Original Article

Clinical Spectrum and Outcome of Neurosarcoidosis: A Retrospective Cohort Study from a Teaching Hospital in India

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Abstract

Context: Neurosarcoidosis (NS) is a chronic disease with a diverse clinical spectrum, therapeutic response, and outcome. There is scarce literature from our country regarding the same. **Aims:** The aim of this study was to evaluate the clinical spectrum, therapeutic responses, and outcomes of NS in an Indian cohort. **Settings and Design:** In a cross-sectional study, we included all patients with NS treated at a quaternary care teaching hospital in India from January 2007 to October 2019. **Subjects and Methods:** Patients older than 18 years of age fulfilling the diagnostic criteria for NS from the Neurosarcoidosis Consortium Consensus Group were included in the study. The therapeutic response and the degree of disability at last follow-up were assessed. **Results:** We identified 48 patients, among them 3 were categorized as having definite NS, 30 probable NS, and 15 possible NS. Cranial neuropathy was the most common presentation (47.9%), followed by myelopathy (25%). Systemic involvement was identified in 95.83% and mediastinal lymph nodes were the most common site. Clinical improvement was seen in 65.8% and disease stabilized in 28.9%, while 5.26% deteriorated. Fifty percent recovered without any residual disability, while 26.3% had minor and 23.7% had major residual sequelae. **Conclusions:** NS is a diverse illness, with a heterogeneous spectrum of clinical presentation, treatment response, and outcome. Cranial neuropathy is the most common presenting feature and has a good prognosis while myelopathy has an unfavorable prognosis. Meningeal and brain parenchymal disease is difficult to diagnose accurately unless systemic involvement is present. The diagnosis of NS should be clinically suspected in the appropriate clinical setting, the presence of systemic involvement should be investigated, and histologic confirmation should be attempted.

Keywords: Cranial neuropathy, multiple cranial nerve involvement, neurosarcoidosis, pachymeningitis, sarcoidosis

Introduction

Sarcoidosis is a multisystem granulomatous disease of unknown origin characterized by noncaseating granulomas in affected organs.[1] Although it most commonly affects the lungs and lymph nodes, sarcoidosis can virtually affect any organ including the nervous system. Nervous system involvement is known as Neurosarcoidosis (NS) and it occurs in about 5% of patients with sarcoidosis.[2] NS is a chronic disease with a broad clinical spectrum as multiple levels of the neuraxis may be involved.[3,4]

An accurate diagnosis of NS can be challenging, as it requires histologic confirmation of the affected tissue and neural tissue is not readily accessible for pathologic examination. Most patients with NS will have involvement of other organ systems such as the lung and lymph nodes, and a biopsy from these affected organs can help in diagnosis. The therapeutic response, prognosis, and outcomes are also variable. Some patients will recover completely after corticosteroid therapy while others will have multiple relapses and can develop residual sequelae.[4]

There is scarce literature from our country regarding the clinical presentation, treatment response, and outcomes of NS. Hence, in this study, we have attempted to assess the clinical spectrum, therapeutic responses, and outcomes of NS in an Indian cohort.

Subjects and Methods

The study included a retrospective analysis of a cohort of patients with NS admitted under the neurology unit at quaternary care teaching hospital in India from January 2007 to October 2019. Patients older than 18 years of age fulfilling the diagnostic criteria for NS from the Neurosarcoidosis Consortium Consensus Group [Table 1] were included in the study.[5]

The study variables obtained from our prospectively maintained electronic database included baseline demographic data, clinical presentation, biochemical profile, serological profile, cerebrospinal fluid (CSF) profile, radiological profile,

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Table 1: Consensus Diagnostic Criteria for Neurosarcoidosis From the Neurosarcoidosis Consortium Consensus Group[5]

Definite
1. The clinical presentation and diagnostic evaluation suggest neurosarcoidosis, as defined by the clinical manifestations and MRI, CSF, and/or EMG/NCS findings typical of granulomatous inflammation of the nervous system after rigorous exclusion of other causes.
2. The nervous system pathology is consistent with neurosarcoidosis.
Type a. Extraneural sarcoidosis is evident.
Type b. No extraneural sarcoidosis is evident (isolated CNS sarcoidosis).
Probable
1. The clinical presentation and diagnostic evaluation suggest neurosarcoidosis, as defined by the clinical manifestations and MRI, CSF, and/or EMG/NCS findings typical of granulomatous inflammation of the nervous system after rigorous exclusion of other causes.
2. There is pathologic confirmation of systemic granulomatous disease consistent with sarcoidosis.
Possible
1. The clinical presentation and diagnostic evaluation suggest neurosarcoidosis, as defined by the clinical manifestations and MRI, CSF, and/or EMG/NCS findings typical of granulomatous inflammation of the nervous system and after rigorous exclusion of other causes.
2. There is no pathologic confirmation of granulomatous disease.

microbiological profile, histopathology of involved tissues, and treatment details. Patients with other causes of granulomatous inflammation such as infections and malignancies were excluded by performing stains for acid-fast bacilli and fungi, microbial cultures, cytology, and GeneXpert MTB on CSF and tissue samples.

