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Review Article

Neurosarcoidosis: Review and Update of the Mimic Disease

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Abstract

Sarcoidosis is a systemic inflammatory disorder characterized by non-caseating granulomas with variable involvement of the lungs, central nervous system (CNS), skin, liver, bone, and eye. Neurosarcoidosis is similarly heterogeneous with diverse anatomical manifestations and response to therapy. The diagnosis of neurosarcoidosis is established by the clinical syndrome, imaging and histopathological findings, and exclusion of other causes. In this narrative review, we summarize recent advances in the diagnosis and treatment of neurosarcoidosis.

***Keywords:** Sarcoidosis; Neurosarcoidosis; Cranial neuropathy; Myelopathy; CSF; Corticosteroids.*

Introduction

Sarcoidosis is a multisystemic granulomatous disorder of unknown etiology that affects people worldwide. It is pathologically characterized by the presence of non-caseating granulomas in the affected organs. The most commonly affected organs are the lungs (90%), skin (15%), eyes (10-30%), liver (20-30%), and lymph nodes (10-20%) [1-3]

Sarcoidosis can lead to symptoms involving the central nervous system or the peripheral nervous system. Neurological complications occur in 5-10% of patients with sarcoidosis [4]. Neurosarcoidosis can manifest in an isolated manner, without symptoms in other locations; this occurs in 10-20% of cases [5].

Epidemiology

The prevalence of sarcoidosis varies significantly across different regions of the world and is estimated to be between 50 to 160 per 100,000 individuals [4]. The annual incidence of sarcoidosis is not certain [6] and appears to vary among geographical regions and genetic backgrounds. For instance, it is two to three times more common in Black Americans compared to White Americans [4]. It is also twice as frequent in females [6].

Pathogenesis

Sarcoidosis is a systemic granulomatous disease of unknown cause. In histopathology, the classic granulomas are non-necrotizing and feature a densely packed central area composed of macrophages, epithelioid cells, multinucleated giant cells, and CD4-positive T lymphocytes [7]. The central areas are surrounded by CD8 and CD4-positive T lymphocytes, B lymphocytes, monocytes, mast cells, and fibroblasts. Regarding genetics, the risk of sarcoidosis is 80 times higher in monozygotic twins [8]. Antigens present in the environment have been proposed as potential triggers in the development of granulomatous inflammatory response and the immune changes seen in sarcoidosis [9]. Similar to other autoimmune diseases, the combination of environmental exposure in individuals genetically predisposed to developing sarcoidosis has been suggested as a pathogenic model.

Clinical Neurological Manifestations

Cranial Neuropathy

Cranial nerve involvement is a very common manifestation of sarcoidosis. Granulomatous infiltration can lead to cranial neuropathy by affecting the nucleus, fascicle, or nerve itself. It often follows a subacute and progressive course. Suspicion of neurosarcoidosis arises when multiple concurrent cranial neuropathies are present. The most commonly affected nerves are the optic, facial, and vestibulocochlear nerves [10].

Peripheral facial nerve paralysis develops in 25 to 50 percent of patients with neurosarcoidosis. Facial nerve paralysis can be unilateral or bilateral (simultaneous or sequential) and recurrent. Heerford's syndrome (parotiditis, fever, anterior uveitis, and peripheral nerve paralysis) is an uncommon manifestation of facial paralysis in sarcoidosis [11].

Isolated paralysis of ocular motor nerves is rare, with the sixth nerve (abducens nerve) most commonly associated as a sole affected nerve [13]. More commonly, multiple ocular motor nerves are affected, often due to involvement within the cavernous sinus [13]. There have been several case reports of patients presenting with a range of supranuclear paralysis, including internuclear ophthalmoplegia and vertical gaze palsy due to sarcoidosis [14].

Sarcoidosis can affect the optic nerve itself or the optic nerve sheath. Optic neuritis is reported as the most common afferent manifestation of neurosarcoidosis (30-70%) [15]. Table 1 outlines the key characteristics of optic neuropathy due to sarcoidosis and the main differences from neuropathy caused by typical demyelinating diseases. Optic neuropathy can be bilateral, involve the chiasm, and carries a poor prognosis despite treatment [16].

