Neurosarcoidosis

Elyse E. Lower, MD a,*, Kenneth L. Weiss, MD b

aInterstitial Lung Disease and Sarcoidosis Center, University of Cincinnati Medical Center, 3235 Eden Avenue, Cincinnati, OH 45267, USA
bUniversity of Cincinnati Medical Center, 3235 Eden Avenue, Cincinnati, OH 45267, USA

Although neurosarcoidosis is a less common manifestation of sarcoidosis, its symptoms can be devastating and occasionally life-threatening. The diagnosis of neurosarcoidosis can be challenging because the disease can present with a myriad of symptoms and diverse roentgenographic findings [1–5]. Although neurologic complications of sarcoidosis are reported in 5% to 10% of patients who have known sarcoidosis [6–8], a prospective series identified neurologic complications in 32 of 123 (26%) patients who had sarcoidosis [9]. In addition, the prospective epidemiologic study of 736 newly diagnosed patients who had sarcoidosis in the United States (ACCESS) identified 34 (4.6%) who had definite or probable neurosarcoidosis [10]. Autopsy studies confirm more neurologic involvement than antemortem reports. Neurosarcoidosis can provide a diagnostic dilemma, particularly for patients who do not carry a known diagnosis of sarcoidosis [2]. This entity is a diagnostic consideration for any patient who has known sarcoidosis who presents with symptoms related to the central or peripheral nervous systems. It is also a diagnostic consideration for patients who do not have confirmed sarcoidosis but who have neurologic symptoms suggestive of neurosarcoidosis. Most patients who have neurosarcoidosis have findings suggestive of multisystem disease, particularly lung and cardiac involvement. Approximately half of patients who have neurosarcoidosis experience neurologic symptoms at the time of the initial sarcoidosis diagnosis [3,11,12].

Neurologic manifestations

Because the granulomas of sarcoidosis can affect virtually any part of the central or peripheral nervous system, patients may present to a variety of health care professionals, including primary care specialists, ophthalmologists, neurologists, otolaryngologists, endocrinologists, infectious disease experts, oncoologists, or pulmonologists. Cranial neuropathies are identified in 50% to 75% of patients who have neurosarcoidosis, with facial palsy reported in 25% to 50% [2,13–16]. Diplopia, impaired visual acuity, pain, and facial palsy are frequent initial complaints. One series identified optic nerve involvement as the most frequent cranial nerve involved [17]. Meningeal disease, including aseptic meningitis and mass lesions, is seen in 10% to 20% of patients [18,19], and hydrocephalus is identified in 10% [2,20]. Patients who have meningeal disease typically present with symptoms of meningitis, including headache and neck stiffness. Approximately 50% of patients who have neurosarcoidosis experience parenchymal brain disease, which can involve endocrinopathies (10%–15%) [21], mass lesions (5%–10%) [22,23], encephalopathy (5%–10%) [24], psychiatric symptoms (19%), and seizures (5%–10%) [3,8]. Psychosis has been the presenting feature of neurosarcoidosis with diffuse meningeal and hypothalamic disease [25–28]. Seizures may be the presenting symptom of patients who have neurosarcoidosis. In the past, seizures were considered a poor prognostic indicator associated with higher mortality perhaps due to the association of seizures with hydrocephalus or mass lesions [8]. More recent series do not confirm this association, suggesting that contemporary cytotoxic therapies may improve prognosis [16,29].

Because the base of the brain is frequently abnormal in neurosarcoidosis, patients may present with evidence of pituitary or hypothalamic dysfunction (Fig. 1) [21,30].
endocrinologic symptoms can include galactorrhea or altered menses, libido, or potency [31]. Altered sleep, body temperature, and appetite may be reported. Excessive thirst may be a symptom of diabetes insipidus [32], altered calcium levels, or diabetes mellitus. Hypothalamic hypothyroidism may develop, creating increased fatigue and changes in weight, hair, and skin [33,34].

