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Neurosarcoidosis of the Cauda Equina

Clinical Course, Radiographic and Electrodiagnostic Findings, Response to Treatment, and Outcomes

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Abstract

Background and Objectives

Sarcoidosis is a multisystem granulomatous disease affecting the nervous system in 3%–5% of cases. It can affect almost any component of the nervous system. Involvement of the cauda equina is an understudied phenotype, and questions remain regarding its natural history and optimal approach to management. This study aims to study the long-term clinical evolution of neurosarcoidosis affecting the cauda equina, response to treatment, and clinical and radiographic outcomes.

Methods

Patients with neurosarcoidosis treated at Emory University between January 1, 2011, and December 8, 2021, were retrospectively evaluated for manifestations of cauda equina disease and included if disease of the cauda equina could be substantiated by MRI or EMG.

Results

Of 216 cases, 14 (6.5%) involved the cauda equina. The median age was 49.5 years, and most were female (85.7%) and African American (64.3%). Chronic (>28 days) presentations were most common (78.6%), but acute (<7 days, 14.3%) and subacute (7–28 days, 7.1%) were also seen. The median modified Rankin Scale (mRS) score at nadir was 3 (range 2–4). Symptoms were asymmetric in 78.6% and included leg numbness (85.7%), leg weakness (64.3%), perineal numbness (35.7%), pain (42.3%), and incontinence (21.4%). On MRI, the cauda equina enhanced in 100%, appeared nodular in 78.6%, and was diffusely involved in 71.4%. Coexisting myelitis was common (cervical 28.6%, thoracic 35.7%, and conus medullaris 28.6%). Intracranial inflammation included leptomeningitis (71.4%) and cranial neuropathies (57.1%). Electrodiagnostic studies were conducted in 3 with only one showing features consistent with a radicular process. Serum and CSF angiotensin-converting enzyme levels were elevated in 38.5% and 0.0%, respectively. CSF white blood cell and protein were elevated in 92.9%. Corticosteroids were tried in all patients with durable stabilization or improvement in only 3 (21.4%). Second-line agents associated with improvement included methotrexate/infliximab (3/4, 75%), methotrexate (3/4, 75.0%), and azathioprine (1/1, 100%). During a median follow-up of 22.5 months, the final median mRS score was 3. Relapses occurred at a median of 6 months in 21.4%. In 9 patients with MRI follow-up, 6 improved (66.7%), 1 stabilized (11.1%), and 2 worsened (22.2%).

Discussion

Characteristic features of cauda equina involvement by neurosarcoidosis include chronically delayed presentations, nodular enhancement on MRI, poor response to corticosteroids, and substantial resultant neurologic disability.

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Glossary

ACE = angiotensin-converting enzyme; **Ig** = immunoglobulin; **mRS** = modified Rankin Scale; **NCS** = nerve conduction study; **OCB** = oligoclonal band.

Sarcoidosis is a multisystem disorder of presumed autoimmune etiology thought to occur in genetically susceptible individuals in response to unidentified environmental antigens.[1] The lymphatic system, lungs, eyes, and skin are most commonly affected, but approximately 3–5% of patients develop clinically evident neurologic disease, often within the first 2 years of developing systemic sarcoidosis.[2-5] Neurologic manifestations are the presenting symptoms in roughly half of patients with neurosarcoidosis with multiorgan disease, and the most common clinicoradiographic phenotypes are cranial neuropathies, leptomeningitis, and parenchymal disease of the brain and spinal cord.[4-7]

Injury to the cauda equina often presents with bowel, bladder, and sexual dysfunction as well as altered sensation in the saddle region.[8,9] Depending on the extent of lumbosacral nerve root involvement, patients may also experience sensorimotor deficits in the lower extremities. A structural explanation is almost always present (disc herniation and vertebral facture among others), but less commonly, nonstructural etiologies are found, including vascular, infectious, and inflammatory diseases.[10,11] Neurosarcoidosis has only rarely been described as a potential cause of cauda equina syndrome, most often in single case reports or small series.[12-15]

In this retrospective cohort analysis, we review the clinical features, diagnostic testing results, treatment strategies, and long-term outcomes of 14 patients with neurosarcoidosis involving the cauda equina. We attempt to clarify the following points: (1) the frequency with which neurosarcoidosis affects the cauda equina; (2) the correlation between radiographic abnormalities of the cauda equina and symptoms suggestive of the syndrome; (3) its clinical course and responsiveness to treatment; and (4) final neurologic sequelae.

