Neurosarcoidosis: Clinical manifestations, diagnosis and treatment

Kenkichi Nozaki¹, Marc A. Judson²

1. Medical University of South Carolina, Department of Neurosciences, Division of Neurology, Charleston, South Carolina 29425, United States of America
2. Albany Medical College, Division of Pulmonary and Critical Care Medicine, Albany, New York 12208, United States of America

Correspondence:
Kenkichi Nozaki, Medical University of South Carolina, Neurosciences, 96, Jonathan Lucas street, suite 301 CSB, Charleston, SC 29425, USA.
nozaki@musc.edu

Summary

Sarcoidosis is an idiopathic granulomatous disease affecting multiple organs. Neurosarcoidosis, involving the central and/or peripheral nervous systems, is a relatively rare form of sarcoidosis. Its clinical manifestations include cranial neuropathies, meningitis, neuroendocrinological dysfunction, hydrocephalus, seizures, neuropsychiatric symptoms, myelopathy and neuropa-thies. The diagnosis is problematic, especially when occurring as an isolated form without other organ involvement. Distinguish- ing neurosarcoidosis from other granulomatous diseases and multiple sclerosis is especially important. Although biopsy of neural tissue is the gold standard for the diagnosis of neurosarcoidosis, this is often not practical and the diagnosis must be inferred though other tests, often coupled with biopsy of extraneural organs. Corticosteroids and other immuno-suppressants are frequently used for the treatment of neurosarcoidosis. This article reviews the epidemiology, pathogenesis, pathology, clinical features, diagnosis, diagnostic tests, diagnostic criteria, and therapy of neurosarcoidosis.
with isolated neurologic involvement [5]. Neurological involvement is recognized as an unusual but potentially life-threatening form of sarcoidosis, along with pulmonary, cardiac and renal involvement [4].

In this review, we will describe the neurological manifestations of sarcoidosis. Usually, the term “neurosarcoidosis” refers to sarcoid involvement of the brain, spinal cord and peripheral nerves and does not include muscle involvement. However, because the muscles are integrally related to the peripheral nervous system, we will review the clinical aspects of muscle sarcoidosis involvement as well.

Epidemiology

Sarcoidosis occurs throughout the world, affecting both sexes, all races, and all ages. It has predilection for adults less than 40 years of age, peaking in individuals between 20 to 29 years old. The age-adjusted annual incidence rate in the United States is estimated 35.5 per 100,000 for Blacks and 10.9 per 100,000 for Whites. Swedes, Danes and U.S. Blacks appear to have the highest prevalence rates in the world [2].

The frequency of neurosarcoidosis depends upon the method of detection. Symptomatic neurological involvement is seen in 5 to 13% of sarcoidosis [6–9]. In a prospective study of 123 patients with sarcoidosis, 32 (26%) had a diagnosis of sarcoidosis and neurological disorders [10]. However, it is likely that the true frequency of neurosarcoidosis is less than this, because many sarcoidosis patients with neurological problems do not have neurosarcoidosis. In support of this contention, a retrospective case series of 649 sarcoidosis patients, the authors found that only 45% (33/74) of those with neurological problems had neurosarcoidosis as the cause [7]. The lowest estimated prevalence of neurosarcoidosis was 1 per 100,000 from a case series in South-West England and South Wales [11]. This low prevalence may have been related to issues of detection; alternatively, the prevalence may truly be lower in this specific population. In an autopsy case series of systemic sarcoidosis, central nervous system (CNS) involvement was identified in 14% of cases [12]. Imaging evidence of CNS disease is seen in about 10% of patients with systemic disease [8,13]. It is estimated that isolated neurosarcoidosis, without clinical evidence of sarcoidosis in extraneural organs, occurs in less than 1% of sarcoidosis patients [13].

Pathogenesis

Currently, the etiology of sarcoidosis is unknown. Although several etiologies for the disease are hypothesized including infectious agents (mycobacteria, propionibacteria), and non-infectious environmental exposures [14], an abnormal immune response has been widely accepted as important. This abnormal immune response is probably partially dependent on genetic factors.

Immunologic abnormalities observed in sarcoidosis have included intra-alveolar and interstitial accumulation of CD4+ cells with helper-inducer activity, increased in situ production of type 1 helper T (Th1) cell derived cytokines, as well as production of interleukin-2 (IL-2), interferon-gamma (IFN-γ) [2], and interleukin-12 (IL-12) [15]. In sarcoidosis, production of these cytokines by mononuclear phagocytes is dysregulated [15]. These observations suggest that sarcoidosis is a Th1 mediated granulomatous disorder. According to this schema, sarcoidogenic antigens (which are presently unknown) are processed by antigen presenting cells and presented via HLA Class II molecules on their surface; the processed antigen-HLA Class II complex is then recognized and bound by receptors on CD4+ Th1-cells. IL-12, secreted by macrophages and IFN-γ secreted by CD4+ Th1 then produces a positive feedback loop that enhances the production of these Th1 cytokines [15]. In addition, alveolar macrophages produce pro-inflammatory cytokines including TNF-α [16]. These cytokines, chemokines, and other mediators recruit additional mononuclear phagocytes, T-cells, and fibroblasts to the site of inflammation. Epitheloid cells and giant cells, both of which are thought to derive from mononuclear cells, develop and aggregate to form compact granulomas [15]. Although the disease course is usually self-limiting, this granulomatous inflammation progresses to fibrosis in a subset of patients.

Pathology

The characteristic lesion of sarcoidosis is a discrete, compact, noncaseating epithelioid cell granuloma which consists of highly differentiated mononuclear phagocytes and lymphocytes. The central portion of the granuloma consists of predominantly CD4+ lymphocytes, whereas CD8+ lymphocytes are present in the peripheral zone [2]. Langhans’s type multinucleated giant cells are frequently seen. The chronic phase of the disease develops when a fibrotic response develops around the granulomas by presently unknown mechanisms [17].

CNS neurosarcoidosis is thought to develop from an initial granulomatous inflammatory meningitis. Subsequently, parenchymal
brain involvement typically occurs from extension of granulomatous inflammatory exudates from the subarachnoid space along Virchow–Robin spaces [5]. It has been suggested that CNS involvement may sometimes be a consequence of perineural spread from sinonasal sarcoidosis, particularly with a possible invasion into the hypothalamic-hypophyseal region [18–20]. In peripheral nerves, granulomas accumulate mainly in the epineurium and perineurium. Mononuclear cell accumulation is seen in the endoneurium [5]. Necrotizing vasculitis is seen in approximately 20% of nerve biopsies. Sarcoidosis nerve fiber lesions are mainly axonal related to either mechanical compression by noncaseating granulomas and/or to an ischemic process due to vasculitis [21].

**Clinical manifestations**

Neurological symptoms are the initial clinical manifestation of sarcoidosis in approximately 50 to 70% of neurosarcoidosis cases [7,11,22–26]. Neurological involvement is typically seen within two years of the initial diagnosis of sarcoidosis [7,25,27]. Almost all cases of neurosarcoidosis are associated with other organ involvement, including intrathoracic/lungs (88 to 94%), eyes (37 to 55%) and skin (30%) [7,9]. The frequency of extraneural sarcoidosis organ involvement was similar between patients with and without neurological manifestations [9]. In one case series, 81% of neurosarcoidosis patients who initially presented with isolated neurological involvement eventually developed extraneurologic involvement, usually within 5 years [22]. Multiple neurosarcoidosis manifestations or lesions occur in the same patient in up to three-fifths of cases [7,10].

