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Research Article

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Clinical, Laboratory and Neuroimaging Findings in Patients with Sarcoidosis Involving the CNS: Study of 29 Cases

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Abstract

Introduction: Sarcoidosis is a rare idiopathic systemic inflammatory disorder characterized by the formation of the non-caseating granulomas. Neurological complications involve approximately 5% of the patients with systemic sarcoidosis. Most literatures on neurosarcoidosis are anecdotal case reports. Studies of a series of cases of neurosarcoidosis are sparse. In this report, we studied clinical, laboratory and neuroimaging findings in patients with sarcoidosis involving the central nervous system (CNS).

Methods: Clinical charts were retrospectively reviewed for the past 10 years to identify patients with a clinically conformed diagnosis of sarcoidosis, which was proven by a previously biopsied histological evaluation. Subjects with neurological presentation and clinically diagnosed neurosarcoidosis were collected. Subjects with identifiable etiologies causing a CNS structural lesion and/or dysfunction other than sarcoidosis, incomplete data, or sarcoidosis without nervous system complications were excluded. The collected data of clinical, laboratory and neuroimaging findings were analyzed.

Results: Twenty-nine patients (age: 51.7 ± 9.0 years, range: 36 - 77, female / male = 21 / 8) were studied. Common clinical presentations were seizures (34.5%); Bell's palsy (17.2%) with facial hypoesthesia (13.8%); limb weakness (13.8%) and/or numbness (6.9%); abducens nerve paresis (6.9%); hydrocephalus (6.9%), nystagmus (3.4%), and optical neuritis (3.4%). MRI showed abnormalities in discrete areas in the brain and spinal cord involving the parenchyma in different anatomic locations, leptomeninges and cranial nerves. Abnormal laboratory findings showed elevated ACE level in plasma and cerebrospinal fluid, impaired liver functions with reduced level of triglycerides, and elevated protein with decreased glucose and mild lymphocytosis in cerebrospinal fluid.

Conclusion: Diagnosis of neurosarcoidosis remains a clinical challenge. Seizures were most frequently seen at presentation in patients with sarcoidosis involving the CNS. Laboratory studies of impaired liver function with reduced triglycerides, and CSF elevated levels of ACE and protein with decreased glucose and mild lymphocytosis may aid in differentiating neurosarcoidosis from other CNS inflammatory demyelinating disorders.

Key words

Impaired liver function, Neurosarcoidosis, Sarcoidosis, Seizure

Introduction

Sarcoidosis is a rare systemic inflammatory disorder with unknown etiology. It is characterized by the formation of discrete, compact, noncaseating epithelioid cell granulomas, which can involve any organ [1]. Neurologic complications occur in approximately 5% of patients with sarcoidosis [2]. Most of clinical studies were from anecdotal case reports and the studies on a series of cases of neurosarcoidosis are sparse. To better understand its clinical features, we studied clinical manifestations, laboratory and neuroimaging findings in patients with sarcoidosis involving the central nervous system (CNS).

Methods

We retrospectively reviewed the charts of whom were admitted from January 1, 2001 to December 31, 2010 at Temple University Hospital to identify patients with a clinically confirmed diagnosis of sarcoidosis. Subjects with neurological complications and confirmed diagnosed sarcoidosis, which was proven by a previously biopsied histological evaluation, were initially collected. Subjects were excluded with identifiable etiologies, other than sarcoidosis, causing central nervous system structural and functional abnormalities, such as history of traumatic brain injury, chemo and/or radiation therapy, lupus, HIV, etc.; incomplete data; or sarcoidosis without nervous system complications. The demographic data, clinical presentations, laboratory and neuroimaging findings were collected and studied. This study was approved by Temple University Institutional Review Board.