Methods

Patient Identification and Selection

Patients with a diagnosis of sarcoidosis seen by a provider affiliated with the Department of Neurology at Emory University (outpatient and inpatient units) in the last 10 years (January 1, 2011–December 8, 2021) were identified for possible inclusion. All patients were retrospectively reviewed for the possibility of cauda equina involvement and were included if disease of the cauda equina could be substantiated by contrasted lumbar spine MRI or EMG and nerve conduction studies (NCSs). Patients without a final diagnosis of neurosarcoidosis were excluded. All ranges of diagnostic certainty (definite, probable, and possible) were included as defined by the 2018 Criteria of the Neurosarcoidosis Consortium Consensus Group, but patients with a possible level of diagnostic certainty (those lacking neural or extraneural pathologic confirmation of sarcoidosis) were required to otherwise exhibit typical clinical, radiographic, and treatment responses observed for neurosarcoidosis.[16]

Data Extraction and Analysis

At least 2 neurologists reviewed each patient's data (G.A.B., R.G.-S., and S.K.H.), including 1 with neuromuscular expertise (R.G.-S.) and 1 with neuroimmunology expertise (S.K.H.). Primary data sources included outpatient neurology and rheumatology clinic notes, inpatient neurology consultations, ancillary testing results and reports (serum and CSF investigations, MRI, EMG/NCS), and records received from outside our hospital system. Extracted data were stored in a central coded database. Continuous variables were expressed as medians and ranges. Categorical variables were denoted by percentages or proportions. In situations of missing data, the denominator for proportions was reduced. Microsoft Excel was used to perform calculations.

Definitions and Classifications

Clinical improvement was defined as complete (return to premorbid neurologic baseline with no sequelae of cauda equina disease), partial (if any improvement in symptoms or neurologic signs were detectable above cauda equina disease nadir), stable (no change in neurologic symptoms or signs), or worsened (further neurologic deterioration beyond the initial presentation to Emory despite treatment). Modified Rankin Scale (mRS) scores were calculated retrospectively at disease nadir and again at the time of last available clinical follow-up. Clinical symptoms were attributed predominately to disease of the cauda equina if (1) the patient's presentation was consistent with such (asymmetric findings, weakness, sensory loss, pain, and dysautonomia referable to the lumbosacral nerve roots); (2) neuroimaging did not suggest a potential alternative explanation; and (3) the majority of patient disability was due to symptoms of cauda equina disease. In the setting of comorbid myelitis as determined by spinal cord MRI, particular emphasis was placed on examination findings that could not be attributable to the chronic phase of spinal cord disease, including hyporeflexia, dermatomal patterns of sensory loss, and radicular pain. Patient presentations were classified as being secondary to 2 clinicoradiographic phenotypes (codominant phenotypes) if another phenotype was present and reasonably capable of substantially contributing to the patient's presentation.

Standard Protocol Approvals, Registrations, and Patient Consents

The Institutional Review Board of Emory University approved this retrospective cohort analysis and granted a complete waiver of consent.

Data Availability

Subject to ethics board approval, deidentified data will be made available to qualified investigators on request.

Results

Patient Characteristics

During the period of January 1, 2011–December 8, 2021, a total of 216 patients were diagnosed with neurosarcoidosis at Emory, of which 14 patients (6.5%) were confirmed to have involvement of the cauda equina. Neurosarcoidosis was diagnosed concurrently with systemic sarcoidosis in 10/14 (71.4%) cases and subsequent to it in 1 case (7.1%). Neurosarcoidosis was isolated in 3 cases (21.4%), 1 of which was biopsy proven by dural biopsy. The other 2 cases had typical clinical manifestations of neurosarcoidosis (leptomeningitis and myelitis), an inflammatory CSF profile, and responded appropriately to typical immunomodulatory treatments used for sarcoidosis (glucocorticoids and methotrexate). As per the 2018 consensus diagnostic criteria, 2 patients (2/14, 14.3%) were classified as having definite neurosarcoidosis (confirmed by neural biopsy), 8 patients (8/14, 57.1%) as probable neurosarcoidosis (established by extraneural biopsy), and 4 patients (4/14, 28.6%) as possible neurosarcoidosis (pathology not obtained).