The therapeutic response at the time of the last follow-up was classified as improvement, stable disease or relapsing as compared to the baseline status. The degree of disability at last follow-up was assessed according to the Modified Oxford Handicap Scale (MOHS).[6] Patients were then classified into three groups corresponding to "No disability"(MOHS score 0), "Minor disability" (MOHS score 1,2), and "Severe disability" (MOHS score 3,4,5). Only patients with a minimum follow-up of 3 months were included for the analysis of the therapeutic response and disability assessment.

The statistical analysis was performed using IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp. Descriptive analysis was performed using the Chi-square test. Statistical significance was taken to be at the two-tailed 0.05 level.

Results

We identified a total of 48 patients who met the diagnostic criteria for NS during the study period. The baseline characteristics of the cohort are presented in Table 2. The mean age at the time of diagnosis was 41.8 years (SD: 13.01). There were 27 males (56.3%) and 21 females (43.8%). One patient also had a history of autoimmune disease in the form of pernicious anemia and inflammatory small joint arthritis.

Clinical features

Three patients (6.3%) in our cohort had a prior diagnosis of sarcoidosis outside the nervous system. All three of them had pulmonary sarcoidosis with mediastinal lymph node involvement, out of which one patient also had involvement of the liver. The time interval between the diagnosis of pulmonary sarcoidosis and neurological involvement in the three patients was 12, 48, and 84 months, respectively. In the remaining 45 patients (93.8%), neurological symptoms were the first clinical manifestation of sarcoidosis. The mean duration of neurological symptoms in our cohort was 14.08 months (range: 0.5–96). The most common neurological symptoms at presentation were limb weakness and sensory disturbances, present in 20 patients (41.7%). This was followed by headache, facial weakness, and bowel-bladder symptoms, which was present in 12 patients (25%) each. Constitutional symptoms in the form of fever, anorexia, and weight loss were present in 7 patients (14.6%).

Seven patients (14.58%) had more than one neurological feature at presentation. Cranial neuropathy was the most common presenting feature of NS, seen in 23 patients (47.9%). This was followed by myelopathy in 12 patients (45.8%) and peripheral neuropathy in 10 patients (20.8%).

Among the 23 patients presenting with cranial neuropathy, 11 patients (47.8%) had involvement of a single cranial nerve, while the remaining 12 patients (52.2%) had involvement of multiple cranial nerves. Facial nerve palsy was the most common cranial neuropathy, occurring in 12 out of the 23 patients (52.17%). It was unilateral in 8 patients and bilateral in 4 patients. Six patients each out of the 23 patients (26.08%) had optic neuritis and trigeminal nerve involvement at presentation, out of which one patient had bilateral optic neuritis and bilateral trigeminal nerve involvement.

Among the 12 patients presenting with myelopathy, the onset of symptoms was chronic in 9 patients (75%) and subacute in the remaining 3 patients (25%). The thoracic region was involved in 10 out of the 12 patients (83.3%), while two patients each had cervical region and conus-cauda region involvement.

Among the 10 patients presenting with peripheral neuropathy, 6 patients (60%) had a subacute onset, 2 patients (20%) had an acute onset, and the remaining 2 patients (20%) had a chronic onset. Polyradiculoneuropathy was the most common pattern of peripheral neuropathy, present in 6 patients (60%). The electrodiagnosis was primarily axonal in 7 patients and primarily demyelinating in the remaining 3 patients.

Ancillary tests

ESR was elevated (>20 mm/h) in 26 patients (54.2%), while CRP was elevated (>6 mg/L) in 13 patients (29.5%). Hypercalcemia (>10.4 mg/dL) was seen in one patient (2.1%). The serum angiotensin-converting enzyme (ACE) level was elevated (>52 U/L) in 20 patients (41.7%), while it was normal in the remaining 28 patients (58.3%). The mean value of ACE was 62.17 U/L (range: 15–200).

