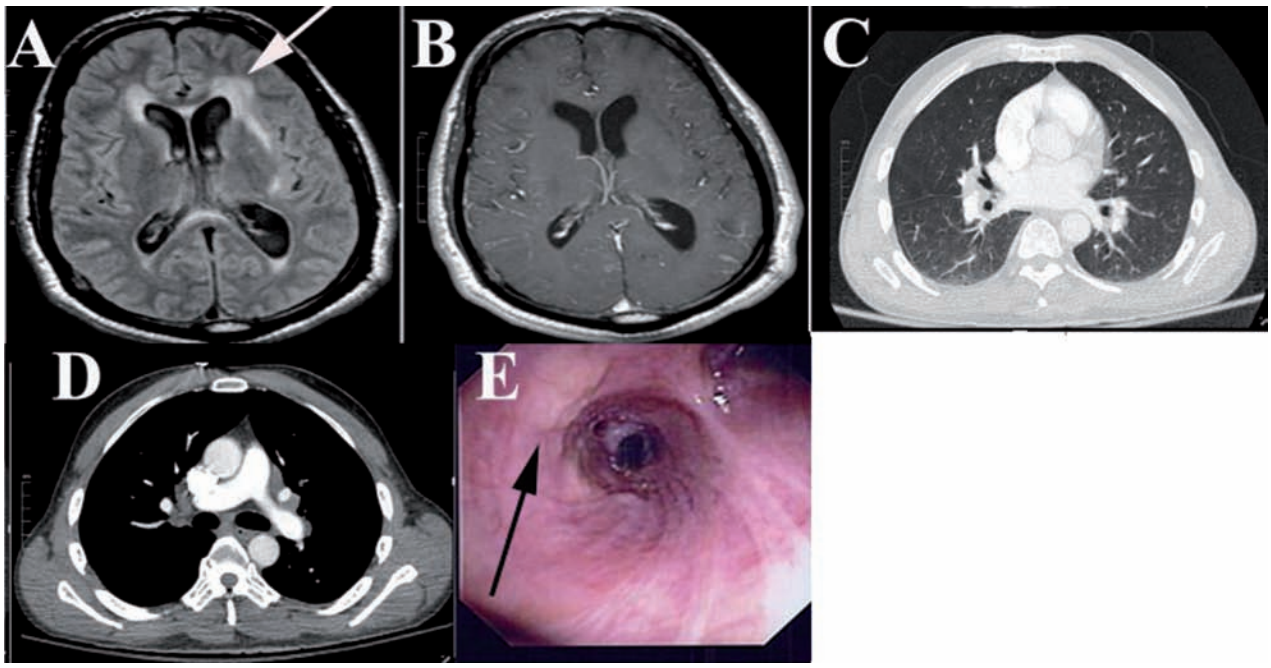

Fig. 3. A and **B,** MRI of another patient who presented with tremors and personality changes. **A** and **B** shows abnormal FLAIR/T2 signal enhancement over the frontal lobes bilaterally with leptomeningeal and sulci enhancement (white arrow). **C** and **D** show CT of chest of the same patient. (**C**) The lung window shows significant subpleural and peripheral nodular opacities and thickness of bronchopulmonary bundles but lack of fibrotic changes. (**D**) Mediastinal window shows multiple small lymph nodes. (**E**) Fiberoptic image of carina during bronchoscopy shows endobronchial nodules and mucosal lesions in which endobronchial biopsies were positive for non-caseating granulomas (Black arrow)

sented with bilateral optic neuropathy and 16 (30%) had T2 hyperdense non-enhancing white matter lesions (7). Koczman et al. and Heuser et al. reported similar findings (19,20). The findings of a retrospective study reviewing the brain MRI images of biopsy proven sarcoidosis included a variety of manifestations, including isolated mass lesion, diffuse intraparenchymal inflammatory lesions in the brain and spinal cord, leptomeningeal enhancement, hydrocephalus, and intracranial hemorrhage (21). Patients with neurosarcoidosis may not have any pulmonary symptoms. However, our study reveals that despite the absence of respiratory symptoms at presentation they are most likely to have positive changes on chest CT consistent with sarcoidosis, positive biopsies on hilar lymphadenopathy and/or a reduction in DLCO. We found that 71% of our patients with neurosarcoidosis had chest CT findings consistent with sarcoidosis. Pawate et al. revealed similar numbers, when they combined findings from both chest X-ray and chest CT with 34 of their 50 (68%) patients showing evidence of lung involvement (7). Joseph et al. also reported pulmonary involvement in their series of patients. They found 14 out of 29 (48%) patients had abnormalities on chest X-ray (6). Chest CTs were only performed in six patients in this series. Our study reports a larger series and larger number of patients who underwent a diagnostic chest CT and/or bronchoscopy to rule out other infections prior to starting treatment or to rule out pulmonary sarcoidosis due to higher prevalence of this disease in the Detroit area. Chen et al. reported hilar lymphadenopathy or pulmonary infiltrates on chest X-rays of most of their patients with neurosarcoidosis, but none of these patients had a chest CT done (22). Our study found that 39 out of 69 (67%) patients with neurosarcoidosis had a positive biopsy of mediastinal lymph nodes. Most other studies reported only one or two cases in which biopsies were obtained from lung or hilar lymphadenopathy (23). Prior series by Pawate et al. and Joseph et al. only reported 2 cases of mediastinal lymph node biopsies which were both positive. Our study is the first to report significant pulmonary involvement in patients with neurosarcoidosis, even in the absence of pulmonary symptoms. Our data indicates that subtle changes can now be seen on chest CT hence pulmonary evaluation including chest CT and bronchoscopy with possible lung and mediastinal lymph node biopsies are needed for early and safer diagnosis of patients who are suspected to have neurosarcoidosis.