The median age of onset was 49.5 years (range 40–60 years), and cauda equina involvement was an inaugural feature of neurosarcoidosis in 13/14 cases (92.9%). In the remaining case, it began 3 years after neurosarcoidosis was originally diagnosed following biopsy of a dural-based mass at the cervicomedullary junction. The majority were female (12/14, 85.7%) and African American (9/14, 64.3%). Lymphadenopathy, particularly hilar and mediastinal, was the most common extraneural manifestation of sarcoidosis (9/14, 64.3%), but pulmonary (7/14, 50%) and bone (4/14, 28.6%) disease were also common. Other diagnostic and general features of sarcoidosis for the cohort are detailed in Table 1.

Clinical Presentation

Specifics regarding clinical presentation are outlined in Table 2. Chronic presentations (>28 days) were most common (11/14, 78.6%). Symptoms were usually asymmetric (11/14, 78.6%), and lower extremity numbness (12/14, 85.7%) and weakness (9/14, 64.3%), perineal numbness (5/14, 35.7%), pain (6/14, 42.3%), incontinence (4/14, 28.6%), and erectile dysfunction (1/14, 7.1%) were the most common presenting symptoms and signs. True cauda equina syndrome (as opposed to incidental radiographic involvement) was present in 13/14 patients (92.9%). Cauda equina syndrome was the predominant neurosarcoidosis phenotype forcing patient presentation in 8/14 cases (57.1%), but it was a co-dominant phenotype in 4 other cases who also had optic neuritis (1), myelitis (2), and multiple cranial neuropathies (1). In 1 case, myelitis was the primary symptom generator, and in another, involvement of the cauda equina was felt to be incidental to hydrocephalus. The median nadir mRS score was 3 (range 2–4).

Radiographic Findings

Ancillary testing is detailed in Table 3. Most patients (12/14, 85.7%) underwent MRI of the lumbar spine with and without contrast as the initial preferred imaging. Two patients underwent a noncontrasted examination first, which was followed by contrasted examinations later (2 weeks and 6 months in those 2 cases). The median delay to imaging confirming disease of the cauda equina was 2 months (range 0–23 months). Characteristic features on contrasted MRI of the lumbar spine included enhancement (14/14, 100%),

Table 1 General Features of Sarcoidosis in 14 Patients With Involvement of the Cauda Equina

General sarcoidosis overview	
Diagnostic classification per 2018 consensus diagnostic criteria,[16] n (%)	
Possible	4/14 (28.6)
Probable	8/14 (57.1)
Definite	2/14 (14.3)
Biopsy sites, n (%)	
Hilar or mediastinal	6/10 (60)
Abdominal lymph node	1/10 (10)
Brain parenchyma	1/10 (10)
Cutaneous	1/10 (10)
Dural	1/10 (10)
Extraneural sites, n (%)	
LAD, hilar or mediastinal	9/14 (64.3)
Pulmonary	7/14 (50)
LAD, other	6/14 (42.9)
Bone	4/14 (28.6)
Bone marrow	2/14 (14.3)
Cutaneous	1/14 (7.14)
Hepatic	1/14 (7.14)
Spleen	1/14 (7.14)

Abbreviation: LAD = lymphadenopathy.
A reduction in the denominator from 14 reflects a lack of data for a particular variable. Diagnostic confidence is graded by the 2018 criteria of the Neurosarcoidosis Consortium Consensus Group.[16]

Table 2 Presenting Clinical Features of the Cauda Equina Cohort

Clinical presentation of sarcoid cauda equina syndrome	
Onset acuity, n (%)	
Hyperacute (<1 d)	0 (0.0)
Acute (2–7 d)	2 (14.3)
Subacute (7–28 d)	1 (7.1)
Chronic (>28 d)	11 (78.6)
Cauda equina symptoms and signs	
Nadir mRS score, median (range)	3 (2–4)
Symptoms isolated to cauda equina, n (%)	4 (28.6)
Symmetry, n (%)	
Symmetric	3 (21.4)
Asymmetric	11 (78.6)
Numbness	12 (85.7)
Leg	12 (85.7)
Perineal	5 (35.7)
Weakness	9 (64.3)
Pain	6 (42.9)
Low back	5 (35.7)
Radicular	4 (28.6)
Dysautonomia	3 (21.4)
Urinary incontinence	4 (28.6)
Fecal incontinence	2 (14.3)
Erectile dysfunction	1 (7.1)
Clinicoradiographic phenotypes	
Dominant, n (%)	
Cauda equina syndrome	8 (57.1)
Hydrocephalus	1 (7.1)
Myelitis	1 (7.1)
Codominant with CES, n (%)	
Myelitis	2 (14.3)
Multiple cranial neuropathies	1 (7.1)
Optic neuritis	1 (7.1)