Previous data suggest that spinal cord involvement occurs in less than 5% of patients who have sarcoidosis and in less than 10% of patients who have neurosarcoidosis [3,35–37]. Newer studies using magnetic resonance (MR) imaging criteria suggest that spinal cord involvement may be more prevalent than previously reported. Spinal cord involvement may be the initial presentation of sarcoidosis. In a study by Bradley and colleagues [38], only 4 of 17 patients who had spinal cord sarcoidosis were previously diagnosed with sarcoidosis before spinal cord involvement. Patients who have spinal cord sarcoidosis frequently present with insidious, progressive, but nonspecific paresthesias and weakness that can progress to paraplegia [39]. Many patients may experience progressive debilitating symptoms for months before diagnosis. In a recent report, 5 of 17 patients developed paraplegia before a confirmed diagnosis [38]. Compared with spinal cord compression associated with malignancy, patients who have spinal cord sarcoidosis are less likely to experience back pain [38]. Studies suggest that the granulomas of sarcoidosis may have an affinity for the cervical level with extension over multiple cord segments [40–42]. Most clinically apparent spinal sarcoid lesions are intramedullary [43,44], with rare cases reported of intradural extramedullary [45] or cauda equina lesions [46–50]. Schaller and colleagues [51] suggest that intradural extramedullary disease may represent early stage spinal sarcoidosis. Unlike intramedullary disease, extramedullary sarcoid lesions can be surgically excised with favorable results.

Audiovestibular dysfunction is a rare neurologic complication of sarcoidosis. Hearing loss is usually sensorineural, bilateral, and asymmetric. Vestibular impairment is frequently encountered and usually associated with abnormal vestibular testing. A review of 48 case reports concluded that the manifestations are the result of vestibulocochlear nerve neuropathy [52].
Approximately 15% of patients experience a variety of peripheral neuropathy manifestations, including axonal, sensory, motor, mononeuropathy, mononeuropathy multiplex, demyelinating, and Gullain-Barre syndrome [4,53]. The pathologic process may be focal or multifocal, with virtually all levels and classes of nerve fibers being involved [54,55]. Of equal frequency is myopathy (15%), which can present as nodules, polymyositis, or atrophy [56]. Symptomatic improvement is usually noted with corticosteroids [54]. The prognosis is usually better for patients who have peripheral symptoms of paresthesias, muscle weakness, and stocking-glove numbness compared with patients who have central nervous system (CNS) symptoms.

The diverse manifestations and percentage of individual neurosarcoidosis involvement are summarized in Table 1. The range of presentations may be due to differences in ethnic background, methods of detection, or interest of the reporting physicians.

**The diagnostic dilemma of neurosarcoidosis**

Because of the diverse clinical presentations, patients are often classified as having definite, probable, or possible neurosarcoidosis based on the confirmed diagnosis of multisystem sarcoidosis, the pattern of neurologic disease, and the response to treatment. Two groups have proposed criteria for neurosarcoidosis based on the probability of neurologic involvement [17,57]. Table 2 compares the two proposals in terms of definite, probable, and possible neurosarcoidosis diagnosis. In Judson and colleagues’ [57] proposal, all patients are required to have biopsy confirmation of sarcoidosis in the nervous system or elsewhere. Consequently, patients who have known sarcoidosis with features supportive of neurosarcoidosis are considered “definite.” Zajicek and colleagues [17] assigned a “definite” neurosarcoidosis category to patients who had biopsy confirmation of neurologic involvement. This approach has been supported by others [58]. From a practical perspective, the presence of “definite” or “probable” disease categorization has been used as an indication for therapy [59].

Confirming the diagnosis of neurosarcoidosis depends on whether the symptoms develop in a patient who has known sarcoidosis or in a patient who does not have known sarcoidosis. Patients who have confirmed sarcoidosis who develop symptoms or findings suggestive of neurologic sarcoidosis should be evaluated for exclusion of other disease entities, such as cerebrovascular disease, complications of metabolic diseases such as diabetes, and malignancies. Infections can be a consequence of sarcoidosis, treatment for the sarcoidosis [60], or other conditions. Fig. 2 reveals the MR image of a patient followed at our clinic for pulmonary and cutaneous sarcoidosis. This patient had discontinued systemic therapy for more than 5 years when she presented with ataxia, and the MR imaging revealed a cerebellar lesion (Fig. 2). Because of the atypical presentation after many years off therapy, a biopsy was performed, which revealed toxoplasmosis. The patient was confirmed to be infected with HIV.

Clinicians can be challenged to diagnose neurosarcoidosis in patients who have suggestive neurologic findings but have no confirmed diagnosis of sarcoidosis. An extensive differential diagnosis includes primary neurologic diseases, such as multiple sclerosis (MS) [61], lymphoma, craniopharyngioma, primary CNS neoplasmia, primary CNS infections including neurosyphilis, HIV, or toxoplasmosis, brucellosis, Whipple’s disease, and autoimmune diseases (including systemic lupus erythematosus, Sjogren syndrome, Behcet’s disease, Vogt-Koyanagi-Harada disease, lymphocytic hypophysitis, pachymeningitis, and isolated angiitis of the CNS) [2].