**Cranial neuropathies**

Cranial neuropathies are the most common manifestation of neurosarcoidosis [3,7–9,11,26–30], and a facial nerve palsy is the most frequent of these [7,9]. Unilateral facial nerve involvement is common, though bilateral involvement is seen in up to one-third of patients [7,10]. Bilateral involvement may occur either simultaneously or sequentially [7]. Although facial nerve palsy from sarcoidosis has been thought to result from inflammation in the parotid gland, there is no clear temporal correlation between facial nerve palsies and parotitis. An alternative explanation is that the facial palsy results from a meningeal reaction [26]. Facial palsy is usually a short-term complication of sarcoidosis. In one case series of facial palsy associated with sarcoidosis [9], complete recovery was seen in 23 out of 24 patients (96%).

Optic neuritis is another common sarcoïd cranial neuropathy, and in fact, is the most common in some series [11,25,26,31]. It typically presents with blurred vision or visual field defects [32]. Bilateral optic neuropathy generally has a poor prognosis, whereas unilateral optic neuritis portends a better chance of recovery [31]. Optic nerve damage is caused by granulomatous infiltration or compression with resultant atrophy [7].

Eight cranial nerve dysfunction from sarcoidosis typically presents as sensorineural hearing loss. The loss of hearing and vestibular function may be intermittent. It is probably due to granulomatous meningitis [7]. Bilateral involvement is highly suggestive of neurosarcoidosis [33]. Other cranial neuropathies can occur [11], and multiple cranial nerve involvement may be seen [7]. In general, isolated cranial neuropathies present acutely and resolve, whereas multiple cranial neuropathies usually have a chronic course [5].

**Meningitis/Meningeal involvement**

As previously mentioned, sarcoidosis has a predilection to infiltrate the meninges and can cause aseptic meningitis. Its clinical manifestations are similar to other causes of meningitis, including fever, headache and rigid neck [32]. Aseptic meningitis usually presents acutely [5]. Sarcoid meningitis usually has a good prognosis, even if it recurs [7]. However, chronic persistent meningitis may develop and usually requires long-term therapy [32]. The clinician must be cognizant that Cryptococcal meningitis may present similarly to sarcoid meningitis; furthermore, sarcoidosis may be associated with cryptococcal meningitis because of impairment of cell-mediated immunity from chronic corticosteroid therapy [34]. Meningeal mass lesions may occur and be mistaken for meningiomas [33].

**Hydrocephalus**

Hydrocephalus is seen in 5 to 38% of neurosarcoidosis patients [7,8,10,25,27,29,35]. This is a rare presenting manifestation of sarcoidosis [35,36]. This condition usually has a chronic course [5]. Communicating hydrocephalus arises from meningeal arachnoid granulation involvement [37]. Non-communicating hydrocephalus occurs due to compression of the aqueduct or fourth ventricle by granulomas [7]. Hydrocephalus has a poor long-term prognosis with a mortality rate of approximately 75% [36]. Ventricular drainage is often useful for symptomatic cases and may be lifesaving [36].

**Headache**

Headache is a common symptom in neurosarcoidosis, seen in 17 to 48% of cases [11,24,28,31]. These headaches may be the result of varied neurologic conditions, including aseptic meningitis, encephalopathy, a mass lesion, or hydrocephalus [38].

**Seizures**

Seizures may occur with neurosarcoidosis. It is controversial whether seizures reflect serious brain pathology and a poor outcome [3,11] In a large case series of 79 neurosarcoidosis by Krumholz et al. [29], seizures due to neurosarcoidosis were seen in 13 (15%) cases and were significantly associated with severe forms of neurosarcoidosis, including intracerebral masses, encephalopathy or vasculopathy, or hydrocephalus.
Neuropsychiatric symptoms
There is a high prevalence of depression in sarcoidosis (60 to 66%) [39,40]. Sarcoidosis patients also demonstrate a high prevalence of significant stress (55%), which may be associated with a variety of physiologic, mental and social problems [39]. CNS involvement with sarcoidosis may cause encephalopathy or psychosis. These symptoms may be due to granulomatous infiltration of arteries and veins or perivascular inflammation [7]. Psychiatric symptoms from neurosarcoidosis are usually associated with diffuse meningeal enhancement [37]. However, psychosis can present with obstructive hydrocephalus [37]. When psychosis occurs in patients who are receiving corticosteroids, corticosteroid-induced psychosis also needs to be considered. Other neuropsychiatric manifestations of neurosarcoidosis include cognitive changes, memory loss and altered sensorium [24,28].

Neuroendocrinological dysfunction
Neurosarcoidosis may cause neuroendocrine dysfunction, such as hypothalamic dysfunction, diabetes insipidus, adenopituitary failure and amenorhea-galactorrhea syndrome [41]. Polyuria and polydipsia are the most common presentations, caused either by diabetes insipidus or a disordered control of thirst [7,42]. The hypothalamus is the most frequently involved of all the endocrine glands, which is predominantly due to granulomatous infiltration into the hypothalamo-hypophysial region [42]. Other clinical manifestations include morbidity obesity from sarcoid invasion into the satiety center, insomnia, complete loss of the counter-regulatory response to hypoglycemia caused by hypothalamic involvement [43], extreme variations in body temperature, and marked personality changes [42].

Myelopathy/Radiculopathy
Although spinal cord sarcoidosis was previously believed to be a rare manifestation of the disease [44], recent case series have shown high frequency of this manifestation (16 to 43%) [11,25,26,31]. The signs of spinal cord sarcoidosis typically mimic those of a spinal cord tumor or meningomyelitis [45]. The condition often presents with insidious development of paresthesias or weakness, although occasionally sudden paraplegia may occur [44]. Spinal sarcoidosis can also present as a meningitic-radiculary syndrome [26]. Involvement of the cauda equina has been reported [11,46]. Myelopathy in sarcoidosis usually has a poor prognosis and high risk of severe neurological sequel [11,44,46]. Chronic spinal cord dysfunction is often refractory to either medical or surgical treatment, especially in the presence of spinal cord atrophy [25].

Radiculopathy is a rare manifestation of sarcoidosis. In a review of 17 cases of sarcoïd radiculopathy [47], lower extremity weakness occurred in 12 (71%), lower extremity areflexia in 10 (59%), and sphincter dysfunction in 6 (35%). All cases involved the thoracolumbar or lumbosacral roots, except one case of a cervical polyradiculopathy. An association with CNS involvement was also found.