Table 2: Baseline Characteristics of the Cohort

Characteristic	*n* (%)	Characteristic	*n* (%)
Presenting symptoms		**Presenting features***	
Limb weakness	41.7%	Cranial neuropathy**	23 (47.9%)
Limb sensory disturbances	41.7%	2nd CN	6 (26.08%)
Headache	25%	3,4,6th CN	5 (21.73%)
Facial weakness	25%	5th CN	6 (26.08%)
Bowel-bladder symptoms	25%	7th CN	12 (52.17%)
Truncal sensory disturbances	22.9%	8th CN	3 (13.04%)
Vision loss	16.7%	9 & 10th CN	4 (17.39%)
Double vision	14.6%	12th CN	1 (4.34%)
Facial sensory loss	12.5%	Myelopathy	12 (25%)
Seizures	8.3%	Peripheral neuropathy	10 (20.80%)
Dysarthria-dysphagia	8.3%	Polyradiculoneuropathy	6
Hearing loss	6.3%	Polyradiculopathy	1
Ataxia	4.2%	Mononeuritis multiplex	1
Constitutional symptoms	14.6%	Sensory ataxic	1
		Small fiber	1
		Chronic meningitis	6 (26.08%)
		Pachymeningitis	5
		Leptomeningitis	1
		Neurovascular	3 (6.30%)
		Brain Parenchymal	3 (6.30%)
MRI Brain	38	**CT Chest/Abdomen**	48
Meningeal involvement	22 (57.89%)	Cervical LN	26 (54.16)
Focal dural	13 (59.1%)	Mediastinal LN	44 (91.66)
Cavernous sinus/Orbital apex	7	Axillary LN	12 (25%)
Meckel's cave	3	Abdominal LN	17 (35.41%)
Posterior fossa (Falco-tentorial)	6	Lung involvement	22 (45.83%)
Cerebral convexity	2	Pleural involvement	4 (8.33%)
Diffuse dural	6 (27.3%)	Liver/spleen involvement	8 (16.66%)
Focal nodular leptomeningeal	4 (18.2%)	Cardiac involvement	1 (2.085%)
Basal leptomeningeal	3 (13.6%)		
Brain parenchymal involvement	13 (34.21%)		
Multiple nonenhancing WM lesion	10 (76.92%)		
Enhancing intraparenchymal lesion	4 (30.76%)		
Infarcts	4 (30.76%)		
Cranial nerve involvement	10 (26.31%)		
MRI Spine	28	**Biopsy Site**	
Spinal cord involvement	19 (67.8%)	Lymph node	28 (75.7%)
Intramedullary lesion	12 (63.15%)	EBUS LN FNA	20
Short segment myelitis	6	US LN FNA	2
LETM	4	CT LN FNA	2
Focal spinal cord atrophy	2	Open LN Biopsy	4
Intradural extramedullary lesion	1 (5.26%)	EBUS Lung	9 (24.3%)
Conus-Cauda involvement	2 (10.52%)	Skin	2 (5.4%)
Diffuse cauda equina involvement	4 (21.05%)	Liver	2 (5.4%)
		Nerve-Muscle	4 (10.4%)
		Meninges	1 (2.7%)
		Brain	1 (2.7%)
		Spinal cord	1 (2.7%)

CN=cranial nerve, LN=lymph node, LETM=longitudinally extensive transverse myelitis, EBUS=endobronchial ultrasound, FNA=fine needle aspiration. *Seven patients (14.58%) had more than one neurological feature at presentation. **Twelve patients (52.2%) had involvement of multiple cranial nerves

CSF analysis

CSF analysis was performed in 46 out of the 48 patients. CSF pleocytosis was present in 14 patients (30.4%) and all the cases had a mononuclear pleocytosis. The mean CSF total cell count was 16.22 cells/μl (range: 1–240). Five patients had a mild pleocytosis (<25 cells/μl), 8 patients had a moderate pleocytosis (26 to 100 cells/μl), and 1 patient had a marked pleocytosis (>100 cells/μl). A low CSF glucose of

42 mg/dL was present in one patient (2.2%) and an elevated CSF protein (>45 mg/dL) was present in 21 patients (45.7%). The mean values of CSF glucose and protein were 67.91 mg/dL (range: 42–137) and 70.04 mg/dL (range: 18–517), respectively. CSF oligoclonal bands were done in 14 patients and were present only in 1 patient.