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**Table 1**

Summary of neurologic manifestations and reported frequency

<table>
<thead>
<tr>
<th>General class</th>
<th>Subset</th>
<th>Frequency of manifestations of neurosarcoidosis (reported range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cranial neuropathy</td>
<td>First</td>
<td>1%–10%</td>
</tr>
<tr>
<td></td>
<td>Seventh</td>
<td>25%–50%</td>
</tr>
<tr>
<td>Meningeal</td>
<td>Hydrocephalus</td>
<td>10%</td>
</tr>
<tr>
<td>Parenchymal brain lesions</td>
<td>Hypothalamic</td>
<td>10%–15%</td>
</tr>
<tr>
<td></td>
<td>Mass lesions</td>
<td>5%–10%</td>
</tr>
<tr>
<td>Spinal cord</td>
<td>Encephalopathy</td>
<td>5%–10%</td>
</tr>
<tr>
<td></td>
<td>Intramedullary</td>
<td>Most frequent spinal lesion</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td></td>
<td>15%</td>
</tr>
</tbody>
</table>
Because 50% of patients who have neurosarcoidosis have other systemic disease, patients should be evaluated for involvement of other organs, including lung, skin, lymph nodes, or eye. Although other clues, such as elevated serum angiotensin enzyme or serum immunoglobulins, hypercalcemia, or hypercalciuria, may suggest the diagnosis of sarcoidosis, none of these tests is confirmatory [2,4,62]. Diagnostic radiologic evaluation may include chest X ray and CT. Fig. 3 shows the chest X ray and CT scan of a patient who presented with weakness in her legs and was found to have a spinal cord lesion. Other imaging includes MR imaging, whole-body fluorodeoxyglucose positron emission tomography (PET), or gallium scan. Recently, Teirstein and colleagues [63] reported on the value of PET scan in identifying alternative areas to biopsy in patients who have possible sarcoidosis. Depending on clinical symptoms, pulmonary function tests or ophthalmologic and endoscopic nasal examinations may be rewarding.

Patients who have possible CNS sarcoidosis require a detailed examination related to

Table 2
Criteria for neurosarcoidosis

<table>
<thead>
<tr>
<th>Zajicek et al [17]</th>
<th>Judson et ala [57]</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Definite</strong></td>
<td></td>
</tr>
<tr>
<td>Clinical presentation suggestive of neurosarcoidosis with exclusion of other possible diagnoses and the presence of positive nervous system histology</td>
<td>1. Positive MR imaging with uptake in meninges or brainstem</td>
</tr>
<tr>
<td></td>
<td>2. Cerebral spinal fluid with increased lymphocytes or protein</td>
</tr>
<tr>
<td></td>
<td>3. Diabetes insipidus</td>
</tr>
<tr>
<td></td>
<td>4. Seventh cranial nerve paralysis</td>
</tr>
<tr>
<td></td>
<td>5. Positive peripheral or central nerve biopsy</td>
</tr>
<tr>
<td><strong>Probable</strong></td>
<td></td>
</tr>
<tr>
<td>Clinical syndrome suggestive of neurosarcoidosis with laboratory support for CNS inflammation (elevated levels of CSF protein or cells, the presence of oligoclonal bands or MR imaging evidence compatible with neurosarcoidosis) and exclusion of alternative diagnoses together with evidence for systemic sarcoidosis (through positive histology, including Kveim test, or at least two indirect indicators from Gallium scan, chest imaging, and serum angiotensin-converting enzyme)</td>
<td>1. Other abnormalities on MR imaging</td>
</tr>
<tr>
<td></td>
<td>2. Unexplained neuropathy</td>
</tr>
<tr>
<td></td>
<td>3. Positive electromyelogram</td>
</tr>
<tr>
<td><strong>Probable</strong></td>
<td></td>
</tr>
<tr>
<td>Clinical presentation suggestive of neurosarcoidosis with exclusion of alternative diagnoses where the above criteria are not met</td>
<td>1. Unexplained headaches</td>
</tr>
<tr>
<td></td>
<td>2. Peripheral nerve radiculopathy</td>
</tr>
</tbody>
</table>

a Only applied to patients who had biopsy-confirmed sarcoidosis.

Fig. 2. (A–C) Axial T2-weighted images through cerebellum demonstrating nonspecific, ill-defined hyperintense T2 signal right hemispheric lesion with mass effect and edema. Biopsy proved toxoplasmosis.
neuroendocrinologic or hypothalamic dysfunction. This includes tests of thyroid function and tests for diabetes mellitus, diabetes insipidus, hypercalcemia, hypercalciuria, cortisol, prolactin, estradiol or testosterone, follicular stimulating hormone, and luteinizing hormone.