Peripheral neuropathy
The prevalence of peripheral neuropathy in neurosarcoidosis varies depending on its location. In one prospective case series [10], peripheral nervous system involvement including both symmetric peripheral neuropathy and peripheral mononeuropathy occurred in 22 (69%) of 32 patients with neurosarcoidosis. The authors claimed that their relatively high reported frequency of this complication was the result of thorough neurological examinations. The most common type of the peripheral neuropathy in sarcoidosis is a symmetric axonal polyneuropathy [5,10]. Mononeuritis multiplex may also occur [7]. In a large case series of 57 patients with a sarcoid neuropathy of the extremities [48], polyradiculoneuropathy (39%) and polynueopathy (33%) were the most common presentations. Most patients developed neuropathy in an acute or subacute fashion (89%). Almost all (98%) had a sensory deficit which was much more common than motor abnormalities (37%). The pathologic process was focal or multifocal and involved most classes of nerve fibers at variable levels (from nerve roots to peripheral nerves).

Chronic pain is one of the most commonly reported symptoms among patients with sarcoidosis. Small fiber neuropathy is being considered as a cause of this pain. Small fiber neuropathy in sarcoidosis usually presents with pain, numbness, burning dyesthesias, and vibrating or electric shock-like sensations [49]. It may also cause autonomic disturbances including cardiac sympathetic dysfunction [49,50]. The mechanism responsible for the development of small fiber neuropathy in sarcoidosis is unclear [51].

Myopathy
Muscle involvement is frequently seen in sarcoidosis, but is usually asymptomatic [5,7]. Symptomatic muscle involvement is rare and can be classified into nodular sarcoïd myopathy, acute to subacute myositis and chronic myopathy [52,53]. Muscle nodules are usually palpable and painless. These nodules are not associated with muscle weakness [52,53]. Serum muscle enzyme levels are usually normal [52]. Sarcoïd muscle nodules consist of fibrous tissue in the central region surrounded by granulomatous infiltration. The acute myositis form presents with diffuse muscle swelling and pain affecting proximal muscles symmetrically that progresses to muscle contracture, hardening and hypertrophy [52,53]. Serum muscle enzymes are typically elevated [52]. The pathology of the myositis form reveals cellular infiltration in the interstitium with epithelioid cells, lymphocytes and giant cells. Perifascicular atrophy may occur.
Chronic myopathy usually presents with a slowly progressing weakness and atrophy in proximal symmetric muscles [52]. Pseudohypertrophy is occasionally seen [53]. Serum muscle enzymes are usually normal [52]. The muscle pathology of the myopathic form consists of microscopic granulomas distributed among muscle fibers and often concomitant fibrosis [52]. Muscle fiber atrophy and neurogenic changes may be present as well [10].

A form of inclusion body myositis has been reported in sarcoidosis [54]. The pathological features of this condition indistinguishable from non-sarcoid inclusion body myositis, with the presence of rimmed vacuoles, eosinophilic inclusions, and amyloid deposits [54]. The muscle weakness is asymmetric in these cases, which contrasts the symmetric and proximal weakness typical of most sarcoid myopathies.

**Pediatric neurosarcoidosis**

Children with neurosarcoidosis show different clinical manifestations compared to adults. In a review of twenty-nine pediatric neurosarcoid cases (age ≤ 18 years at symptom onset) [55], seizures occurred in 38% and occurred in the majority (73%) of those under age 12. In addition, a low rate of cranial nerve palsies as a presenting manifestation (21%) was observed compared to adults. It is postulated that the manifestations of neurosarcoidosis in children evolve to those of adults by the end of adolescence.

**Prognosis**

Prognosis of each clinical manifestation of neurosarcoidosis is summarized in *(table I)*. Patients with acute meningitis, myopathy, peripheral neuropathy or cranial neuropathy (except optic neuropathy) have a low risk for progression. On the other hand, intracranial disease including hydrocephalus and chronic meningitis have an increased risk of progression [28]. Seizures also portend a poor prognosis and a high mortality [3, 26]. Sarcoid spinal cord disease carries poorer prognosis compared to other manifestations, as over 70% of these cases deteriorate during follow-up [26]. In a case series containing 31 patients with spinal cord sarcoidosis, one-third of the patients had a monophasic course, another third had a relapsing–rheating course, and the remaining third had a progressive course [56]. There is no correlation between the extraneurologic manifestations and clinical outcome of neurosarcoidosis [22]. The age of death was younger and the disease course was shorter in patients who died of CNS and cardiac sarcoidosis, compared to those who died of pulmonary sarcoidosis [57].

**Diagnosis**

The diagnosis of sarcoidosis requires compatible clinical findings, histologic demonstration of noncaseating granulomas and exclusion of other diseases [2]. Since the disease may mimic other infectious diseases, demyelinating diseases, neoplasms and neurologic manifestations of connective tissue diseases, the diagnosis can be challenging. Although a tissue biopsy is considered the gold standard for the diagnosis, often the diagnosis of neurosarcoidosis must be made indirectly as nervous system biopsies are often prohibitively invasive [3, 25]. In terms of histopathology, foreign bodies and infectious causes of granulomatous inflammation need to be excluded [17]. At a minimum, mycobacterial and fungal diseases should be searched for with stains and cultures of biopsied material [1]. On some occasions, when tuberculosis cannot be completely excluded, an empiric diagnostic or therapeutic trial of antituberculous therapy should be considered [58]. In severe cases where tuberculosis remains a diagnostic possibility, antituberculous and antisyrocardoid therapy may be given concurrently. Clinical clues that may assist in distinguishing tuberculosis from sarcoidosis include the results of tuberculin skin testing, whole blood interferon release assays in response to tuberculosis antigens, or a history of tuberculosis exposure [58].

In cases of isolated CNS neurosarcoidosis without extraneural involvement, it is problematic to exclude multiple sclerosis (MS) as an alternative possibility. Indeed, patients with neurosarcoidosis are frequently diagnosed initially with MS because of a considerable overlap of clinical and laboratory features [59]. *(table II)* summarizes the differentiating features of neurosarcoidosis from MS. Both conditions demonstrate a diverse distribution of lesions in CNS and have a relapse/remitting course [60]. Optic neuritis occurs more frequently in MS, while inflammation of anterior segment (anterior uveitis) occurs more frequently in sarcoidosis. However, both of
these presentations may occur in either condition [60]. Typical radiological findings, such as leptomeningeal or dural enhancement or involvement of pituitary/hypothalamus help to differentiate neurosarcoidosis from MS (vide infra). Both diseases may cause periventricular lesions on MRI making their differentiation problematic [60].

The differential diagnosis of neurosarcoidosis also includes Lyme disease (which also may cause facial nerve palsies and root irritation syndromes), Wegener’s granulomatosis (which may have meningeal involvement), Behcet’s disease, vasculitis, meningeal carcinomatosis, tuberculosis and lymphoma [26]. In sarcoidosis patients, progressing multifocal leukoencephalopathy (PML) can occur which mimics neurosarcoidosis, though the coincidence of PML and sarcoidosis is rare. It is hypothesized that the shift of the CD4/CD8-ratio with an additional lack of JC-virus specific cytotoxic T-cells promotes the development of PML in sarcoidosis. In addition, the administration of corticosteroids or other immunosuppressive agent for sarcoidosis can exacerbate viral infection. A positive CSF-testing for JC-virus is diagnostic of PML. In CSF-negative cases with suspicious MRI, however, a histological and molecular investigation of a stereotactic brain biopsy is necessary [61].