Neuroradiology

MRI of the brain was done in 38 out of the 48 patients. Meningeal involvement was the most frequent feature, present in 22 patients (57.89%). Focal dural involvement was the most frequent pattern seen in our cohort, seen in 13 patients (59.1%), while diffuse dural involvement was seen in 6 patients (27.3%). Leptomeningeal involvement was seen in 7 patients (31.81%). The brain parenchyma was involved in 13 patients (34.21%). The most frequent feature of parenchymal involvement was the presence of multiple nonenhancing white matter lesions, present in 10 out of the 13 patients (76.92%). Enhancing intraparenchymal lesions [Figure 1a] were present in 4 out of the 13 patients (30.76%). Cranial nerve involvement in the form of thickening and enhancement was present in 10 patients (26.31%). MRI spine was done in 28 out of the 48 patients. Spinal cord involvement was present in 19 patients (67.8%). The most frequent feature of spinal cord involvement was the presence of intramedullary lesions, present in 12 out of the 21 patients (63.15%). Intramedullary involvement was in the form of short segment myelitis in 6 patients, longitudinally extensive transverse myelitis (LETM) [Figure 1b] in 4 patients, and focal spinal cord atrophy in 2 patients. Diffuse cauda equina involvement was present in 4 patients (21.05%).

Systemic involvement

All patients underwent evaluation for the presence of systemic sarcoidosis. CT thorax/abdomen was done in all patients. FDG-PET scan was done in 24 patients (50%). Forty-six patients (95.83%) were found to have systemic involvement, with the remaining 2 patients having isolated NS. The most frequent feature of systemic involvement was lymphadenopathy, present in 44 patients (91.7%). Mediastinal lymph nodes were the most common site of lymph node involvement, present in all of the 44 patients. Pulmonary involvement was present in 22 patients (45.83%) and hepatosplenomegaly was seen in 10 patients (20.8%). Ocular involvement was seen in 1 patient (2.08%) in the form of retinal vasculitis. Skin involvement was seen in 2 patients (6.3%).

Biopsy

Thirty-seven patients (77.08%) underwent biopsy as part of the diagnostic evaluation. Eleven patients (29.72%) underwent biopsy from more than one site. Lymph nodes were the most common extraneural site of biopsy, with 28 out of 37 patients (75.67%) undergoing lymph node biopsy. Nine out of the 37 patients (24.32%) underwent a lung biopsy. Twenty patients underwent endobronchial ultrasound (EBUS)-guided transbronchial needle aspiration of intrathoracic lymphadenopathy and 9 patients underwent EBUS-guided transbronchial needle aspiration of pulmonary lesions. Nervous system tissue was biopsied in 6 out of the 37 patients (16.21%). Four patients underwent a nerve-muscle biopsy, one patient underwent a spinal cord biopsy, and one patient underwent a combined meningeal and brain biopsy. The biopsy of 33 out of 37 patients (89.2%) showed the presence of noncaseating granulomas.

Classification

Based on the criteria, 3 patients (6.25%) were classified as having Definite NS, with 2 patients being Definite NS Type a, and 1 patient being Definite NS Type b. Thirty patients (62.5%) were classified as having Probable NS and fifteen patients (31.25%) as having possible NS [Figure 2]. The distribution of gender, various laboratory parameters, and diagnostic categorization according to clinical presentation is given in Table 3.

Therapeutic response and residual disability

All 48 patients received corticosteroids (CS) in the form of pulse intravenous methylprednisolone, followed by

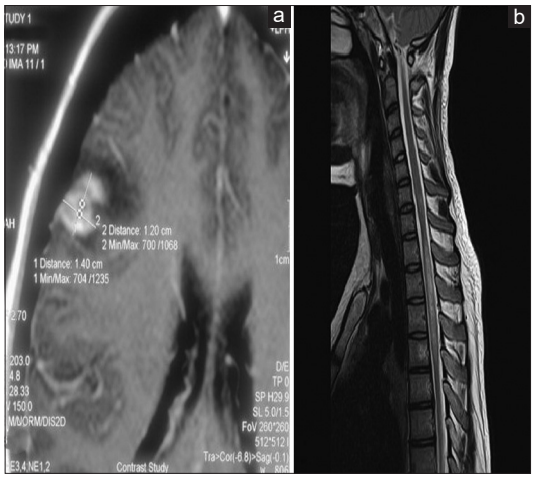

Figure 1: Neurosarcoidosis presenting as a parenchymal enhancing lesion (a) and LETM (b)