The vestibulocochlear nerve is less commonly affected than the previously mentioned nerves, causing vestibular dysfunction and/or hearing loss.

Table 1: Differential Diagnosis between Sarcoidosis-Related Neuropathy and Demyelinating Diseases [15].

	Optic Neuritis associated with sarcoidosis	Optic neuritis associated with demyelination disorders of the central nervous system
Demographic	Bimodal peak 20-40 and 50-60 years Women > Men Afro-american > caucasians	20-30 years old Women >> Men Caucasians >> Afro-american
Beginning	Subacute	Subacute
Clinical Signs	Loss of vision moderate to severe Disc inflammation > retrobulbar Pain 20-30% Unilateral > Bilateral	Retrobulbar > Disc inflammation Pain 60% Unilateral
Imaging	Hyperintensity on images T2 and enhancement contrast. Presence of others granulomas elsewhere to along the optic nerve pathway	Hyperintensity on images T2 and enhancement contrast. Periventricular, yuxtacortical and cortical lesions. Perpendicular periventricular changes (Dawson`s fingers)
Treatment	Good answer to steroids.	Good answer to steroids
Prognostic	High early relapse rate	Most get better

Meningitis

Sarcoidosis can manifest as a chronic meningitis syndrome due to inflammation of the pachymeninges or leptomeninges. Brain MRI may show leptomeningeal enhancement often associated with a nodular component, causing a clinical-radiological dissociation (findings that appear more severe than the clinical symptoms) and can lead to cranial neuropathy or crises. Communicating hydrocephalus is also characteristic, usually occurring due to chronic meningitis. The occurrence of pachymeningitis is less common [17].

Myelopathy

Sarcoidosis can affect the spinal cord through various mechanisms, including parenchymal infiltration, leptomeningeal involvement, extradural space, or extra-spinal tissues leading to spinal canal compression. It typically occurs in up to 26% of patients with neurological manifestations of sarcoidosis. It usually causes longitudinally extensive myelitis (defined as affecting at least 3 vertebral segments) [18].

MRI reveals linear or nodular leptomeningeal enhancement associated with parenchymal hyperintensity in T2-weighted sequences. Radiological features suggesting a diagnosis of sarcoidosis-related myelitis include the appearance of subpial enhancement in the dorsal region of the spinal cord involving at least 2 spinal segments for at least 2 months after treatment [19]. Another finding that may suggest sarcoidosis as the etiology is the "trident sign," which presents as posterior subpial enhancement accompanied by enhancement of the central canal in contrast-enhanced T1 sequences [20].

Sellar and Parenchymal Involvement

Neurosarcoidosis can also affect the cerebral parenchyma, leading to nodular or diffuse lesions in the white matter, as well as hypothalamic-pituitary lesions. These lesions can result in hypothalamic-pituitary dysfunction, affecting LH/FSH (89%), TSH (67%), and causing diabetes insipidus (65%) [22]. In some cases, hemorrhagic or ischemic strokes can occur due to granulomatous angiitis [21].

Peripheral Neuropathy

Manifestations in the peripheral nervous system can take the form of mononeuropathy, multiple mononeuritis, or polyneuropathy, involving sensory, motor, or sensorimotor components. Electromyography typically shows an axonal neuropathy pattern, although cases of acute demyelinating neuropathy mimicking Guillain-Barré syndrome have been described [23]. Small fiber neuropathy is common in systemic sarcoidosis, presenting as altered perception of pain and temperature in the distal extremities [24].

Muscular Involvement

Muscle involvement in sarcoidosis can appear as nodules, acute, subacute, or progressive myopathy, and muscle atrophy.

Diagnosis

Diagnostic Criteria

In 2018, diagnostic criteria for neurosarcoidosis were published based on expert consensus. Diagnosis was categorized as definite, probable, or possible based on clinical findings, phenotype, and confirmation through biopsy [25]. (Table 2)

Table 2: Diagnostic Criteria for the Diagnosis of Neurosarcoidosis.