The differential diagnosis of sarcoid peripheral neuropathy includes necrotizing vasculitis, Lyme disease, lymphomatous neuropathy, carcinomatous polyradiculopathy, lepromatose leprosy, HIV-associated neuropathy and Sjogren’s neuropathy [48]. Since a significant number of sarcoidosis patients require corticosteroid therapy, polynuropathy secondary to glucose intolerance may also develop.

Sarcoïd myopathy is sometimes challenging to differentiate from other inflammatory myopathies, including polymyositis, and dermatomyositis [7]. It is most problematic to differentiate sarcoïd myopathy from a non-sarcoïd granulomatous myopathy that may be caused by a vasculitis, connective tissue disease, inflammatory bowel disease, infection, or may be idiopathic (cryptogenic) [53]. It may be impossible to reliably determine

| TABLE II |
| Differentiating features of central nervous system (CNS) sarcoidosis from multiple sclerosis (MS) |

<table>
<thead>
<tr>
<th>Clinical manifestations</th>
<th>CNS sarcoidosis</th>
<th>MS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relapsing/remitting course</td>
<td>Common</td>
<td>Very common</td>
</tr>
<tr>
<td>Diverse neurological findings</td>
<td>Common</td>
<td>Very common</td>
</tr>
<tr>
<td>Extranuclear involvement</td>
<td>Highly suggestive</td>
<td>Possible (esp. rheumatologic)</td>
</tr>
<tr>
<td>Visual apparatus</td>
<td>Anterior segment &gt; Optic nerve</td>
<td>Optic nerve &gt; Anterior segment</td>
</tr>
<tr>
<td>Cranial neuropathy</td>
<td>Highly suggestive</td>
<td>Possible, but not common</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>MR findings</th>
<th>CNS sarcoidosis</th>
<th>MS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leptomeningeal enhancement</td>
<td>Highly suggestive</td>
<td>Rare</td>
</tr>
<tr>
<td>Dural enhancement</td>
<td>Highly suggestive</td>
<td>Rare</td>
</tr>
<tr>
<td>Enhancing mass adjacent to meninges</td>
<td>Highly suggestive</td>
<td>Rare</td>
</tr>
<tr>
<td>Enhancement of parenchymal lesions</td>
<td>Persistent (more than a few weeks)</td>
<td>Transient (within a few weeks)</td>
</tr>
<tr>
<td>Hydrocephalus</td>
<td>Highly suggestive</td>
<td>Rare</td>
</tr>
<tr>
<td>Involvement of hypothalamus/pituitary</td>
<td>Highly suggestive</td>
<td>Rare</td>
</tr>
<tr>
<td>Non-enhancing periventricular WM lesions</td>
<td>Common</td>
<td>Common</td>
</tr>
<tr>
<td>Spinal cord</td>
<td>Intradural extramedullary &gt; Intramedullary</td>
<td>Intramedullary</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CSF findings</th>
<th>CNS sarcoidosis</th>
<th>MS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphocytosis, Elevated protein level</td>
<td>Common</td>
<td>Common</td>
</tr>
<tr>
<td>Hypoglycorrhachia</td>
<td>Suggestive</td>
<td>Rare</td>
</tr>
<tr>
<td>Elevated ACE level</td>
<td>Suggestive</td>
<td>Possible</td>
</tr>
<tr>
<td>Oligoclonal bands</td>
<td>Possible</td>
<td>Highly suggestive</td>
</tr>
</tbody>
</table>

ACE: angiotensin converting enzyme; CNS: central nervous system; CSF: cerebrospinal fluid; MR: magnetic resonance; MS: multiple sclerosis; WM: white matter.
that a granulomatous myopathy is caused by sarcoidosis when it is not associated with concurrent neurosarcoidosis or systemic sarcoidosis [53]. In these cases, certain clinical features may prompt the clinician to consider sarcoidosis. These include the fact that a sarcoid myopathy usually demonstrates severe proximal weakness with functional disability, while non-sarcoid granulomatous myopathy without systemic sarcoidosis is associated with milder and predominantly distal weakness [62,63]. Since a significant number of sarcoidosis patients are receiving corticosteroid therapy, a corticosteroid-induced myopathy also should be considered [32].

**Diagnostic tests**

**Histology**

Granulomatous inflammation on tissue biopsy is the most specific diagnostic test for sarcoidosis. However, biopsy is not 100 percent specific as alternative causes of granulomatous inflammation may occur. Biopsy from central or peripheral nervous tissue may be associated with significant morbidity, and therefore the diagnosis of neurosarcoidosis is often made indirectly by histologic confirmation in extraneural sites coupled with clinical evidence of neurosarcoidosis. When a biopsy of CNS tissue is performed, the sites commonly biopsied are the meninges and mass lesions. The sensitivity of meningeal biopsy improves when the specimen is obtained from lesions that are enhanced on imaging studies [33]. However, for the reasons outlined above, brain biopsy consists of only 10 to 30% of total biopsies performed for neurosarcoidosis [3,11,27,28,31]. Instead, extraneural tissues such as the lung or lymph node are more frequently biopsied for diagnosis [3,10,28,31]. When a brain biopsy is performed, an adequate sample should be taken, since granulomatous changes can be seen in the periphery of the primary cerebral tumors [33]. The Kveim test is an old diagnostic test for sarcoidosis where a splenic suspension from a spleen involved with sarcoidosis is inoculated intradermally [64]. If in 4 to 6 weeks a skin nodule appears at the inoculation site, it is biopsied, and reveals non-caseating granulomas, this is highly specific for the diagnosis of sarcoidosis. Unfortunately, the test is not extremely sensitive, both the sensitivity and specificity vary depending upon the spleen that is used, and the suspension is not FDA approved. Therefore, the Kveim test is not a standard diagnostic test for sarcoidosis. However, it may be considered in cases of neurosarcoidosis (especially in cases of presumed isolated neurosarcoidosis) as a Kveim test (skin) biopsy is much less invasive than biopsy of neural tissue.

**Imaging of the extraneural organs**

Chest imaging usually demonstrates abnormalities in cases of suspected neurosarcoidosis and is strong supporting evidence for the diagnosis [31,65]. In patients with normal chest radiographs, chest CT, gallium, and PET scan are helpful in establishing the multisystemic sarcoideal involvement [3]. High resolution chest CT reveals nodules along the bronchovascular bundle and subpleural regions. Lymphadenopathy is more commonly observed on chest CT than on chest radiograph. Ground glass attenuation, often thought to represent acute alveolitis, has been shown to represent granulomatous inflammation [1]. Because chest CT scans normally image the superior portion of the abdomen, they may show evidence of extrathoracic disease such as hepatomegaly, splenomegaly, hepatic or splenic nodules, or upper abdominal adenopathy [66]. Whole-body Gallium (Ga)-67 scanning may detect multisystem disease [26]. Positive uptake is seen in 45 to 85% of sarcoidosis cases [11,23,26,67]. Gallium scanning is occasionally useful for selection of a biopsy site. Ga-67 citrate is taken up at active sarcoidosis sites, as well as in inflammatory and malignant disorders, including tuberculosis and lymphomas [26]. The appearance of a Panda-pattern (bilateral salivary gland and parotid gland uptake) combined with a Lambda-pattern (bilateral hilar and right paratracheal lymph node uptake) may support the diagnosis of sarcoidosis, though these findings are present in only a small number of patients. Ga-67 scans are cumbersome to use as they require an initial gallium injection proceeded by scanning 48 to 72 hours later [2]. F-18 fluorodeoxyglucose positron emission tomography (PET) scanning has been found to frequently display positive activity in areas with active granulomatous inflammation from sarcoidosis [68]. PET scans are expensive and cannot definitively diagnose sarcoidosis as a positive result may be the result of malignancy or an alternative inflammatory condition. Therefore, PET scans are not routinely performed in the diagnostic evaluation of sarcoidosis. However, a PET scan can be useful in the diagnosis of sarcoidosis by identifying potential diagnostic biopsy sites and suggesting the presence of disease in relatively inaccessible organs such as the brain. In a large prospective trial of the application of PET scans in sarcoidosis patients, this modality helped identify potential biopsy sites [69].