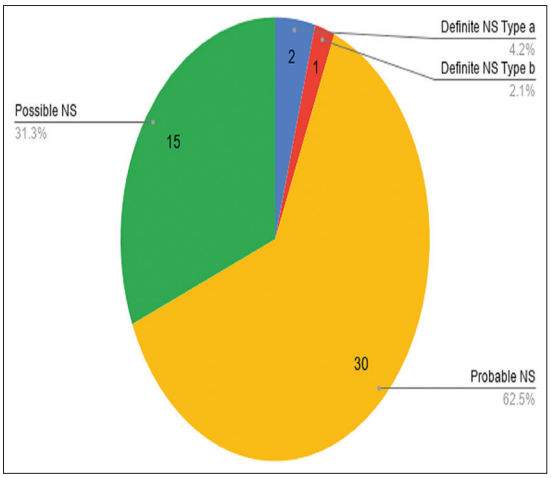

Figure 2: Classification of patients in our cohort according to the Consensus Diagnostic Criteria for Neurosarcoidosis

tapering doses. Forty-seven patients (97.91%) were started on steroid-sparing medication at the time of initial diagnosis. The choice of steroid-sparing medications was mycophenolate in 22 patients (46.8%), pulse intravenous cyclophosphamide in 18 patients (38.3%), rituximab in 5 patients (10.6%), and azathioprine in 2 patients (4.3%).

Of the 48 patients of our cohort, 38 patients had a follow-up of more than 3 months. The mean duration of follow-up was 34.55 months (range: 4–232). Out of the 38 patients, 25 (65.8%) had clinical improvement and 11 (28.9%) remained clinically stable during follow-up. Nineteen patients (50%) had complete remission. Thirty-four patients (89.5%) were off steroids and 4 patients (10.5%) were off immunosuppressive therapy on follow-up. Two patients (5.26%) developed recurrent relapses in spite of immunosuppressive therapy and were steroid dependent. Out of the 38 patients, 19 (50%) recovered without any residual disability, while 10 patients (26.3%) had minor residual sequelae and 9 patients (23.7%) had severe residual sequelae. The therapeutic response and residual disability according to clinical presentation are given in Table 4.

Discussion

Sarcoidosis can occur at any age. However, the peak incidence is in the third to fifth decade and women are more affected.[7,8] The mean age at the time of diagnosis was 41.8 years in our cohort; however, males were more affected than females. Neurological complications are seen in 5% to 15% of patients and are the presenting feature in around 50% of patients with sarcoidosis.[8,9]

Cranial neuropathy

The most commonly reported presenting feature of NS is cranial neuropathy, occurring in about 55% of patients.[8,9] Any cranial nerve can be involved, and over one-half of patients have multiple cranial nerve involvement.[9] In our cohort, cranial neuropathy was the most common presenting feature, seen in 47.9% of patients, out of which 52.2% had multiple cranial nerve involvement. Facial nerve palsy is the most common cranial neuropathy, occurring 25% to 50% of patients with NS.[8,10] About one-third of facial nerve palsies are bilateral and could be either concurrent or sequential.[10] In our cohort also, facial nerve palsy was the most common cranial neuropathy, seen in 52.17% and it was bilateral in 33.33%. Optic neuritis is the next most frequent cranial neuropathy, occurring in 7%

Table 3: Gender, laboratory parameters, and diagnostic categorisation according to clinical presentation*

Parameter	CN (*n*=23)	MLP (*n*=12)	PN (*n*=10)	MEN (*n*=6)	NV (*n*=3)	PAR (*n*=3)
Male sex	11 (47.8%)	10 (83.3%)	5 (50%)	1 (16.7%)	2 (66.7%)	1 (33.3%)
Female sex	12 (52.2%)	2 (16.7%)	5 (50%)	5 (83.3%)	1 (33.3%)	2 (66.7%)
Normal ACE	14 (60.8%)	9 (75%)	4 (40%)	4 (66.6%)	0	3 (100%)
Elevated ACE	9 (39.2%)	3 (25%)	6 (60%)	2 (33.4%)	3 (100%)	0
CSF Normal cells	16 (69.5%)	7 (58.3%)	6 (60%)	5 (83.3%)	3 (100%)	3 (100%)
CSF Mild Pleocytosis	2 (8.7%)	3 (25%)	1 (10%)	1 (16.7%)	0	0
CSF Moderate Pleocytosis	5 (21.8%)	2 (16.7%)	2 (20%)	0	0	0
CSF Marked Pleocytosis	0	0	1 (10%)	0	0	0
CSF Normal Protein	14 (60.8%)	3 (25%)	3 (30%)	5 (83.3%)	2 (66.7%)	3 (100%)
CSF Elevated Protein	9 (39.2%)	9 (75%)	7 (70%)	116.7%)	1 (33.3%)	0
Definite NS	1 (4.3%)	1 (8.3%)	1 (10%)	1 (16.7%)	0	0
Probable NS	12 (52.2%)	8 (66.7%)	7 (70%)	4 (66.6%)	3 (100%)	1 (33.3%)
Possible NS	10 (43.5%)	3 (25%)	2 (20%)	1 (16.7%)	0	2 (66.7%)