Results

Twenty-nine subjects (age: 51.7 ± 9.0 years, range: 36 - 77, female / male = 21 / 8) who fulfilled the inclusion criteria were studied. Common clinical presentations and physical examinations showed seizures (34.5%); Bell's palsy (17.2%) with facial hypoesthesia (13.8%); limb weakness (13.8%) and/or numbness (6.9%); abducens nerve paresis (6.9%); hydrocephalus (6.9%), nystagmus (3.4%), and optical neuritis (3.4%) (Table 1). MRI showed abnormalities in discrete locations such as subcortical (55.2%), cortex of frontal (27.6%), parietal (20.7%), temporal (17.2%), cerebellum (13.8%), pons (10.3%), leptomeninges (20.7%), optic nerve (10.3%); facial nerve (6.9%); and spinal cord of thoracic (6.9%), lumbar (6.9%) and cervical (3.4%) abnormalities (Table 2, Figure 1). Of these patients, 20 with abnormal and 9 normal pulmonary appearances were shown on chest X-ray or CT; and 7 were not but 22 were actively treated with steroid (prednisone 2.5-50 mg/day) at admission (data not shown). Laboratory studies showed abnormal cerebrospinal fluid (CSF) findings including increased level of angiotensin converting enzyme (ACE, 66% of tested patients), protein (70%), decreased level of glucose (50%) and lymphocytic pleocytosis (20%). Routine laboratory findings showed increased level of ACE (60%); impaired liver functions, particularly increased level of alkaline phosphatase (29.6%); and decreased triglycerides (33.3%) (Table 3).

Table 1: Demographic and clinical data.

Number of patients	29
Age (years, M ± SD)	51.7 ± 9.0
Female / Male	21 / 8
Comorbidity	n (%)
Hydrocephalus	2 (6.9)
Seizure	10 (34.5)
Limb weakness	4 (13.8%)
Numbness	2 (6.9)
Nystagmus	1 (3.4)
II (Optic Neuritis)	1 (3.4)
III (Opthalmoplegia)	0 (0)
IV (Opthalmoplegia)	0 (0)
V (Facial hypoesthesia)	4 (13.8)
VI (Opthalmoplegia)	2 (6.9)
VII (Bell's palsy)	5 (17.2)
VIII	0 (0)
IX, X	0 (0)
XI	0 (0)
XII	0 (0)

Common clinical presentations were seizure (34.5%); Bell's palsy (17.2%) with facial hypoesthesia (13.8%); limb weakness (13.8%) and/or numbness (6.9%); abducen nerve paresis (6.9%); hydrocephalus (6.9%), nystagmus (3.4%), and optical neuritis (3.4%).

Table 2: Abnormal MRI findings.

MRI Abnormality	n (%)
Medulla	1 (3.4)
Pons	3 (10.3)
Midbrain	1 (3.4)
Cerebellum	4 (13.8)
Frontal	8 (27.6)
Parietal	6 (20.7)
Temporal	5 (17.2)
Occipital	2 (6.9)
Cortical	1 (3.4)
Subcortical	16 (55.2)
Leptomeninges	6 (20.7)
CN VII/VIII	2 (6.9)
CN II Enhancement	3 (10.3)
MRI C-spine	1 (3.4)
MRI L-spine	2 (6.9)
MRI T-spine	2 (6.9)

MRI showed abnormalities in the area of subcortical (55.2%); cortex of frontal (27.6%); parietal (20.7%); leptomeninges, (20.7%); temporal (17.2%); cerebellum (13.8%); pons (10.3%); optic nerve (10.3%); and facial nerve (6.9%).