In summary, our study is the first to evaluate the role of pulmonary involvement in patients with confirmed diagnosis of neurosarcoidosis. The retrospective nature of our study limited the possibility for us to obtain complete information on all patients hence our proportions could be underestimated but this method remains the most feasible and practical way to study this disease condition.

Author Contributions:

Dr. Kingah was involved in designing the study, acquisition of data, statistical analysis, interpretation of the data collected, and drafting of the manuscript

Dr. Alam was involved in conceptualization of the study, acquisition of data and revising the manuscript for intellectual content

Dr. Chugh was involved in conceptualization of the study, acquisition of data, interpretation of the data and revising the manuscript for intellectual content

Dr. Kamholz was involved in conceptualization of the study, drafting the manuscript revising the manuscript for critically important intellectual content

Dr. Samavati was involved in conceptualization of the study, drafting of the manuscript and revising the manuscript for critically important intellectual content

Disclosures:

Dr. Samavati, Lobelia has a grant sponsored by the National Institutes of Health, R01#HL113508

References

1. Hunninghake GW, Costabel U, Ando M, et al. ATS/ERS/WASOG statement on sarcoidosis. American Thoracic Society/European Respiratory Society/World Association of Sarcoidosis and other Granulomatous Disorders. Sarcoidosis Vasc Diffuse Lung Dis 1999; 16: 149-173.
2. Iannuzzi MC, Rybicki BA, Teirstein AS. Sarcoidosis. N Engl J Med 2007; 357: 2153-2165.
3. Delaney P. Neurologic manifestations in sarcoidosis: review of the literature, with a report of 23 cases. Annals of internal medicine 1977; 87: 336-345.
4. Mayock RL, Bertrand P, Morrison CE, et al. Manifestations of Sarcoidosis. Analysis of 145 Patients, with a Review of Nine Series Selected from the Literature. The American journal of medicine 1963; 35: 67-89.
5. Siltzbach LE, Ehrlich JC. The Nickerson-Kveim reaction in sarcoidosis. The American journal of medicine 1954; 16: 790-803.
6. Joseph FG, Scolding NJ. Neurosarcoidosis: a study of 30 new cases. Journal of neurology, neurosurgery, and psychiatry 2009; 80: 297-304.
7. Pawate S, Moses H, Sriram S. Presentations and outcomes of neurosarcoidosis: a study of 54 cases. QJM: monthly journal of the Association of Physicians 2009; 102: 449-460.

8. Stern BJ, Krumholz A, Johns C, et al. Sarcoidosis and its neurological manifestations. Archives of neurology 1985; 42: 909-917.
9. Bernays RL, Kollias SS, Khan N, et al. Histological yield, complications, and technological considerations in 114 consecutive frameless stereotactic biopsy procedures aided by open intraoperative magnetic resonance imaging. Journal of neurosurgery 2002; 97: 354-362.
10. Wen DY, Hall WA, Miller DA, et al. Targeted brain biopsy: a comparison of freehand computed tomography-guided and stereotactic techniques. Neurosurgery 1993;32:407-412; discussion 412-403.
11. Gupta D, Dadhwal DS, Agarwal R, et al. Endobronchial Ultrasound-Guided Transbronchial Needle Aspiration vs Conventional Transbronchial Needle Aspiration in the Diagnosis of Sarcoidosis. Chest 2014; 146: 547-556.
12. Pue CA, Pacht ER. Complications of fiberoptic bronchoscopy at a university hospital. Chest 1995; 107: 430-432.
13. Bourbonnais JM, Samavati L. Clinical predictors of pulmonary hypertension in sarcoidosis. Eur Respir J 2008; 32: 296-302.
14. Costabel U, Hunninghake GW. ATS/ERS/WASOG statement on sarcoidosis. Sarcoidosis Statement Committee. American Thoracic Society. European Respiratory Society. World Association for Sarcoidosis and Other Granulomatous Disorders. Eur Respir J 1999; 14: 735-737.
15. Standardization of Spirometry, 1994 Update. American Thoracic Society. American journal of respiratory and critical care medicine 1995; 152: 1107-1136.
16. American Thoracic Society. Single-breath carbon monoxide diffusing capacity (transfer factor). Recommendations for a standard technique--1995 update. American journal of respiratory and critical care medicine 1995; 152: 2185-2198.
17. Zajicek JP, Scolding NJ, Foster O, et al. Central nervous system sarcoidosis--diagnosis and management. QJM : monthly journal of the Association of Physicians 1999; 92: 103-117.
18. Carlson ML, White JR Jr, Espahbodi M, et al. Cranial Base Manifestations of Neurosarcoidosis: A Review of 305 Patients. Otology & neurotology : official publication of the American Otological Society, American Neurotology Society [and] European Academy of Otology and Neurotology 2014.
19. Heuser K, Kerty E. Neuro-ophthalmological findings in sarcoidosis. Acta ophthalmologica Scandinavica 2004; 82: 723-729.
20. Koczman JJ, Rouleau J, Gaunt M, et al. Neuro-ophthalmic sarcoidosis: the University of Iowa experience. Seminars in ophthalmology 2008; 23: 157-168.
21. Spencer TS, Campellone JV, Maldonado I, et al. Clinical and magnetic resonance imaging manifestations of neurosarcoidosis. Seminars in arthritis and rheumatism 2005; 34: 649-661.
22. Chen RC, McLeod JG. Neurological complications of sarcoidosis. Clinical and experimental neurology 1989; 26: 99-112.
23. Oksanen V. Neurosarcoidosis: clinical presentations and course in 50 patients. Acta neurologica Scandinavica 1986; 73: 283-290.