**Brain and spine MRIs**

Brain MRI is considered the most sensitive noninvasive test for neurosarcoidosis; it is more sensitive at detecting neurosarcoidosis lesions than brain CT [26,67]. However, a normal MRI does not exclude the diagnosis of neurosarcoidosis [37], especially in patients with cranial neuropathies or in corticosteroid treated patients [67]. Improvement in neurosarcoidosis lesions on brain MRI strongly correlates with clinical response to therapy [25]. MRI can be used as a tool to differentiate CNS sarcoideal lesions into reversible or irreversible ones, and to adjust treatment to prevent irreversible CNS damage [70]. The most common brain MR finding of neurosarcoidosis is leptomeningeal involvement [13], seen in the form of nodules or plaques which reveal focal or diffuse thickening...
with contrast enhancement (figure 1) [67]. Detection of meningeal sarcoidosis on MRI usually requires gadolinium enhancement, as it was detected with this contrast agent in 17 out of 20 neurosarcoid patients (85%), whereas it was observed in only three patients (15%) on non enhanced studies [71]. Leptomeningeal involvement most frequently affects the suprasellar and frontal basal meninges [24]. Leptomeningeal involvement around the hypothalamus (figure 2) and pituitary infundibulum may be seen with basilar leptomeningeal involvement or as an isolated finding [13]. Basal meningeal involvement is not specific for neurosarcoidosis as it is also seen in other diseases such as tuberculosis, Wegener granulomatosis, fungal meningitis, lymphoma and leptomeningeal carcinomatosis [24,71].

Sarcoid granulomas can involve the dura as focal masses or diffuse dural thickening [13]. It can mimic meningiomas and schwannomas, but the presence of noncontiguous dural enhancement favors dural sarcoidosis rather than these tumors [24]. A hypointense appearance on T2-weighted images suggests dural sarcoidosis, although this finding is not specific [24]. Dural and leptomeningeal involvement are rarely present together in the same region, probably because the formation of membranes by arachnoid cells prevent extension of sarcoid granulomas in either direction [23].

Cranial nerve involvement may occur concomitantly with leptomeningeal involvement or as an isolated finding (figure 3) [13]. Concomitant clinical and radiological manifestations of cranial nerve involvement do not frequently occur. In addition, clinical resolution of cranial neuropathies often is not associated with imaging resolution [23]. Neurosarcoidosis may present as a solitary or multiple enhancing intraparenchymal mass and may be mistaken for a primary or secondary tumor or a demyelinating disease (figure 4) [13,67]. When enhancement persists, it suggests neurosarcoidosis rather than MS [26]. In addition, linear enhancement along blood vessels in the region of white matter lesions suggests neurosarcoidosis. This finding corresponds to Virchow–Robin spaces and is considered to be the result of infarctions caused by granulomatous vasculitis [33].

Non-enhancing brain parenchymal lesions tend occur in periventricular white matter [23]. These lesions are not specific and indistinguishable from those seen in multiple sclerosis, hypertension and vasculitis [13,23,26,60]. In addition, there is a poor correlation between the non-enhancing white matter lesions and clinical symptoms; furthermore, these lesions do not reliably respond to antituberculosis therapy [24]. Hence non-enhancing lesions, unlike enhancing lesions, are thought not be the result of granulomatous inflammation [23].
Sarcoidosis may involve the intramedullary spaces (figure 5), intradural extramedullary spaces, intraspinal epidural spaces, or the vertebral bodies [44]. Lesions may occur in any portion of the spinal cord but are most frequently in the cervical or upper thoracic regions [13,23]. They often extend over several spinal segment [25]. These lesions may cause cord swelling and enhancement in the periphery of the cord or in multiple locations [23]. Extramedullary intradural lesions in the form of leptomeningeal sarcoidosis infiltration are present in up to 60% of sarcoid spinal cord lesions [13]. These lesions usually present as a sterile meningitis [45].

Laboratory studies
Cerebrospinal fluid (CSF) abnormalities may suggest the diagnosis of neurosarcoidosis [72]. Typical CSF findings include elevated protein levels and a lymphocytosis. Pleocytosis and hypoglycorrhachia imply an active inflammatory phase of CNS sarcoidosis [7]. Positive oligoclonal bands are seen in 19 to 37% of neurosarcoidosis cases [11,26,31]. However, all these tests are insensitive and relatively nonspecific for the diagnosis of neurosarcoidosis [72]. In addition, a normal CSF study does not exclude neurosarcoidosis [3]. CSF analysis is usually normal with isolated facial nerve palsies, although abnormal
CSF findings are found in up to 80% of facial nerve palsy cases when other neurological manifestations of sarcoidosis are present [33]. Although the CSF findings of neurosarcoidosis are not specific, a lumbar puncture with CSF analysis should be performed for suspected neurosarcoidosis to exclude other disorders, including cryptococcal, tuberculous, and lymphomatous meningitis [7].

The usefulness of CSF angiotensin converting enzyme (ACE) levels for the diagnosis of neurosarcoidosis is controversial. ACE is a membrane-bound glycoprotein produced by epithelioid cells of granulomatous tissue. ACE was first reported to be increased in CSF of CNS sarcoidosis in the mid 1980’s [72]. The CSF ACE level can be elevated in disorders other than neurosarcoidosis, including inflammatory conditions (multiple sclerosis, Guillain–Barre syndrome, Behcet’s disease), brain tumors (medulloblastoma, ependymoma) and neurodegenerative diseases [3]. A poor correlation has been demonstrated between serum and CSF ACE levels, suggesting that CSF ACE levels may be intrathecally synthesized and not passively transferred one from the serum [31]. Analysis of two large case series [72–74] showed that the CSF ACE test is insensitive for the diagnosis of neurosarcoidosis (24–55%) but is relatively specific (94–95%). Based on these data, CSF ACE levels cannot replace a tissue biopsy for the diagnosis of neurosarcoidosis; however, an elevated level would provide supporting evidence for the diagnosis [72].

**Other studies**

Because ocular sarcoidosis and neurosarcoidosis often occur concomitantly [75,76], an ophthalmologic evaluation is often useful to suggest the diagnosis of neurosarcoidosis. A slit lamp and fundoscopic examination should be performed as sarcoidosis may affect any portion of the eye [26].