Table 3: Laboratory data

Labs	Reference	Mean ± SD	Range	Abnormal [n (%)]	Tested (n)
CSF					
ACE	< 2.9 u/l	4.7 ± 3.5	1 - 8	*2 (66%)	3
Protein	< 40 mg/dl	75.3 ± 45.7	27 - 157	*7 (70%)	10
Glucose	> 60 mg/dl	75.1 ± 24.2	49 - 113	#5 (50%)	10
WBC	< 5/dl	7.9 ± 23.6	0 - 250	*2 (20%)	10
Hematology					
Hgb	11.5 - 16.0 g/dl	11. ± 1.6	8.3 - 13.8	#6 (20.1%)	29
Platelets	140 - 400 thousand/ul	233.4 ± 105.8	69 - 435	#3 (10.3%)	29
MCV	80 - 100 fL	84.2 ± 18.3	72 - 101	#3 (10.3%)	26
Serum					
IGG	0.5 - 6.1 mg/dl	5.5 ± 1.3	4.6 - 6.4	*1	2
ACE	8 - 52 u/l	54.8 ± 23.4	26 - 90	*3 (60%)	5
Na	135 - 145 mmol/L	136.9 ± 4.6	129 - 148	*1 (3.4%); #6 (20.1%)	29
K	3.5 - 5.0 mmol/L	3.9 ± 0.4	43529	#2 (6.8%)	29
Cl	95 - 105 mmol/L	99.4 ± 19.1	96 - 116	*4 (13.8); #3 (10.3%)	23
BUN	10 - 20 mg/dl	13.3 ± 8.6	15401	*4 (13.8%)	26
Cr	0.7 - 1.4 mg/dl	1.2 ± 1.3	0.6 - 8	*3 (10.3%)	26
Calcium	8.5 - 10.5 mg/dl	9.2 ± 0.7	8 - 11.4	*1 (3.4%)	25
Magnesium	1.5 - 2.5 mg/dl	2.0 ± 0.3	1.3 - 2.7	#2 (6.8%)	29
Phosphate	2.5 - 4.5 mg/dl	3.5 ± 0.9	1.3 - 5.7	*1 (4%); #3 (12%)	25
AST	15 - 65 u/L	34.5 ± 34.3	7 - 149	*2 (7.4%)	27
ALT	15 - 40 u/L	42.4 ± 80.6	4-438	*5 (18.5%)	27
AKP	35 - 125 u/L	112.3 ± 98.6	41 - 174	*8 (29.6%)	27
B12	200 - 1100 pg/ml	547.5 ± 244.6	335 - 1018	0	13
Folate	3.4 - 5.4 ng/ml	10.2 ± 5.1	4 - 19.6	0	14
Homocysteine	< 10.4 umol/L	9.1 ± 1.9	7.6 - 12.8	*1	6
CRP	0.08 - 0.8 mg/dl	0.8 ± 0.8	0.4 - 2.5	*1 (16.6%)	6
ESR	< 20 mm/h	16.2 ± 8.9	25720	*6 (46.2%)	13
TSH	0.29-5.1 miu/L	1.5 ± 1.0	0.2 - 4.2	#3 (15%)	20
Chol	125 - 200 mg/dl	195.9 ± 69.9	131 - 361	*1 (8.3%)	12
HDL	> = 46 mg/dl	45.6 ± 13.1	27 - 67	#3 (23.1%)	13
TG	< 150 mg/dl	89.5 ± 83.5	20 - 367	&5 (33.3%)	15
LDL	< 130 mg/dl	132.3 ± 58.7	81 - 258	*4 (33.3%)	12

CSF: cerebrospinal fluid; ACE: angiotensin converting enzyme; WBC: white blood cell; Hgb: hemoglobin; MCV: Mean corpuscular volume; BUN: blood urea nitrogen; AST: aspartate aminotransferases; ALT: alanine aminotransferases; AKP: alkaline phosphatase; B12: vitamin B12; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; TSH: thyroid stimulating hormone; HDL: high density lipoprotein; LDL: Low density lipoprotein. *: > upper normal limit/dl; #: < lower normal limit/dl; &: < 50 mg/dl.

Discussion

Sarcoidosis is a rare idiopathic systemic inflammatory disorder characterized by the formation of the non-caseating granulomas [1]. The incidence of sarcoidosis has been estimated from 1 to 40 per 100,000 populations in the USA [3]. Sarcoidosis has been defined as a disease that commonly affects young and middle-aged adults and frequently presents with bilateral hilar lymphadenopathy, pulmonary infiltration, and ocular and skin lesions. The liver, spleen, lymph nodes, salivary glands, heart, nervous system, muscles, bones, and other organs may also be involved [3, 1]. Neurological involvement has been described in 5% of sarcoid patients [2].

In this observational study, high incidence of seizures was ultimately recognized. Cranial nerves exiting from the

middle fossa were more likely involved than those from the anterior and posterior fossa, particularly the facial, trigeminal and abducens nerves. MRI abnormality was demonstrated in leptomeninges and subcortical locations in more than half of our neurosarcoid patients, and in the frontal, parietal, temporal, cerebellar, occipital, brainstem, than in cortical areas (in order) (Tables 1, 2) and (Figure 1). Our study supported the notion that the clinical manifestations vary significantly in patients with sarcoidosis involving the CNS in discrete anatomic locations. The high rate of seizures seen in our patients might be due to sampling bias because the severe sarcoid patients were transferred to our University hospital.