Abbreviations: CES = cauda equina syndrome; mRS = modified Rankin Scale.

nodularity of the spinal nerve roots (11/14, 78.6%), and diffuse involvement of the cauda equina (10/14, 71.4%). A leptomeningeal pattern was seen in all cases, with 3 (3/14, 21.4%) cases also exhibiting a simultaneous pachymeningeal pattern. Six patients (6/14, 42.9%) had coexisting spinal cord parenchymal disease (myelitis) with the following spinal cord segments involved: cervical (4), thoracic (5), and conus medullaris (4). Lymphadenopathy was uncommonly seen on lumbar spine MRI (3/14, 21.4%), but when found, widespread lymphadenopathy was eventually discovered (including hilar/mediastinal lymphadenopathy) and led to positive lymph node biopsies revealing noncaseating granulomas in all 3. Abnormal fluorodeoxyglucose uptake in the cauda equina was seen in 1/5 cases (20%) on whom PET-CT was performed.

Cranial MRI was abnormal in 12/14 (85.7%). Common findings included a leptomeningeal pattern (10/14, 71.4%) and cranial nerve involvement (8/14, 57.1%). The optic (5/14, 35.7%) and trigeminal (5/14, 35.7%) nerves were most frequently affected among the cranial nerves. Of the 8 patients with evidence of cranial nerve involvement on MRI, 5 (5/8, 62.5%) were clinically symptomatic, including 4 patients with optic neuropathy and 1 patient with trigeminal neuropathy. Cerebral parenchymal disease was seen only in 3/14 cases (21.4%).

Electrodiagnostic Findings

Of the 14 included patients, only 3 had electrodiagnostic studies. One showed evidence of a mild right-sided S1 radiculopathy without any evidence of a polyneuropathy. The other 2 patients had normal electrodiagnostic studies. None of the studies evaluated both lower extremities, so asymmetry could not be determined. All 3 of these patients underwent MRI of the spinal cord parenchyma at the time of suspected cauda equina syndrome, and all 3 patients' MRIs were negative for coexisting myelitis.

Serum and CSF Investigations

The serum angiotensin-converting enzyme (ACE) level was high in 5/13 patients (38.5%), all of whom had either pulmonary nodules or hilar/mediastinal lymphadenopathy. Hypercalcemia was found only in 1/13 cases (7.7%). The erythrocyte sedimentation rate was abnormally high (26–63 mm/h) in 8/11 patients tested (72.7%) and was low grade (<40 mm/h) in 6/8 (75%). C-reactive protein was abnormal in only 3/9 (33.3%, range 17.3–175.5 mg/L).

CSF was abnormal in 13/14 cases (92.9%), including pleocytosis in 13/14 (92.9%, median 27 white blood cells/mm^3, range 0–172), elevated protein in 13/14 (92.9%), and hypoglycorrhachia in 7/13 (53.8%). CSF-restricted oligoclonal bands (OCBs) were found in 4/5 (80%) cases tested for it, but testing for OCBs was either not performed or not reported in the remaining 9 cases. The CSF immunoglobulin (Ig) G index was elevated in 4/8 cases (50%). In the 4 cases with CSF-restricted OCBs, the IgG index was elevated in 2/4 (50%). CSF ACE levels were negative in all 6 cases for which testing was performed.

Treatment

All patients received corticosteroids as a component of first-line therapy, including 9/14 (64.3%) initially managed with

Table 3 Results of Ancillary Testing (MRI, Electrodiagnostic Studies, Serum, and CSF) in the Cauda Equina Cohort