Electrodiagnostic studies, including nerve conduction studies and electromyography should be performed in symptomatic patients with clinical evidence of peripheral nervous system involvement, especially peripheral neuropathy. The most common finding of peripheral nerve sarcoidosis is axonal neuropathy [10,48]. Visual and brain stem auditory evoked responses are frequently abnormal even in asymptomatic patients. These tests may be useful for monitoring the course of the disease [33].

There is no gold standard for the diagnosis of small fiber neuropathy [77]. Discordant criteria for the diagnosis include psychophysical tests (temperature sensation thresholds [78]), neurophysiological tests (laser evoked potentials [79], contact heat evoked potentials [80], and quantitative sudomotor axon testing [81]), and results from skin or nerve biopsies (intraepidermal nerve fiber quantification [82,83]).

**Diagnostic criteria**

Currently, validated and widely accepted diagnostic criteria for neurosarcoidosis are not available. Two proposed diagnostic criteria are listed below.
Proposed diagnostic criteria by Zajicek et al.

These criteria [26] (box 1) require a biopsy from CNS tissue for a definite diagnosis of neurosarcoidosis to be established, whereas probable and possible neurosarcoidosis can be established using clinical criteria without the need for a biopsy. A review of 13 CNS biopsy confirmed cases of neurosarcoidosis failed to identify specific clinical findings that were reliable diagnostically [11]. This fact emphasizes that the presumption that the diagnosis of neurosarcoidosis is tenuous in patients without a tissue biopsy, whether from neural tissue or extraneural tissue. These criteria or related variations have been used in several case series [24–26,31,58].

Proposed diagnostic criteria of neurosarcoidosis by Judson et al.

These diagnostic criteria [4] require histologic evidence of granulomatous inflammation in neural or extraneural tissue for a definite diagnosis of neurosarcoidosis to be made. Additional neurologic clinical criteria are required if an extraneural tissue is biopsied. These criteria therefore obviate the need to obtain a neural tissue biopsy in many cases. We propose to add positive spinal cord MR findings, especially with intradural extramedullary or elongated intramedullar lesions (> 3 spine levels) as definite neurosarcoidosis in the criteria. (box 2).

**Diagnostic workup**

The diagnosis of neurosarcoidosis is not necessarily problematic in patients with an established diagnosis of extraneural sarcoidosis. However, it is important to note that abnormal neurologic findings are often unrelated to neurosarcoidosis. Other plausible causes of neurologic abnormalities should be considered and excluded.

In a patient without a prior history of sarcoidosis being evaluated for neurosarcoidosis, an evaluation should be performed not only concerning the neurological problem, but also for clinical evidence of extraneural sarcoidosis. At a minimum, this should include a medical history focusing on pulmonary, dermatologic, and ocular problems as well as a chest radiograph. Additional tests that should often be considered include serum liver function tests, serum calcium, chest CT scanning, and an ophthalmologic evaluation. It may be prudent to perform a tuberculin skin test or whole blood interferon release assay versus tuberculosis antigens to exclude tuberculosis as a consideration. (box 1) lists tests that should typically be considered as part of a diagnostic evaluation for sarcoidosis. (table III) outlines the neurological tests that should be considered to evaluate different forms of neurosarcoidosis.

As mentioned, we believe histologic evidence of either extraneurual or neural tissue is essential for establishing the diagnosis of sarcoidosis. Biopsy of an organ that is accessible and does not present much risk should be considered first, including the skin, lacrimal glands, and peripheral lymph nodes. Lung biopsy via

---

**Box 1**

Proposed diagnostic criteria of neurosarcoidosis by Zajicek et al. [26].

**Definite**

Clinical presentation suggestive of neurosarcoidosis with exclusion of other possible diagnoses and the presence of positive nervous system histology.

**Probable**

Clinical syndrome suggestive of neurosarcoidosis with laboratory support for CNS inflammation (elevated levels of CSF protein and/or cells, the presence of oligoclonal bands and/or MRI evidence compatible with neurosarcoidosis) and exclusion of alternative diagnoses together with evidence for systemic sarcoidosis (either through positive histology, including Kveim test, and/or at least two indirect indicators from Gallium scan, chest imaging and serum ACE).

**Possible**

Clinical presentation suggestive of neurosarcoidosis with exclusion of alternative diagnoses where the above criteria are not met.

ACE, angiotensin converting enzyme; CNS, central nervous system; CSF, cerebrospinal fluid; MRI, magnetic resonance imaging.

---

**Box 2**

Adapted from the proposed diagnostic criteria of neurosarcoidosis by Judson, et al. [4].

**Definite**

- Positive magnetic resonance imaging (MRI) with uptake in meninges or brain stem
- Cerebrospinal fluid with increased lymphocytes and/or protein
- Diabetes insipidus
- Bell’s palsy
- Cranial nerve dysfunction
- Biopsy of neural tissue showing granulomatous inflammation

**Probable**

- Other abnormalities on MRI
- Unexplained neuropathy
- Positive electrodiagnostic studies

**Possible**

- Unexplained headaches
- Radiculopathy
  - Assumes no other cause identified (such as infection, trauma, pre-existing condition, or co-existing disease) for the neurologic manifestation
  - Requires a tissue biopsy showing granulomatous inflammation in at least one extraneural organ unless the nervous system is biopsied.
### Proposed neurological workup for neurosarcoidosis

<table>
<thead>
<tr>
<th>Clinical manifestations</th>
<th>Recommended tests</th>
<th>Typical findings in neurosarcoidosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cranial neuropathies</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Optic neuritis</td>
<td>Brain and orbit MRI's, CSF</td>
<td>Swelling and enhancement of the optic nerve(s)</td>
</tr>
<tr>
<td>Other cranial neuropathies</td>
<td>Brain MRI (including thin slice of the brain stem), CSF</td>
<td>Enhancement of cranial nerve(s) associated with leptomeningeal involvement</td>
</tr>
<tr>
<td>CNS involvement</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meningitis</td>
<td>Brain MRI, CSF</td>
<td>Leptomeningeal involvement (thickening and enhancement)</td>
</tr>
<tr>
<td>Seizures</td>
<td>EEG, Brain MRI, CSF</td>
<td>EEG with epileptogenic changes, Various brain MR findings including leptomeningeal involvement, mass, hydrocephalus and WM changes</td>
</tr>
<tr>
<td>Neuroendocrine</td>
<td>Endocrinology consultation, Brain MRI (including dynamic study of pituitary), CSF</td>
<td>Mass in the pituitary and/or hypothalamus associated with leptomeningeal involvement</td>
</tr>
<tr>
<td>Neuropsychiatry</td>
<td>Neuropsychiatric tests, Brain MRI, CSF</td>
<td>Various brain MR findings including leptomeningeal involvement, mass, hydrocephalus and WM changes</td>
</tr>
<tr>
<td>Other brain disease</td>
<td>Brain MRI, CSF</td>
<td>Same as above</td>
</tr>
<tr>
<td>Myelopathy</td>
<td>Cervical and/or thoracic spine MRI, CSF</td>
<td>Extramedullar (dural swelling and enhancement) &gt; Intramedullar (cord swelling and enhancement with predominancy in the periphery of the cord)</td>
</tr>
<tr>
<td>PNS involvement</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>Electrodiagnostic studies</td>
<td>NCS with axonal polyneuropathy, mononeuropathy multiplex</td>
</tr>
<tr>
<td>Myopathy</td>
<td>Electrodiagnostic studies, Serum muscle enzyme</td>
<td>EMG with myopathic pattern</td>
</tr>
</tbody>
</table>

CNS: central nervous system; CSF: cerebrospinal fluid; EEG: electroencephalography; EMG: electromyography; MRI: magnetic resonance imaging; NCS: nerve conduction study; PNS: peripheral nervous system; WM: white matter.