CN=cranial neuropathy, MLP=myelopathy, PN=peripheral neuropathy, MEN=meningeal disease, NV=neurovascular, PAR=brain parenchymal disease.
*Seven patients (14.58%) had more than one neurological feature at presentation

Table 4: Therapeutic response and disability according to clinical presentation*

	CN (*n*=19)	MLP (*n*=11)	PN (*n*=7)	MEN (*n*=5)	NV (*n*=2)	PAR (*n*=2)
Therapeutic response						
Improving	16	4	5	4	0	1
Stable	1	7	2	0	2	1
Relapsing	2	0	0	1	0	0
P	**0.003**	**0.010**	0.781	0.121	0.075	0.773
Disability						
Nil	13	1	4	4	0	0
Minor	6	2	2	1	1	2
Severe	0	8	1	0	1	0
P	**0.003**	**<0.0001**	0.809	0.288	0.346	0.052

CN=cranial neuropathy, MLP=myelopathy, PN=peripheral neuropathy, MEN=meningeal disease, NV=neurovascular, PAR=brain parenchymal disease.
*Data of 38 patients who had a follow-up of more than 3 months, 7 patients (18.42%) had more than one neurological feature at presentation

to 35% of patients with NS, with bilateral involvement slightly more common than unilateral disease.[11] In our cohort, both optic neuritis and trigeminal nerve involvement were seen frequently after facial nerve palsy.

The mechanism of cranial neuropathy in NS is epineural inflammation, perineural inflammation, and external compression by granulomatous inflammation in the meninges.[12] Out of the 23 patients with cranial neuropathy in our cohort, 7 patients (30.43%) had imaging features of isolated direct involvement of cranial nerves in the form of hyperintensity and enhancement, 10 patients (43.47%) had compression from surrounding meninges, and 3 patients (13.04%) had cranial neuropathy due to combined direct involvement and meningeal compression.

The prognosis of cranial nerve involvement is generally good with patients showing a good response to CS and complete recovery in more than 85% of cases.[11] In our cohort, 84.2% of patients with cranial neuropathy had improvement with treatment ($P = 0.003$) and 68.42% had complete remission of symptoms with no residual disability ($P = 0.003$). However, two patients had a relapsing course with steroid dependence in spite of the use of steroid-sparing medications.

Myelopathy

Myelopathy in NS is seen in up to 20% of patients.[8,11] NS has a predilection for the thoracic and cervical regions of the spinal cord.[13,14] It can also present as a myeloradiculopathy with features of a conus-cauda syndrome or as an isolated cauda equina syndrome.[11] There can be involvement of intramedullary, intradural, and extradural portions with intramedullary involvement being more common.[13] Myelopathy in NS has a subacute to chronic onset.[11,14] In our cohort, myelopathy was seen in 25% of patients and all of them had a subacute to chronic onset. The thoracic region was most commonly involved and intramedullary involvement was seen in 63.15%.

The prognosis and outcome of patients with spinal cord involvement are not so favorable. They have a high incidence of permanent neurologic deficits unless they are promptly recognized and treated with aggressive CS and steroid-sparing therapy. In our cohort, 36.36% of patients showed improvement in symptoms while the remaining were clinically stable after initiation of treatment ($P = 0.010$). However, 72.72% of patients had severe residual disability ($P = 0.000$) and all of them presented more than 12 months after the onset of symptoms.

Peripheral neuropathy

Peripheral neuropathy is not rare in NS and is seen in about 20% of patients and a variety of patterns are reported.[10] It mainly occurs via direct granulomatous infiltration or compression.[15] The most common pattern is that of a polyradiculoneuropathy, the onset can be acute to subacute and can even mimic Guillain–Barre syndrome.[15,16] The electrodiagnosis is typically axonal; however, primary demyelinating neuropathy with conduction blocks has also been reported.[15] In our cohort, 20.8% of patients presented with peripheral neuropathy. Polyradiculoneuropathy was the most common pattern and the majority presented with an acute to subacute onset. Two patients presented with an acute onset mimicking Guillain–Barre syndrome with nerve-muscle biopsy of one patient and skin biopsy of the other patient showing granulomatous inflammation. The electrodiagnosis was primarily axonal in one patient and primarily demyelinating with conduction blocks in the other. One patient in our cohort presented with a small fiber neuropathy. Small fiber neuropathy has been reported in up to 40% of patients with sarcoidosis.[17]

Prognosis of peripheral neuropathy appears to be more benign than other types of NS, as most patients respond favorably to CS.[15] In our cohort, 66.66% of patients had improvement and only one patient had severe residual sequelae.