Ancillary testing results	
Lumbar spine MRI findings, n (%)	
Abnormal, any capacity	14/14 (100)
Cauda equina enhancement	14/14 (100)
Cauda equina nodularity	11/14 (78.6)
Diffuse root involvement	10/14 (71.4)
Leptomeningitis	14/14 (100)
Pachymeningitis	3/14 (21.4)
Lymphadenopathy	3/14 (21.4)
Cervicothoracic spine MRI findings, n (%)	
Abnormal, any capacity	6/14 (42.9)
Cervical myelitis	4/14 (28.6)
Thoracic myelitis	5/14 (35.7)
Conus medullaris	4/14 (28.6)
Cranial structures involved by MRI, n (%)	
Abnormal, any capacity	12/14 (85.7)
Meninges	10/14 (71.4)
Leptomeninges	10/14 (71.4)
Pachymeninges	2/14 (14.3)
Optic nerve/chiasm	5/14 (35.7)
Other cranial nerves	5/14 (35.7)
Brainstem	2/14 (14.3)
Cerebral parenchyma	2/14 (14.3)
Hypothalamus	1/14 (7.1)
Pituitary gland and stalk	1/14 (7.1)
Electrodiagnostic findings, n (%)	
Sural present	3/14 (21.4)
Motor amplitude normal	3/3 (100)
Motor amplitude absent	0/3 (0)
Conduction velocity slowing	0/3 (0)
1–2 root levels involved	1/3 (33.3)
3–4 root levels involved	0/3 (0)
>4 root levels involved	0/3 (0)
Serum (elevated), n (%)	
ACE	5/13 (38.5)
Calcium (nonionized)	1/13 (7.7)
ESR	8/11 (72.7)
CRP	3/9 (33.3)
CSF, n (%)	
Pleocytosis	13/14 (92.9)
Elevated protein	11/14 (78.6)
Hypoglycorrhachia	7/13 (53.8)
Oligoclonal bands	4/5 (80)
IgG index, elevated	4/8 (50)
ACE, elevated	0/6 (0)

Abbreviations: ACE = angiotensin-converting enzyme; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; IgG = immunoglobulin G. Abnormalities for serum refer to elevations in the values of the variables listed.

IV methylprednisolone (for 3–5 days) followed by high-dose prednisone tapers (typically beginning at 60 mg daily). Most of these patients (11/14, 78.6%) required second-line treatment with corticosteroid-sparing agents. Of the remaining 3, two required a repeat course of corticosteroid treatment following recurrence after tapering of the initial round of prednisone. The outcome of the third patient was unknown on account of lack of follow-up.

Specifics regarding corticosteroid-sparing immunosuppressants are displayed in Table 4. Methotrexate, alone or in combination, was the most commonly used noncorticosteroid immunotherapy (used in 9 cases total). Combination methotrexate and infliximab led to improvement in 3/4 (75%) patients. Four patients were treated with methotrexate monotherapy, resulting in improvement in 3 cases and stabilization in one other. Azathioprine monotherapy was successful in the single case in which it was used. All other rounds of immunotherapy failed: one each of adalimumab, cyclophosphamide, and combination rituximab and methotrexate. Mycophenolate mofetil was tried in 1 patient, but the outcome was unknown. The 1 patient (definite diagnosis of neurosarcoidosis via dural biopsy, inflammatory CSF profile with hypoglycorrhachia) who failed combination methotrexate and infliximab also failed adalimumab and cyclophosphamide.

Outcomes

The median clinical follow-up duration was 22.5 months (interquartile range: 14.8–56.8 months, full range: range 0–295 months), and 2 patients were lost to follow-up. The final median mRS score at the last clinic follow-up visit was 3 (range 1–4). Weakness (9/14, 64.3%), ambulatory difficulties (8/14, 57.1%), numbness (7/14, 50%), and bladder disturbances (7/14, 50%) were the most common persistent neurologic sequelae. Per provider clinical perceptions at the last available clinical encounter, no patients experienced complete

Table 4 Known Outcomes Related to Corticosteroid-Sparing Treatments

Treatment and outcomes					
Treatment	**Total**	**Improved**	**Stabilized**	**Failed**	**Final mRS score**
Adalimumab	1	0	0	1	4
Azathioprine	1	1	0	0	1
Cyclophosphamide	1	0	0	1	4
Methotrexate monotherapy	4	3	1	0	2.5
Methotrexate/infliximab	4	3	0	1	2.5
Methotrexate/rituximab	1	0	0	1	3

Abbreviation: mRS = modified Rankin Scale.
The 1 patient treated with mycophenolate mofetil was not included in this table because of the outcome being unknown.

improvement, 9/14 (64.3%) partially improved, 2/14 (14.3%) stabilized, and 3/14 (21.4%) worsened. No patients died. Relapses of cauda equina disease were seen in 3 cases (3/14, 21.4%) at a median of 6 months. All relapses occurred in the setting of tapering prednisone; only 1 case was treated with another immunosuppressant (rituximab) at the time of the prednisone taper.