1 MRI should be performed with and without gadolinium contrast.
2 The minimal requirement of CSF study is cell count with differentiation, protein, glucose. Typical findings in neurosarcoidosis include lymphocyte dominant pleocytosis, elevated protein and hypoglycorrhachia. Additional tests should be considered based on the differential diagnosis, including bacterial and fungal cultures, polymerase chain reaction for tuberculosis, herpes simplex virus and cytomegalovirus, antibody tests for human immunodeficiency virus and syringe disease, IgG studies and oligoclonal bands.
3 Electrodiagnostic studies include nerve conduction study and electromyography.
4 Serum muscle enzyme tests include creatine kinase and aldolase.

Bronchscopy is more invasive than the above sites, but much less so than biopsy of neural tissue. In cases of isolated neurosarcoidosis where there is no evidence of extraneural involvement, biopsy may need to be obtained from the nervous system. Biopsy of the dura and/or leptomeninges are safer than the CNS parenchyma, especially in cases of spinal cord sarcoidosis. Sarcoidosis patients with lesions affecting the sinusal or ophthalmologic areas or with manifestation of hypogonadism or diabetes insipidus should be tested for hypothalamic-pituitary lesions. In addition, because there is a poor relationship between imaging findings and endocrine dysfunction, specific evidence of endocrine dysfunction should be evaluated both in terms of patient symptoms and serum levels of appropriate hormones. This could be serum measurement of estradiol, testosterone, follicle-stimulating hormone, luteinizing hormone, prolactin, thyroid-stimulating hormone, free thyroxine, cortisol, adrenocorticotropic hormone, growth hormone, insulin-like growth factor-1. Hormonal evaluation and MRI of the pituitary should be performed once a year, and after any changes to therapy [19].

### Therapy

Neurosarcoidosis usually does not spontaneously remit, with the exception of facial nerve palsy [58]. In general, neurological manifestations caused by acute inflammation usually respond to anti-inflammatory medication, while chronic manifestations are less likely to respond [7]. (Table IV) summarizes dose, side effects and monitoring of medications commonly used for neurosarcoidosis.

### Corticosteroids

Corticosteroids are considered the drug of choice for the treatment of sarcoidosis. Although no standard treatment has been...
Neurosarcoïdosis: Clinical manifestations, diagnosis and treatment

Box 3
Proposed initial extraneurologic evaluation for a patient with presumed neurosarcoïdosis.

Initial evaluations
- Medical history including history of tuberculosis exposure and occupational history
- Chest X-ray (posteroanterior)
- Pulmonary function tests: spirometry, DLCO and KCO
- CBC, LFT, Serum calcium
- Urine analysis
- Electrocardiogram
- Ophthalmology consultation
- Tuberculin skin test

CBC: complete blood count; LFT: serum liver function tests; DLCO: diffusing capacity of the lung for carbon monoxide; KCO: carbon monoxide transfer coefficient.

established in neurosarcoïdosis [84], patients with neurosarcoïdosis usually respond well to high-dose corticosteroid therapy. Neurological conditions which respond well to corticosteroids include intracranial and intraspinal mass lesions, papillitis and peripheral neuropathy [7,10]. Surgical resection of CNS neurosarcoïdosis lesions should be considered as a procedure of last resort reserved for life-threatening situations or when corticosteroids and/or other pharmacotherapy fails [10]. Intravenous methylprednisolone (IVMP) is used in refractory cases not responding to oral agents or for intolerable side effects [10]. However, in neurosarcoïdosis cases where the manifestations are severe, such as an altered sensorium, visual loss, or weakness, IVMP is usually given immediately. In general, neurosarcoïdosis is not as responsive to corticosteroid therapy as sarcoidosis in other organs [9]. A significant percentage of patients are refractory to corticosteroids or relapse when corticosteroids are tapered to lower doses [9,27,58]. These latter patients often require long-term high-dose corticosteroid therapy and a trial of additional agents [27]. In a large neurosarcoïdosis case series, the neurological condition deteriorated in more than 70% of patients who were given corticosteroids alone. In addition, there was a tendency of recurrence of symptoms at doses of prednisone less than 20 to 25 mg/day [26].

Immuno-modulating/Cytotoxic agents

Immuno-modulating and cytotoxic agents are often required in the management of neurosarcoïdosis because of the high frequency of patients who are refractory or develop side effects to corticosteroids. In patients with neurosarcoïdosis that is

<table>
<thead>
<tr>
<th>Agents</th>
<th>Dose</th>
<th>Monitoring</th>
<th>Major side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corticosteroids (for mild to</td>
<td>Prednisone equivalent:</td>
<td>CBC, Blood sugar, Electrolytes,</td>
<td>Glucose intolerance, Obesity, Psychosis, Osteoporosis, Hypertension</td>
</tr>
<tr>
<td>moderate disease [Figure 6]</td>
<td>40–100 mg/d (initial dose)</td>
<td>Weight, Blood pressure</td>
<td></td>
</tr>
<tr>
<td>Corticosteroids (for severe</td>
<td>Methylprednisolone:</td>
<td>CBC, Blood sugar, Electrolytes,</td>
<td>Glucose intolerance, Obesity, Psychosis, Osteoporosis, Hypertension</td>
</tr>
<tr>
<td>disease [Figure 6]</td>
<td>500–1000 mg IV QD for 3–5 d (may repeat Qwk)</td>
<td>Weight, Blood pressure</td>
<td></td>
</tr>
<tr>
<td>Methotrexate</td>
<td>7.5 to 25 mg/week</td>
<td>CBC, LFTs, Renal function,</td>
<td>GI upset, Hepatotoxicity, Pneumonitis, BM suppression, Teratogenicity, HA, Lethargy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CXR</td>
<td></td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>1 g/m² IV Q4wk</td>
<td>CBC, LFTs, U/A, Renal function</td>
<td>Hemorrhagic cystitis, Neutropenia, Cardiac toxicity, Carcinogenicity, Teratogenicity, Azotemia</td>
</tr>
<tr>
<td>Infliximab</td>
<td>5 mg/kg IV Q4-8wk</td>
<td>CBC, TB screening</td>
<td>Infection, Congestive heart disease, Malignancy, Autoimmunity, Demyelinating disease, BM suppression</td>
</tr>
<tr>
<td>Hydroxychloroquine</td>
<td>200–400 mg/d</td>
<td>Ophthalmologic examination</td>
<td>Ocular toxicity, Seizures, Hearing loss, G6PD deficiency</td>
</tr>
<tr>
<td>Chloroquine</td>
<td>250–750 mg/d</td>
<td>Ophthalmologic examination</td>
<td>Ocular toxicity, Seizures, Hearing loss, G6PD deficiency</td>
</tr>
</tbody>
</table>
recalcitrant to corticosteroids, alternative treatment with azathioprine, cyclophosphamide, methotrexate or radiation therapy has been shown to improve the neurological outcome in approximately one-fifth of cases. These therapies allow tapering of the equivalent prednisone dose to 10 to 20 mg/day in more than one-third of cases [27]. A combination of corticosteroids plus either methotrexate, azathioprine or cyclophosphamide for neurosarcoidosis patients with severe CNS involvement (intracranial lesions, hydrocephalus, myelopathy, seizures or encephalopathy) was demonstrated to improve the neurologic outcomes in most neurosarcoidosis patients [28].