Tissue confirmation of noncaseating granulomas remains the gold standard for unconfirmed cases [17]. Patients who have known sarcoidosis who develop CNS masses may be treated empirically with corticosteroids if infection and malignancy are reasonably excluded. Biopsy may be necessary for patients who fail to respond to corticosteroids. Peripheral nerve or muscle biopsy can also be obtained to confirm histology. In patients who have neuropathic symptoms and unrevealing nerve conduction and electromyographic studies, skin biopsies can be pursued.

**Diagnostic imaging**

*Magnetic resonance imaging: brain*

MR imaging with gadolinium contrast enhancement remains the preferred imaging technique for neurosarcoidosis [64]. Leptomeningeal involvement is the most commonly reported imaging abnormality because it is seen in approximately 40% of neurosarcoidosis cases. This disease pattern usually appears as thickening with diffuse or focal/multifocal enhancement of the leptomeninges on contrast-enhanced T1-weighted images (see Fig. 1). Sarcoidosis has a predilection for the basilar meninges [14]; however, involvement of the cortical sulci and perivascular space and cisterns around the base of the brain is indistinguishable from tuberculosis or lymphoma. Spread along the perivascular spaces can lead to parenchymal involvement (Fig. 4). Enhancing parenchymal lesions with contiguous meningeal enhancement on T2-weighted images may be indistinguishable from meningiomas [65]. Isolated contrast-enhanced T1-weighted images of the hypothalamus or pituitary infundibulum can mimic histiocytosis. Often these patients present with diabetes insipidus or amenorrhea.

Cranial nerve abnormalities may be associated with leptomeningeal disease, sinonasal disease, or an isolated finding. MR imaging hallmarks of cranial nerve abnormalities are enlargement and enhancement on T1-weighted contrast imaging (Fig. 5). Although facial nerve (VII) palsy is the most common cranial nerve involved clinically, the optic nerves are most commonly affected radiographically. The optic nerve and optic chiasm are best evaluated with T1-weighted images. Involvement may be bilateral or unilateral with the differential for isolated optic nerve involvement, including optic neuritis, optic nerve glioma, and optic nerve meningioma [17].

Neurosarcoidosis with dural involvement can present as diffuse thickening or focal masses (Fig. 6). These lesions typically enhance with T1-weighted imaging and are relatively hypointense.

**Fig. 3.** (A) Posterior-anterior chest X-ray demonstrating fine nodularity involving primarily mid- and lower lung fields. (B) Axial CT with lung windows demonstrating innumerable scattered 5 mm or less pulmonary nodules diffusely distributed in a subpleural, centrilobular, and perivascular distribution consistent with sarcoidosis.
Fig. 4. (A) Sagittal T2-weighted image showing enlarged empty sella. (B) Coronal postcontrast T1-weighted images demonstrating neurosarcoid involvement of the posterior medulla and diffuse leptomeningeal enhancement throughout the posterior fossa (red arrows). Co-registered axial images: (C) FLAIR, (D) T2, (E) T1, and (F) T1-weighted postcontrast images demonstrating focal parenchymal involvement of the posterior medulla (red arrows). Panel F shows diffuse leptomeningeal enhancement throughout the posterior fossa.
on T2-weighted images. Differential considerations include calcified meningiomas, lymphoma, dural metastases, and hypertrophic cranial pachymeningitis. These patients usually present with headaches and symptoms related to cranial nerve involvement [64,65].

Parenchymal lesions in neurosarcoidosis may be nonenhancing or enhancing. Some series report multiple nonenhancing periventricular white matter lesions with high signal intensity of T2-weighted images (see Fig. 4). These lesions are commonly encountered in patients who have disease other than sarcoidosis, such as MS and vascular disease. Contrast-enhancing parenchymal lesions may be mistaken for primary or metastatic tumors [14,23,66]. Although central necrosis is frequently seen in tumors, it is uncommon in sarcoidosis. Often these patients may present with seizures, and frequently tissue confirmation is necessary.

Hydrocephalus is reported in 5% to 12% of patients who have neurosarcoidosis. Communicating hydrocephalus results from altered cerebrospinal fluid (CSF) resorption secondary to dural or leptomeningeal involvement. Adhesions or loculations in the ventricular system may cause obstructive hydrocephalus. Isolation of the fourth ventricle (ie, trapped fourth ventricle) may occur. Patients who have hydrocephalus often present with ataxia and altered gait, which can be improved with ventricular shunting (Figs. 7 and 8) [67].