Median radiographic follow-up with MRI was 11 months (range 0–256 months). Of the 9 patients with available follow-up MRI data, at the time of last MRI, inflammation resolved in 5 cases (5/9, 55.6%), improved in 1 (1/9, 11.1%), stabilized in 1 (1/9, 11.1%), and worsened in 2 (2/9, 22.2%). Median duration to radiographic improvement or resolution was 10.5 months.

MRI outcomes generally correlated with clinical outcomes. In the 5 patients experiencing radiographic resolution of inflammation, 4 partially improved clinically, and 1 remained stable. One patient with partial improvement on MRI also partially improved clinically. One patient with stable MRI findings remained stable clinically. Both patients with worsening disease on MRI also worsened clinically.

Discussion

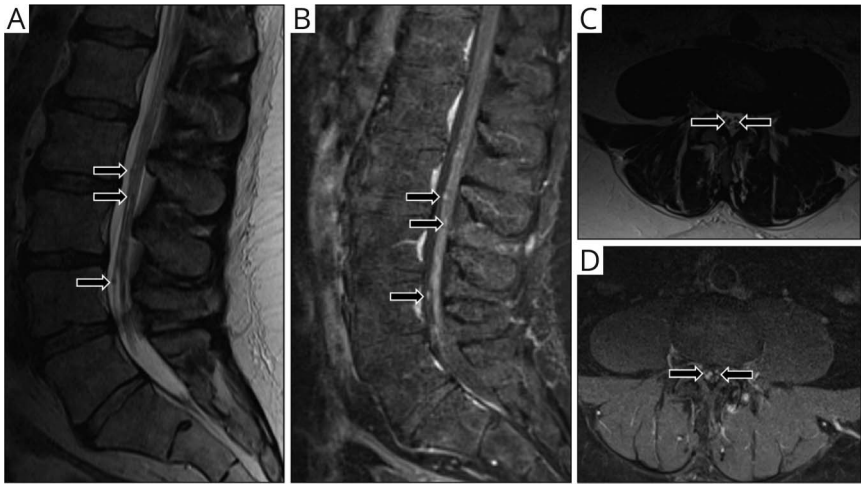
In this single-center retrospective analysis, we review the presenting clinical features, radiographic and electrodiagnostic findings, serum and CSF abnormalities, treatments, and outcomes of 14 patients with neurosarcoidosis phenotypically expressed as disease of the cauda equina. Major findings include cauda equina involvement being (1) an uncommon occurrence as a clinicoradiographic phenotype of neurosarcoidosis; (2) more common in those of female sex; (3) a primary driver of patients' clinical presentations as opposed to an incidental radiographic abnormality; (4) its responsiveness to methotrexate, either alone or in combination with infliximab; and (5) a potentially poor prognostic factor for future recovery.

Our results showed a striking female predominance (6 females: 1 male, 85.7% female) for this particular form of neurosarcoidosis, almost equivalent to that seen in aquaporin-4–positive neuromyelitis optica.[17] This is in stark contrast to recent cohorts of general neurosarcoidosis, where females constitute 52%–63% of cases.[18-20] Males usually comprise a greater share of patients with neurosarcoidosis with myelitis (53%–60%), but female predominance in neurosarcoidosis of the cauda equina was evident despite myelitis being a coexisting component of the disease spectrum in 42.9% of our cases.[21-23]

In our cohort, all patients had spinal leptomeningitis, and a majority also had intracranial leptomeningitis (71.4%). Widespread leptomeningeal disease is a common finding in neurosarcoidosis and often one of the more suggestive features for diagnosis when present.[5,7] Despite the widespread nature of radiographic leptomeningeal disease in our patients, symptomatic cauda equina syndrome was present in almost all (92.9%), and it was the dominant clinical phenotype in over half (57.1%) in addition to being a codominant phenotype in a significant minority (28.6%). By comparison, in the 8 patients with cranial leptomeningitis with radiographic involvement of cranial nerves, only 5 (5/8, 62.5%) experienced a clinical correlate to the MRI findings with the optic nerve being most predisposed to expressing symptoms. These findings suggest that cauda equina involvement in leptomeningeal neurosarcoidosis is a particularly important driver of clinical symptoms even in the presence of widespread disease, and they highlight the importance of conducting full neuraxis imaging to fully understand the extent of a patient's disease.