Meningeal disease

Meningeal disease is seen in approximately 10%–20% of patients with NS.[10] It can present with leptomeningeal involvement or, less commonly with dural involvement and patients typically present with subacute to chronic onset of headache.[10] Leptomeningeal involvement can be diffuse or nodular.[10] Dural involvement can present as focal enhancing dural masses or with diffuse dural thickening.[9,10] In our cohort, meningeal disease due to NS presenting with pachymeningeal involvement was much more common. In our country, it is extremely difficult to make an accurate diagnosis of leptomeningeal involvement due to NS because of the high incidence of tuberculous meningitis. Invariably most of the patients will be treated with antituberculosis therapy and corticosteroids and this probably accounts for the less number of patients with leptomeningeal involvement due to NS. One patient in our cohort presenting with dural involvement was initially diagnosed with a dural neoplasm based on a dural biopsy; however, she had systemic involvement in the form of cardiac sarcoidosis with heart block along with mediastinal lymphadenopathy and biopsy from the mediastinal nodes

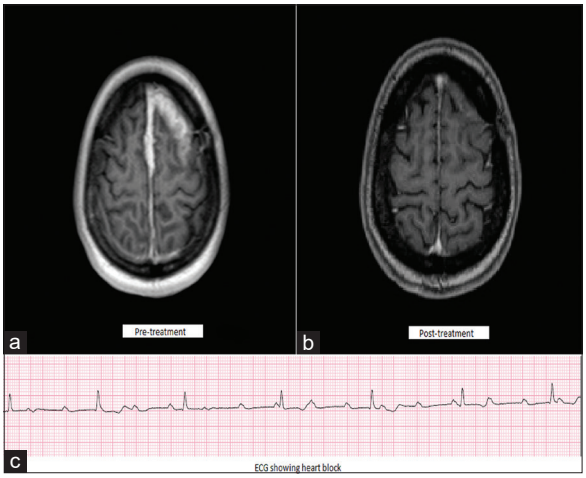

Figure 3: Systemic involvement in Neurosarcoidosis. A 36-year-old female presenting with hypertrophic pachymeningitis (a) along with cardiac involvement manifesting as heart block (c). The pachymeningitis improved with treatment (b)

showed noncaseating granulomatous inflammation [Figure 3]. Prognosis is generally favorable because the disease tends to respond well to treatment with CS even though recurrence is common.[11] In our cohort, all patients with meningeal disease improved without any residual disability.

Brain parenchymal disease

Brain parenchymal involvement has been reported in about 50% of patients with NS.[10] This can be in the form of granulomatous mass lesions presenting as a solitary or multiple nodules that can be seen in any part of the CNS.[9,11] These are difficult to diagnose and a brain biopsy is generally required, although the sensitivity of brain parenchymal biopsy to demonstrate noncaseating granuloma is only 60%.[18] In our cohort, 3 patients presented with granulomatous mass lesions; however, all of them had other features of NS. They are generally steroid-responsive and have a good prognosis. Parenchymal NS can also present with scattered white matter involvement, which can mimic CNS vasculitis and MS.[10] This feature was present in 30.76% of patients of our cohort and was the most frequent feature of brain parenchymal involvement. Stroke as the presenting feature of NS was seen in 6.3% of patients of our cohort. It is a rare complication of NS and the predominant mechanism is leptomeningeal inflammation penetrating the endothelial walls, resulting in large or small artery infarcts.

When to suspect Neurosarcoidosis

The possibility of NS should be considered in the following clinical settings:

Cranial neuropathy–multiple cranial nerve involvement, bilateral facial nerve palsy, recurrent facial nerve palsy, and bilateral optic neuritis.

Myelopathy–subacute to chronic onset, presence of features of myeloradiculopathy, and isolated cauda equina syndrome.

Peripheral neuropathy–subacute polyradiculoneuropathy.

Meningeal disease–hypertrophic pachymeningitis.

Brain parenchymal disease–enhancing solitary or multiple lesions along with nonenhancing scattered white matter involvement.

Systemic involvement and biopsy

In the appropriate clinical setting of NS, the presence of systemic involvement should be pursued. If the initial tests fail to disclose any evidence of systemic involvement, further evaluation with a whole-body FDG-PET scan should be considered. Systemic manifestations of sarcoidosis outside the nervous system at any time during disease course occur in more than 90% of patients, especially in the lungs and mediastinal lymph nodes.[19] In our cohort, systemic involvement was seen in 95.83% of patients, with mediastinal lymphadenopathy seen in all patients and pulmonary involvement seen in 45.83% of patients. In patients with characteristic pulmonary lesions or mediastinal lymphadenopathy, EBUS-guided transbronchial needle aspiration is a promising new procedure that has been found to have a high diagnostic yield (84% to 93% sensitivity) for sarcoidosis.[16] Serum ACE levels when used in isolation are neither specific nor sensitive for the diagnosis of NS and should not be relied on.[20] If a patient has documented systemic involvement, the nervous tissue biopsy is not mandatory.