**Magnetic resonance imaging: spinal cord**

Sarcoidosis can affect the spine in a variety of ways, including the cord or nerve roots, the intradural-extradurally space, the intracanalicular extradural space, or the vertebral bodies and disks [38]. Although intramedullary spinal disease is rare, the devastating clinical manifestations can include paralysis and severe pain. Contrast-enhanced spinal MR imaging can appear as an enhancing enlargement, focal or diffuse enhancement, or atrophy. These imaging findings are nonspecific, and the differential diagnosis includes tumors, MS, and fungal infections. This imaging modality may aid in the diagnosis of the rare neurosarcoioid manifestation of cauda equina syndrome, which may be diagnosed as nodules, thickening, or matted nerve roots (Fig. 9).

Based on the histologic stages of the disease, Junger and colleagues [44] have proposed a MR imaging classification system for spinal sarcoidosis. In Phase 1, early inflammation is identified as contrast-imaged linear leptomeningeal enhancement. By Phase 2, secondary centripetal spread of the leptomeningeal inflammatory process occurs through Virchow spaces to the parenchyma with faint postcontrast enhancement and diffuse edema. By Phase 3, the swelling decreases, and the size of the spinal cord can be normal but associated with focal areas of enhancement, and this inflammatory process resolves into Phase 4 with normal size or atrophy of the spinal cord without enhancement. Phases 2 and 3 are more commonly reported.

**Other imaging modalities**

MR imaging may be nonspecific for sarcoidosis [64,68]. A recent study of 22 patients who had sarcoidosis with CNS symptoms revealed a diverse constellation of nonspecific MR imaging findings [69]. In 46% of these patients, the periventricular and white matter lesions identified on the T2-weighted images mimicked those seen in MS. Supratentorial and infratentorial mass lesions mimicked tumor metastases in 36%. Solitary intra-axial masses could not be differentiated from high-grade astrocytomas in 9% of patients, and solitary extra-axial masses mimicked meningiomas in 5%. MR imaging may also be negative because of small or peripheral lesions or the effect of therapy [16,17].

CT scan of the brain is less sensitive than MR imaging for neurosarcoidosis [17]. There are cases
Fig. 6. (A) Sagittal T2-weighted and coronal postcontrast T1-weighted images demonstrating thick, hypointense T2, contrast-enhancing dural enhancement along the frontal lobes and falx cerebri (red arrows). Co-registered axial (C) FLAIR, (D) T2, (E) T1-weighted, and (F) T1-weighted postcontrast images demonstrating hypointense FLAIR/T2 thickening of the dura along the frontal lobes, right greater than left, and along the falx with prominent enhancement (red arrows).
in which CT scan with contrast provides additional information. In a study of 14 patients who had CNS manifestations of neurosarcoidosis by MR imaging and CT, MR imaging detected lesions in all patients (100%) but was less accurate than CT in depicting disease in two patients. The CT detected lesions in 12 patients and was less accurate than MR imaging in delineating hypothalamic involvement in two patients and periventricular white-matter disease in three patients [70].

PET scanning with 18-F-fluorodeoxyglucose is a useful imaging modality in patients who have malignancy. Recent reports suggest that PET scanning can detect granulomatous involvement of multiple organs in sarcoidosis [63,71–73]. Alternative imaging with C-11 methionine and 18-F-fluorodeoxyglucose PET may improve localization of neurosarcoidosis [73].

A new MR imaging technique with the acronym IDEAL ASSIST (iterative decomposition of water and fat with echo asymmetric and least-squares estimation automated spine survey iterative scan technique) can provide rapid coverage of the entire spine with optimized fat–water separation (Fig. 10).

Cerebrospinal fluid analysis

Although neurosarcoidosis can be associated with an abnormal CSF analysis, no specific pattern is diagnostic [14,74]. Table 3 summarizes the CSF findings in sarcoidosis and other inflammatory disorders. In two large studies of neurosarcoidosis, increased protein, increased lymphocytes, or both were reported in 73% and 81% of patients [16,17]. Although an increased IgG index can be seen, the presence of oligoclonal bands is rare [9,75,76], with rare cases reported in patients who have neurosarcoidosis [77]. Where appropriate, cultures and special stains should be performed to exclude other granulomatous and infectious diseases, particularly tuberculosis and Cryptococcus. These diseases can also occur as complications of therapy for systemic sarcoidosis [60].