Cauda equina involvement offers an interesting perspective on the CSF changes that occur in neurosarcoidosis as CSF is collected proximate to regions of high inflammation. We found our cohort to express an inflammatory CSF profile in almost all cases, including findings of pleocytosis in 92.9%, elevated protein in 92.9%, and hypoglycorrhachia in 53.8%.

Figure 1 Nodular Enhancement of the Cauda Equina Affected by Neurosarcoidosis



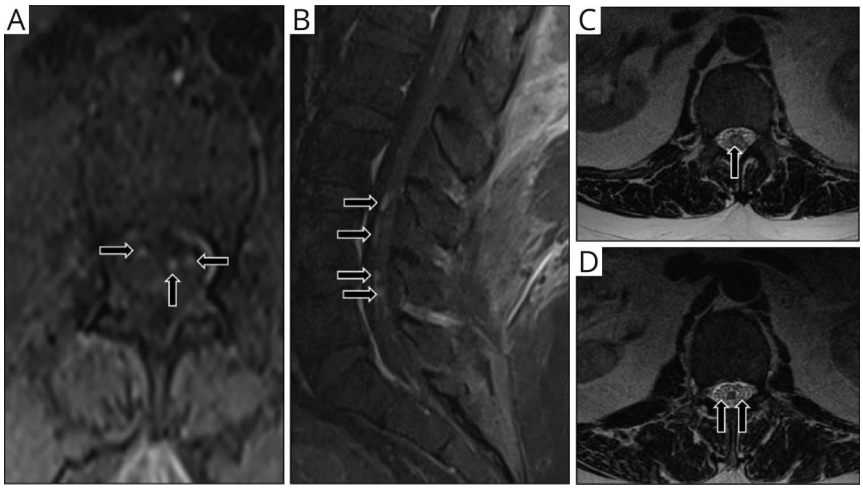
T2-weighted (A) and T1-weighted postcontrast (B) sagittal images of the lumbar spine demonstrating multiple T2 hyperintense enhancing nodules along the cauda equina nerve roots. Corresponding T2-weighted (C) and T1-weighted postcontrast (D) axial images of the lumbar spine again demonstrating multifocal nodular thickening of the cauda equina nerve roots with associated enhancement. Arrows indicate the finding of interest within each subpanel.

These abnormalities are more frequent than in generalized neurosarcoidosis cohorts, but similar to the CSF profile of patients with diffuse leptomeningeal disease.[5,19,20,24] Despite direct sampling of inflammation, CSF ACE levels were normal in all 6 patients tested, adding further credence to the low utility of this test for the diagnosis of neurosarcoidosis.[25]

The most pertinent MRI finding was a nodular pattern of cauda equina enhancement, an example of which can be seen in Figure 1. Coexisting myelitis (including of the conus medullaris as demonstrated in Figure 2) and lymphadenopathy were additional radiographic clues that contributed to the diagnostic evaluation that eventually established the diagnosis of neurosarcoidosis. Electrodiagnostic studies were conducted in 3 patients, but only 1 showed evidence of radiculopathy. This suggests that electrodiagnostic studies are not as sensitive as MRI and should not be used to rule out a diagnosis if cauda equina is suggested clinically. Electrodiagnostic studies can be considered in patients unable to have MRI or when spinal fluid evaluation is not conclusive.

Corticosteroids were the initial treatment choice in all of our patients, but they were rarely adequate for long-term management. Even in those who ultimately did well with corticosteroids (only 2 patients with adequate follow-up), a repeat course was required to stabilize their disease. Methotrexate monotherapy and combination methotrexate and infliximab were the 2 most common corticosteroid-sparing regimens used in our cohort. Although our patient numbers are too few for statistical comparison, the final median mRS score for

Figure 2 Leptomeningitis and Conus Medullaris Involvement Accompanying Neurosarcoidosis Affecting the Cauda Equina



Axial (A) and sagittal (B) T1-weighted postcontrast images of the lumbar spine demonstrating patchy leptomeningeal enhancement of the cauda equina nerve roots. Axial T2-weighted images of the lumbar spine demonstrating abnormal high T2-signal in the conus medullaris (C) and diffuse thickening of the cauda equina nerve roots, filling the thecal sac (D). Arrows indicate the finding of interest within each subpanel.

patients treated with either of these methotrexate-based regimens was 2.5, which was better than that of those not treated with these regimens (median mRS score of 3.5). Although these findings may suggest the potential for methotrexate to be a reasonable first step in corticosteroid-sparing treatment for cauda equina disease in neurosarcoidosis, the authors would like to emphasize that treatment decisions were highly individualized in this limited series with numerous factors taken into consideration in the process of management decision-making.