Isolated CNS involvement

In our cohort, there were 2 patients with isolated CNS involvement. One patient had a combined presentation with cranial neuropathy, brain parenchymal involvement, and myelopathy. The other patient presented with involvement of multiple cranial nerves along with pachymeningeal involvement and was diagnosed based on a combined dural and brain biopsy. Hence, in those with isolated CNS involvement, a biopsy of the affected region is usually the final and most definitive step in diagnosing NS.[16] A CNS biopsy must also be considered when a patient does not respond to immunosuppressive therapy or has worsening lesions, to rule out any alternative diagnoses.[16]

Therapeutic response

Corticosteroids (CS) are the first line of treatment in NS and patients require a prolonged course.[18] The initial response is good but the disease tends to relapse when the dose is reduced, especially in patients with myelopathy, enhancing parenchymal brain lesions and multiple cranial neuropathies.[2,10] Thus, steroid-sparing medications are often required as second-line therapy and combination therapy with both CS and steroid-sparing medications should be considered as initial therapy, especially in those presenting significant nervous system involvement.[21] This approach can reduce the incidence of CS complications, may allow the use of a minimal dose of CS and even discontinuation of CS once the disease is stable.[16] In our cohort, all patients received CS and 97.91% received a combination of CS and steroid-sparing medications as initial therapy. On follow-up, 89.5% of patients in our cohort were off steroids and 10.5% were off immunosuppressive therapy.

Comparison between current series and available literature

Fritz *et al*.[8] performed a systematic review and meta-analysis of patients with NS from 1965 to 2015 and a comparison with the current series is shown in Table 5. In comparison to the available literature, there is a higher occurrence of facial nerve palsy, trigeminal nerve involvement and multiple cranial nerve involvement in our cohort. Less number of patients have been classified as definite NS, more have been classified as possible NS, while the classification of probable NS is similar in comparison to the available literature. The use of steroid-sparing medications is higher in our cohort. The finding on MRI brain and treatment outcomes are comparable to the available literature.

Conclusions

NS is a diverse illness, with a heterogeneous spectrum of clinical presentation, treatment response, and outcome. The possibility of NS should be considered in the appropriate

Table 5: Comparison between current series and available literature

	Current series	Fritz *et al*.[8]
Patient characteristics		
Mean age in years	41.8	43
Sex, male	56.3%	44.6%
History of sarcoidosis	6.3%	31.4%
Presenting features		
Cranial neuropathy	47.9%	55%
2nd CN	26.08%	20.87%
5th CN	**26.08%**	11.78%
7th CN	**52.17%**	24.22%
Multiple CN involvement	**52.2%**	28.4%
Myelopathy	25%	18%
Peripheral neuropathy	20.8%	17.38%
Chronic meningitis	26.08%	16.2%
Systemic involvement		
Present	95.83%	83.77%
Lymphadenopathy	**91.7%**	17.82%
Pulmonary	45.83%	57.38%
Lab features		
Elevated serum ACE	41.7%	35.31%
CSF pleocytosis	**30.4%**	58%
Elevated CSF protein	45.7%	62.68%
Low CSF glucose	**2.2%**	13.78%
MRI Brain		
Meningeal involvement	57.89%	46.22%
Parenchymal involvement	34.21%	50.52%
Cranial nerve involvement	26.31%	25.73%
Diagnosis		
Definite NS	**6.25%**	25.44%
Probable NS	62.5%	59.36%
Possible NS	**31.25%**	15.2%
Treatment		
Corticosteroids	100%	80.5%
Steroid sparing agents	**97.91%**	35.8%
Outcome		
Improvement	65.8%	65.78%
Stable disease	28.9%	24%
Relapses	5.26%	4.57%

CN=cranial neuropathy

clinical setting and the presence of systemic involvement should be investigated. Systemic involvement is common and a biopsy of the involved systemic tissue should be considered. However, in the presence of isolated CNS involvement, we should proceed with the biopsy of neural tissue if feasible.

Cranial neuropathy is the most common presenting feature and has a good prognosis. Myelopathy has an unfavorable prognosis unless early aggressive therapy is initiated. Meningeal and brain parenchymal disease is difficult to diagnose accurately unless systemic involvement is present. Aggressive treatment with a combination of steroids and steroid-sparing medications should be considered early in the disease course.

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Conflicts of interest

There are no conflicts of interest.

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