Methotrexate is often given in combination with corticosteroids for neurosarcoidosis. It has been suggested that methotrexate at a dose of 10 mg weekly, maintains optimal suppression of symptoms and could be used as a first-line corticosteroid sparing agent [26]. Lower and co-workers [9] added methotrexate to 28 neurosarcoidosis patients who failed prednisone monotherapy, and found a beneficial response in 17 (61%). Relapse occurred in most patients who had methotrexate discontinued; this supports the concept that effective antitumor therapy (with corticosteroids or alternative agents) suppresses the disease manifestations but does not change the natural course of the disease [2]. The drug has minimal to no carcinogenicity [2]. It is recommended to postpone pregnancy for at least 6 months after the last dose of methotrexate because of potential teratogenic effects [2]. The toxicity of methotrexate can be minimized by the use of folic or folinic acid [2].

Cyclophosphamide demonstrated subjective, objective and/or symptomatic improvement in eight (89%) of nine assessable neurosarcoidosis patients who failed monotherapy of prednisone or combination therapy of prednisone and methotrexate [9]. Prednisone was successfully tapered to 10 mg/day or less. Another case series reported seven corticosteroid refractory neurosarcoidosis patients to whom cyclophosphamide was given [84]. Four of them showed symptomatic improvement and all seven showed objective improvement in either MRI or CSF. In addition, cyclophosphamide treatment resulted in a reduction of corticosteroid dose in six of seven patients, with the mean dose reduction for the entire group of 58%. Because of its high toxicity and significant side effects, including bone marrow suppression, tetraganecity and carcinogenicity, the use of cyclophosphamide is usually limited to the patients with severe disease refractory to other agents [2].

Azathioprine has been used for chronic sarcoidosis and may show some effectiveness as a corticosteroid-sparing agent [85,86]. However, we are unaware of clinical data concerning the effectiveness of azathioprine for neurosarcoidosis. Azathioprine is less teratogenic compared to cyclophosphamide or methotrexate and is relatively safe [2].

Infliximab is a chimeric monoclonal antibody which blocks TNF-α bioactivity [87]. TNF-α is a key mediator in the formation of sarcoid granulomas and elevated TNF-α levels is associated with a persistent clinical course and granuloma formation. There are case reports and case series to show its efficacy for refractory neurosarcoidosis [88–90]. It is important to be aware that various neurological deficits are reported during treatment with TNF-α blocker, including CNS or PNS demyelination [91]. A few case reports and small series have suggested a potential role for mycophenolate mofetil in the treatment of neurosarcoidosis [92–94]. Interestingly, a retrospective study of 10 neurosarcoidosis cases suggests its efficacy in CNS sarcoidosis but not in sarcoidosis myopathy [95].

Other pharmacotherapy
Chloroquine and its derivative, hydroxychloroquine are anti-malarial drugs that also have anti-inflammatory effects. These drugs are used to treat rheumatoid arthritis and lupus erythematosus [96]. They are also effective in sarcoidosis, especially in those with sarcoidosis-induced hypercalcemia and sarcoidosis skin lesions. Hydroxychloroquine is preferred to chloroquine, since hydroxychloroquine has lower risk of ocular toxicity [2], but has similar efficacy. Since hydroxychloroquine reduces serum glucose levels, it may be useful for patients with steroid induced hyperglycemia [3]. Sharma [96] gave chloroquine sulfate 200 mg twice daily, or chloroquine phosphate 250 mg twice daily to 12 cases of neurosarcoidosis who could not tolerate or did not want to take prednisone, and obtained controlled or stabilized neurological status in ten (83%). In a case series of small fiber neuropathy in sarcoidosis, intravenous immuno-globulin ameliorated intractable neuropathic pain and/or autonomic dysfunction which were resistant to various immuno-suppressants and narcotic analgetics [97]. Infliximab has also been shown to be useful in a few patients with sarcoidosis associated small fiber neuropathy [98].

Radiotherapy
Radiotherapy to CNS might be considered when medical therapy fails or causes intolerable side effects [32]. Based on their own four cases and literature review [99], it has been suggested that:

- radiotherapy is effective in preventing the progression of local symptoms of neurosarcoidosis;
- sarcoid meningitis is responsive to radiotherapy;
- the radiation dose in the treatment of neurosarcoidosis is 20 to 25 Gy.

The mechanism of action for radiation in sarcoidosis is not well understood. However, direct cytotoxicity to the cellular component of the granulomatous lesions, or cellular matrix alterations resulting in the inhibition of autocrine and paracrine signals is considered [100].

Symptomatic treatment
In addition to the specific treatment for sarcoidosis as described above, symptomatic treatment may be required for the management of neurosarcoidosis.
Anticonvulsant alone without antiscaroidosis medications is not effective for epilepsy management, because granulomatous inflammation of the CNS is almost always a contributing cause [3,32]. With a combination of antiepileptic and corticosteroid therapy, Krumholz et al. [29] obtained acceptable seizure control in 85% of cases.

Regarding the management of neuroendocrine involvement of sarcoidosis, corticosteroid therapy improves radiologic lesions, though hormonal dysfunction seems to be related to irreversible neuronal damage [19]. Hormonal therapy is therefore occasionally required for the whole lifetime and that clinicians should be aware of the possibility of the occurrence of adrenal insufficiency when corticosteroids are discontinued. Surgical intervention for neurosarcoidosis is indicated for life-threatening complications such as hydrocephalus, expanding mass lesions, or mass lesions causing increased intracranial pressure [3].

**Strategy for treatment**

(Figure 6) summarizes our suggested treatment approach for neurosarcoidosis (with input from personal communication from Drs. Barney Stern and Robert P. Baughman). Due to its rarity, there is no rigorous study to identify the adequate treatment period in neurosarcoidosis. Based on our experience, specific treatment for neurosarcoidosis needs to be given for at least 6 months. Tapering of medications should be individualized based on the seriousness of the illness, response to therapy, and toxicity of therapy.

**Conclusion**

Neurosarcoidosis is a relatively rare but potentially a life-threatening manifestation of sarcoidosis. Diagnosis of neurosarcoidosis is problematic, and careful evaluation of clinical manifestations and neurological and extraneural tests are often required. Although corticosteroids or immune-suppressants are frequently used for neurosarcoidosis, there is insufficient evidence concerning the efficacy of all agents.

**Disclosure of interest:** Kenkichi Nozaki declare that he has no conflict of interest concerning this article; Marc A. Judson is consultant for Centocor. This manuscript was entirely prepared by the two authors and there was no sponsor for this manuscript.
References


Neurosarcoidosis: Clinical manifestations, diagnosis and treatment