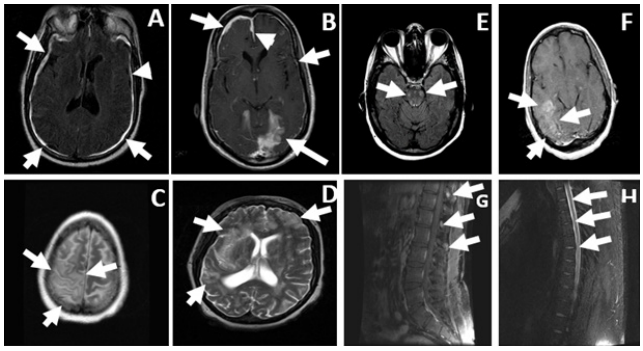

Figure 1: MRI of sarcoidosis. **A.** 66 years old male with diffuse leptomeningeal enhancement on T1 image with gadolinium (GD). **B.** 41 years old male with parenchyma, dural, and leptomeningeal lesions on T1 image with GD. **C.** 57 years old female with right frontal lesion on T2 image. **D.** 50 years old female with right frontal and parietal lesions on T2 image. E. 58 years old female with pontine lesions on T2 image. F. 56 years old female with right temporal--occipital lesions on FLAIR image. **G.** 41 years old male with vertebral lesion on T1 image with GD. **H.** 48 years old male with thoracic spine cord lesions on T2 image.

Peripheral neuropathy caused by neurosarcoidosis is extremely rare. Only 15% of neurosarcoid patients might develop neuropathy [2]. We recently reported that neuropathy related to sarcoidosis may manifest electrophysiologically as mononeuropathy or mononeuropathy multiplex [4]. In CNS neurosarcoidosis, the reported most frequently affected cranial nerves are facial more than optic nerves [2], which is consistent with our observations (Table 1) showing that cranial nerves exiting from the middle fossa were more likely to be involved than those from the anterior and posterior fossa. Notably, in addition to the facial nerve, trigeminal and abducens may also be susceptible in neurosarcoidosis (Table 1).

Findings of abnormal liver function test with decreased triglycerides may suggest liver dysfunction in sarcoidosis (Table 3). A recent report indicated hepatic involvement is common in sarcoidosis, occurring in up to 70% of patients while most patients with sarcoid liver are asymptomatic [5], which supports our observation. CSF abnormalities were observed in a majority of our cohort of CNS sarcoid patients showing a significant proportion of elevated protein (70%) with decreased glucose (50%) and mild lymphocytosis (20%), which were in agreement with previous reports [7]. In parallel to the elevated level in plasma, ACE level was found to be elevated in CSF in our patients. Notably, argument exists regarding if measurement of ACE in plasma or CSF in supporting the diagnosis of neurosarcoidosis [8], which may be an issue in sarcoid patients without CNS involvement.

Diagnosis of neurosarcoidosis is a clinical challenge because of its nonspecific clinical presentations. Neurosarcoidosis is often misdiagnosed or delayed in diagnosis. Autopsy studies have shown a significant rate of subclinical sarcoidosis, with only 50% of cases being diagnosed antemortem [8]. On the other hand, neurosarcoidosis may mimic CNS demyelinating disorder [9] and be misdiagnosed as multiple sclerosis (MS) [10]. Findings of increased CSF protein with simultaneously decreased glucose and mild lymphocytosis may be a helpful biomarker in differentiating neurosarcoidosis from MS, particularly when abnormal oligoclonal bands [7] and elevated IgG in the CSF are encountered. MRI with gadolinium enhancement images has been proven to be highly sensitive in detecting intracranial abnormalities due to neurosarcoidosis [11]. However, there is no specific laboratory test for diagnosing neurosarcoidosis. The confirmatory diagnosis often requires a tissue biopsy for histologic evaluation showing the presence of non-caseating granulomas [1].