Special CSF studies, including angiotensin-converting enzyme and CD4:CD8 ratio, may be useful in detecting neurosarcoidosis in patients who have known sarcoidosis [78]. Increased CSF angiotensin-converting enzyme is relatively insensitive and nonspecific [75]. Elevated levels have been reported in approximately 50% of sarcoidosis cases and in many other diseases, including schizophrenia [76,79]. Increased CD4:CD8 ratio of CSF lymphocytes has also been noted in neurosarcoidosis [80,81]. Flow cytometry requires large numbers of viable lymphocytes, which are usually unavailable.
There are no randomized clinical trials defining the optimal treatment for neurosarcoidosis. In general, patients who have neurosarcoidosis present with a self-limited manifestation or a chronically progressive disease course [2,4,16]. Isolated cranial nerve abnormalities and aseptic meningitis are frequent monophasic presentations in two thirds of patients who have neurosarcoidosis. In particular, patients who have seventh nerve paralysis often have resolution of this symptom spontaneously or with a short course of corticosteroids.

**Treatment of neurosarcoidosis**

There are no randomized clinical trials defining the optimal treatment for neurosarcoidosis. In general, patients who have neurosarcoidosis present with a self-limited manifestation or a chronically progressive disease course [2,4,16]. Isolated cranial nerve abnormalities and aseptic meningitis are frequent monophasic presentations in two thirds of patients who have neurosarcoidosis. In particular, patients who have seventh nerve paralysis often have resolution of this symptom spontaneously or with a short course of corticosteroids.

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**Fig. 9.** (A) Coronal postcontrast T1 image of the head and upper cervical spine demonstrates small enhancing leptomeningeal nodules coating the medulla (solid red arrows) and marked circumferential dural and intradural involvement (yellow arrow) at the C1 and C2 levels severely compressing and deforming the cord (dotted red arrow). (B) Axial postcontrast T1 image at the C2 level redemonstrates marked transverse compression and flattening of the cord (dotted red arrow) by extensive intradural sarcoid involvement (yellow arrow). Sagittal midline T2 image of the cervical spine (C) redemonstrates the large relatively hypointense intradural mass (yellow arrow) markedly compressing and deforming the cord at the C1 and C2 levels. At C4–C5, there is hyperintense T2 signal intramedullary cord involvement (dotted red arrow), and at C7–T1 there is a small nodule along the dorsal cord surface (solid red arrow). Corresponding posttreatment sagittal T2 image (D) demonstrates marked regression of neurosarcoidosis with relatively mild deformity of the C1–C2 cervical cord and intramedullary increased T2 signal (dotted red arrow). The low signal ventral to the cord at this level reflects exaggerated CSF flow phenomena rather than hypointense intradural sarcoid.
Patients who have parenchymal, leptomeningeal disease with multiple cranial nerve abnormalities, myopathy, or spinal disease often experience a chronic remitting-relapsing course. As in other forms of sarcoidosis, the goal of treatment is to palliate symptoms and to prevent irreversible fibrosis in target organs [4,82]. If certain manifestations of neurosarcoidosis, such as spinal cord disease or cauda equina syndrome [38,48–50], are not diagnosed and treated early, life-threatening and devastating complications, including paraplegia, can develop.

Corticosteroids remain the mainstay of treatment for neurologic sarcoidosis. They are most useful early in treatment of the disease because they can lead to rapid reduction of the inflammation and the mass effect. Higher than usual doses of corticosteroids are often used to treat neurosarcoidosis [16,17,83,84]. One recommendation institutes daily treatment with as much as 1 mg/kg...