Disease of the cauda equina was associated with significant residual deficits despite standard treatments used for neurosarcoidosis and despite improvement in radiographic abnormalities in most patients. The presenting median nadir mRS score of the cohort was 3, and by the time of last clinic follow-up over a median of 22.5 months, it was unchanged. Sequelae were significant, particularly with respect to persistent difficulties in ambulation and urination. In most neuroinflammatory syndromes, early treatment is believed to offer the best hope for functional recovery, and we suspect that the significant delay in presentation of our cohort likely played a major role in the development of persistent injury to the cauda equina nerve roots as most presentations were chronic and imaging confirmation of cauda equina disease occurred in a delayed fashion at a median of 2 months. Cauda equina recovery after injury by other mechanisms has also been reported to be largely incomplete with significant residual disability.[9]

The potential causes of cauda equina syndrome are myriad, but structural etiologies constitute the largest share of cases.[8] The main clinical factors differentiating neurosarcoidosis from its more common structural counterparts were a slower pace of onset and a lower proportion of patients with prominent autonomic symptoms. In 1 prior literature review defining the clinical presentation of cauda equina syndrome, bladder (74% of patients) and bowel (57%) dysfunction were especially commonplace, whereas they were less frequently observed in our series (28.6% and 14.3%, respectively).[8] Otherwise, our patients had similar rates of pain, weakness, and sensory loss as have been previously reported for other causes of cauda equina syndrome.[8] An acute onset, especially after trauma, suggests disc pathology or hematoma formation. However, a more chronic presentation, as was often the case in our series on neurosarcoidosis, would suggest more insidious causes. A thorough history and examination are important to develop a differential diagnosis once surgical and infectious causes are ruled out.[8] Furthermore, inflammation of the cauda equina is difficult to visualize without contrast administration for MRI (as is the standard initial imaging approach to cauda equina syndrome), so these important differences highlight the utility of obtaining MRIs with contrast in patients presenting with symptoms developing over a protracted course, including in those with atypical presentations lacking autonomic symptoms.

In comparison to prior smaller reports, we believe that our approach in presenting all of the known cases of neurosarcoidosis involving the cauda equina within our institution limits the impact of publication bias in our cohort. In view of the retrospective nature of this report, all patients with neurosarcoidosis were not systematically evaluated to definitively determine the presence or absence of cauda equina disease, which limits our ability to fully understand the scope of this particular phenotype in general neurosarcoidosis cohorts. The small nature of our cohort also prevents us from drawing definitive conclusions about the best approach to management for these patients. Approximately one-fourth of our patients were assigned a diagnostic certainty level of possible as per the 2018 consensus diagnostic criteria, meaning sarcoidosis was unconfirmed by neural or extraneural pathology.[16] As noted in the Methods section, we were especially selective in incorporating this group by ensuring that their clinicoradiographic profiles and responses to treatment were typical for neurosarcoidosis. Although their inclusion does have the potential to temper conclusions in this report, we examined the impact of removing this group's effect on major conclusions in the paper, and no significant differences were found (data provided in eTable 1, links.lww.com/NXI/A716). In the future, given the limited published information on this phenotype of neurosarcoidosis and its rarity, it will be important to expand the literature on this topic with experience from other groups. Multicenter collaborative efforts would likely offer the most comprehensive way of accomplishing this, as has been demonstrated in other areas of neurosarcoidosis research.[26,27]

Neurosarcoidosis of the cauda equina is an uncommon but distinct clinicoradiographic phenotype of the disease given its robust inflammatory CSF profile, the presence of nodular enhancement of cauda equina nerve roots on MRI, its nonsustained response to corticosteroids, and the tendency for it to produce significant long-term disability. Optimal treatment regimens remain unclear, but methotrexate- and infliximab-based strategies resulted in the best outcomes in our cohort.

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Appendix *(continued)*

Name	Location	Contribution
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Spencer K. Hutto, MD	Emory University School of Medicine, Atlanta, GA	Designed and conceptualized the study; major role in the acquisition of data; analyzed the data; drafted the manuscript for intellectual content; study supervision; creation of tables

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