The drawbacks of our study were that the nature of the study was a retrospective observation with a small sample size in a single tertiary medical center; and the severities of the illness in patients with neurosarcoidosis were variable. Due to the poor follow-up rates, the analysis on the treatment of neurosarcoidosis was not conducted. Significantly, all our patients had a tangible diagnosis of sarcoidosis by previously histological confirmation. Study on clinical, laboratory and neuroimaging findings in these sarcoid patients with neurologic presentations would provide us with useful information in sighting this dilemma and help pursue appropriate approaches to diagnosing and managing patients with neurosarcoidosis.

In summary, diagnosis of neurosarcoidosis remains a clinical challenge. Our study confirmed the notion that neurosarcoidosis involves any part of the CNS causing a variety of clinical manifestations. Seizures were most frequently seen in patients with neurosarcoidosis in the setting of hospital admission. Laboratory studies such as impaired liver function with reduced level of triglycerides and CSF with elevated level of ACE and protein with decreased glucose and mild lymphocytosis may aid in differentiating neurosarcoidosis from MS and other CNS inflammatory demyelinating disorders.

Conflict of Interest

The authors declare no conflict of interest.

References

1. Stern BJ, Royal W, Gelfand J, Clifford D, Tavee J, et al. 2018. Definition and consensus diagnostic criteria for neurosarcoidosis: from the neurosarcoidosis consortium consensus group. *JAMA Neurol* 75(12): 1546-1553. https://doi.org/10.1001/jamaneurol.2018.2295
2. Hoitsma E, Faber CG, Drent M, Sharma OP. 2004. Neurosarcoidosis: a clinical dilemma. *Lancet Neurol* 3(7): 397-407. https://doi.org/10.1016/S1474-4422(04)00805-1
3. Statement on sarcoidosis. 1999. Joint Statement of the American Thoracic Society (ATS), the European Respiratory Society (ERS) and the World Association of Sarcoidosis and Other Granulomatous

Disorders (WASOG) adopted by the ATS Board of Directors and by the ERS Executive Committee, February 1999. *Am J Respir Crit Care Med* 160(2): 736-755. https://doi.org/10.1164/ajrccm.160.2.ats4-99

4. Mehta AK, Luo JJ. 2018. Revisit: neurophysiologic features of neuropathy in patients with sarcoidosis. *J Neurol Exp Neurosci* 4(1): 21-23. https://doi.org/10.17756/jnen.2018-038
5. Tadros M, Forouhar F, Wu GY. 2013. Hepatic sarcoidosis. *J Clin Transl Hepatol* 1(2): 87-93. https://doi.org/10.14218/JCTH.2013.00016
6. Joseph FG, Scolding NJ. 2009. Neurosarcoidosis: a study of 30 new cases. *J Neurol Neurosurg Psychiatry* 80(3): 297-304. https://doi.org/10.1136/jnnp.2008.151977
7. Dale JC, O'Brien JF. 1999. Determination of angiotensin-converting enzyme levels in cerebrospinal fluid is not a useful test for the diagnosis of neurosarcoidosis. *Mayo Clin Proc* 74(5): 535. https://doi.org/10.4065/74.5.535
8. Iwai K, Tachibana T, Takemura T, Matsui Y, Kitaichi M, et al. 1993. Pathological studies on sarcoidosis autopsy. I. Epidemiological features of 320 cases in Japan. *Acta Pathol Jpn* 43(7-8): 372-376. https://doi.org/10.1111/j.1440-1827.1993.tb01148.x
9. Flanagan EP, Kaufmann TJ, Krecke KN, Aksamit AJ, Pittock SJ, et al. 2016. Discriminating long myelitis of neuromyelitis optica from sarcoidosis. *Ann Neurol* 79(3): 437-447. https://doi.org/10.1002/ana.24582
10. Scott TF, Yandora K, Kunschner LJ, Schramke C. 2010. Neurosarcoidosis mimicry of multiple sclerosis clinical, laboratory, and imaging characteristics. *The Neurologist* 16(6): 386-389. https://doi.org/10.1097/NRL.0b013e3181b287df
11. Pickuth D, Spielmann RP, Heywang-Kobrunner SH. 2000. Role of radiology in the diagnosis of neurosarcoidosis. *Eur Radiol* 10(6): 941-944. https://doi.org/10.1007/s003300051042