Fig. 10. Rapid MR imaging screening of entire spine with IDEAL (iterative decomposition of water and fat with echo asymmetric and least-squares estimation) ASSIST (automated spine survey iterative technique) performed with two contiguous 35-cm field of view sagittal stations in a patient who has neurosarcoidosis. T2-weighted water (w) image (first column) demonstrates abnormal intramedullary cervical cord signal (red arrow). T2-weighted fat (f) image depicts steroid treatment–induced epidural lipomatosis in the thoracic (short arrow) and lumbar (long arrow) spine. T1-weighted, post-contrast (+C) water(w) image (third column) demonstrates thick abnormal dural and subdural enhancement throughout entire spinal canal (dotted red arrow), albeit degraded by motion artifact. Rapid postcontrast gradient echo sequence (GRE + C) is performed with breath holding, significantly reducing motion artifact (fourth column) and demonstrates fourth ventricular enlargement (dotted yellow line) as part of the patient’s pan-hydrocephalus, atrophic upper cervical cord (straight yellow arrow) and redemonstrates thick dural and intradural enhancement throughout entire spinal canal (dotted red arrow).
of prednisone or its equivalent [84]. Usually, isolated peripheral nerve palsies or myopathy can be successfully treated with short courses of prednisone; however, prolonged therapy may be necessary. Due to the chronic remitting-relapsing nature of severe neurologic disease, including mass lesions, leptomeningeal, and spinal cord disease, patients often require high-dose, prolonged courses of therapy [85]. Corticosteroid therapy has been the usual initial treatment strategy; however, many patients require alternative treatments due to intolerance of prednisone or persistent disease activity despite corticosteroids. Table 4 summarizes four series that reported on the response rate to corticosteroid therapy alone for neurosarcoidosis [16,17,83,85]. In three of these studies, less than 40% of the patients stabilized or improved with corticosteroid therapy alone. The report by Scott and colleagues [83] selected patients for early aggressive immunosuppressive therapy if they “presented with severe central nervous system ...(intracranial lesions, hydrocephalus, myelopathy, seizures, or encephalopathy).” Of the patients selected to receive corticosteroids alone, 90% were stable or improved on this regimen. Table 4 shows the response to the use of cytotoxic agents with or without corticosteroids. The overall response rate was higher for patients treated with immunosuppressive agents than those treated with corticosteroids alone. Another study [9] of 32 patients who had neurosarcoidosis reported improvement in 16 of 19 (84%) of patients who received corticosteroids. This study included a variety of monophasic and chronic disease patients, and no immunosuppressive therapy was reported.

Because of the failure of corticosteroid therapy to control most cases of neurosarcoidosis, alternatives to corticosteroids have been sought [16,85,86]. Alternative therapies have included immunosuppressive drugs, including cyclophosphamide [16,87], methotrexate [16], azathioprine [83,85], mycophenolate mofetil [88], cyclosporine [85,89], and hydroxychloroquine [90]. None of these agents has been studied in a placebo-controlled trial in patients who have neurosarcoidosis, and there are no evidence-based guidelines for this disease process. Isolated series suggest clinical benefit when drugs such as cyclophosphamide are added to corticosteroids for the treatment of chronic neurosarcoidosis. The aggressive use of immunosuppressive agents for many cases of neurosarcoidosis seems to be supported by the data in Table 4. The cytotoxic
agents methotrexate and azathioprine have reasonable response rates in about two thirds of the patients treated [16,83]. In one study of patients who failed methotrexate, 8 of 10 responded to intermittent, intravenous cyclophosphamide [16]. Similar results have been reported with cyclophosphamide for refractory neurosarcoidosis [87,91]. In addition, alternative immunosuppressive therapies have been beneficial in spinal cord sarcoïdosis. In a small series of 14 evaluable patients who had spinal cord sarcoïdosis, all patients were initially treated with corticosteroids. Subsequently, 5 of 10 patients who were treated with methotrexate alone responded, whereas all seven patients who were treated with cyclophosphamide (including some of the methotrexate failures) responded [38].

Newer targeted agents against tumor necrosis factor–alpha, including infliximab [92–94] and thalidomide [95], may be helpful. There have been some case reports indicating the benefit of infliximab for various manifestations of neurosarcoidosis [94,96–98], with a response seen within months of starting treatment. There is a recent report of successful treatment of spinal sarcoïdosis with thalidomide [99]. As in other organ systems, careful monitoring for toxicity and side effects is mandatory (a more detailed discussion of drug therapy dosing and toxicity occurs elsewhere in this issue).

Neurosarcoidosis remains a relatively rare manifestation of the disease process without evidence-based treatment guidelines. Recommendations are based on case series and reports. The approach we use at our clinic is shown in Fig. 11. Patients are classified as “mild,” “moderate,” or “severe” based on initial presentation. Patients who have a monophasic disease, such as cranial neuropathy, alone are treated as “mild” and treated initially only with corticosteroids. Patients who have intracranial or spinal cord lesions, hydrocephalus, myelopathy, seizures, or encephalopathy are considered “moderate” or “severe” and are treated initially with an immunosuppressive agent plus prednisone [16,83]. Patients who have “severe” disease are started on cyclophosphamide or infliximab. Patients who have milder disease or who respond well to corticosteroids may be started on methotrexate. Because cytotoxic agents may require up to 6 months for maximum benefit, patients may initially receive cyclophosphamide or infliximab to shorten the time to response and minimize excessive corticosteroid toxicity. Patients who have uncontrolled disease despite initial immunosuppressive agents are candidates for cyclophosphamide or infliximab.

Table 4
Outcome of therapy for neurosarcoidosis

<table>
<thead>
<tr>
<th>First author</th>
<th>Number treated</th>
<th>Improved/stable</th>
<th>Treatment</th>
<th>Number treated</th>
<th>Improved/stable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agbogu [85]</td>
<td>26</td>
<td>38%</td>
<td>All^a</td>
<td>19</td>
<td>79%</td>
</tr>
<tr>
<td>Lower [16]</td>
<td>48</td>
<td>29%</td>
<td>Methotrexate</td>
<td>28</td>
<td>61%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Cyclophosphamide^b</td>
<td>10</td>
<td>85%</td>
</tr>
<tr>
<td>Zajidek [17]</td>
<td>34</td>
<td>29%</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Scott [83]</td>
<td>19^c</td>
<td>90%</td>
<td>All</td>
<td>26</td>
<td>85%</td>
</tr>
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^a Cytotoxic agents ± corticosteroids.
^b Only patients who failed methotrexate treatment were treated with cyclophosphamide.
^c Treated with corticosteroids only in selected patients who had mild neurosarcoidosis.

Supportive, nonsystemic treatment of neurosarcoidosis

Although aggressive systemic treatment with corticosteroids and other immunosuppressive agents remains the mainstay of treatment for neurosarcoidosis, management of neurologic complications, including hydrocephalus, seizures, and dysfunction of the pituitary-hypothalamic axis, is important. Asymptomatic or mild hydrocephalus may not require therapy; however, this condition can rapidly deteriorate [100]. In some cases, this can be reversed by aggressive corticosteroid administration and ventricular shunt placement [101]. Granulomatous inflammation may lead to shunt obstruction, and careful monitoring is necessary to detect obstruction or infection [102]. Seizures, which may complicate hydrocephalus or mass lesions, are usually successfully treated by controlling the granulomatous inflammation along with antiepileptic medication [2]. Abnormal CSF findings do not always necessitate treatment, and therapy decisions are usually determined by clinical symptoms. Patients who have pituitary and hypothalamic disease require extensive hormone evaluation and replacement. Although corticosteroids may decrease mass lesions in the
pituitary stalk or hypothalamus, polyuria secondary to diabetes insipidus can be chronic, necessitating desmopressin therapy [103]. Additional hormone replacement for hypopituitarism can include sex hormone replacement with estrogen or testosterone or thyroid replacement [21].

Surgery and radiation therapy have been advocated to ameliorate local symptoms. Because sarcoidosis remains a diagnosis of exclusion, providing tissue for diagnosis and culture is the main indication for surgery. In patients who have known sarcoidosis, additional surgical tissue may become necessary when additional diagnoses, including infection or malignancy, need to be excluded. There seems to be little role for routine complete surgical resection of granulomas. In fact, attempts to completely resect rather than debulk intramedullary lesions from sarcoidosis may worsen the prognosis [35,39,40]. Radiation therapy has been useful in limited cases, usually in the treatment of disease refractory to systemic therapies [104–107].

Painful neuropathy and myopathy may require additional treatment strategies [62]. Ipsilateral hemifacial spasms can be treated with periodic injections of botulinum toxin A [108]. After failure of standard medications, rhizotomy may effectively improve persistent trigeminal neuralgia.

Assessment of treatment response

Assessing clinical response in neurosarcoidosis can be difficult. Although treatment with corticosteroids can improve MR imaging [109], clinical responses may not correlate with roentgenographic improvement [38,110]. Studies suggest that clinical improvement is usually associated with improved MR image abnormalities, particularly contrast-enhancing lesions [85,109,111]. One case series of spinal cord sarcoidosis revealed improved MR image appearance without clinical improvement [110].

Because patients who have neurosarcoidosis may experience delayed relapses when treatment is discontinued [16], patients need to be followed for years after corticosteroids are withdrawn [112]. Because symptoms may recur before MR image changes, the clinician must be sensitive to new neurologic symptoms in a patient who has known neurosarcoidosis in whom treatment has been reduced or withdrawn.

Summary

The diagnosis and management of neurosarcoïdosis remains one of the more difficult aspects of this disease. This manifestation remains challenging because of the diverse range of clinical presentations.
prevalence, difficulties encountered in identifying neurologic lesions, and the refractory nature that can occur with the disease process. Newer treatment options provide the treating physician better options to tailor therapy to the individual patient.

References


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