Definitive:	Clinical presentation and diagnostic evaluation suggest neurosarcoidosis, defined as clinical manifestations and typical findings on MRI, CSF study, and/or EMG/ENG of granulomatous inflammation in the nervous system after rigorous exclusion of other causes. The pathology of the nervous system is consistent with neurosarcoidosis Type A. Extraneural sarcoidosis is evident. Type B. No involvement of sarcoidosis beyond the nervous system (isolated CNS sarcoidosis)
Probable:	Clinical presentation and diagnostic evaluation suggest neurosarcoidosis, defined as clinical manifestations and typical findings on MRI, CSF study, and/or EMG/ENG of granulomatous inflammation in the nervous system after rigorous exclusion of other causes. There is pathological confirmation of systemic granulomatous disease compatible with sarcoidosis.
Possible:	Clinical presentation and diagnostic evaluation suggest neurosarcoidosis, defined as clinical manifestations and typical findings on MRI, CSF study, and/or EMG/ENG of granulomatous inflammation in the nervous system after rigorous exclusion of other causes. There is no pathological confirmation of granulomatous disease

Blood Tests

In serum tests, there is no sensitive or specific marker for the diagnosis of sarcoidosis, so their primary utility lies in excluding alternative diagnoses and monitoring systemic manifestations of sarcoidosis.

It's necessary to request a complete blood count, comprehensive metabolic panel (including liver and kidney function tests), electrolytes (including calcium), vitamin D, glomerular sedimentation rate, C-reactive protein, 24-hour urine analysis, serology for HIV and syphilis, ANA, ANCA (anti-neutrophil cytoplasmic antibodies) for MPO and PR3, IgG AQP4 and MOG antibodies, and tuberculosis testing.

Elevated vitamin D levels and hypercalcemia are often present and should lead us to consider hyperparathyroidism.

Elevated levels of ACE (angiotensin-converting enzyme) are usually seen in 60-75% of patients with pulmonary sarcoidosis, but this test is not sensitive or specific [26]. The value of monitoring ACE during treatment is still not clear.

Cerebrospinal Fluid (CSF) Analysis

CSF analysis in a patient suspected of having neurosarcoidosis should always be performed to observe intrathecal inflammation and exclude other pathologies. There is no pathognomonic result for sarcoidosis.

The analysis should at least include opening pressure, cell count, protein, glucose, IgG, oligoclonal bands (OCB), microbiological cultures for bacteria and mycobacteria, PCR for EBV (Epstein-Barr Virus), VZV (Varicella Zoster Virus), VDRL (Venereal Disease Research Laboratory test), and ACE.

Results may show [18]: Elevated opening pressure (10%), hyperproteinorrachia (66%) above 250 mg/dL, pleocytosis in 50% of cases (predominantly mononuclear). Glucose levels can be normal or low. IgG index might be elevated, and oligoclonal bands could be present. Elevated ACE concentration is occasional but can also appear in infectious meningitis or meningeal carcinomatosis. Interleukin-2 levels might be elevated, but this test is not routine.

Imaging Techniques

Contrast-enhanced magnetic resonance imaging (MRI) is the imaging technique to be performed when neurosarcoidosis is suspected. Findings can be quite diverse, involving cerebral parenchyma, perivascular infiltration, and lepto- and pachymeningeal involvement [27,28]:

In the cerebral parenchyma, lesions may appear nodular, iso-hypointense on T1-weighted images, and hyperintense on T2 and FLAIR images. Generally, they enhance after contrast administration, but the absence of enhancement is not an exclusion criterion (Figure 1) [29].

At the pachymeningeal level, there can be homogeneous enhancement and occasionally the presence of masses that are hypointense on T2-weighted images (a characteristic but not pathognomonic sign) (Figure 2). Leptomeningeal enhancement can be focal or generalized, nodular, or smooth, and it can lead to hydrocephalus.

Involvement of the pituitary and hypothalamus can be confined to the infundibulum.

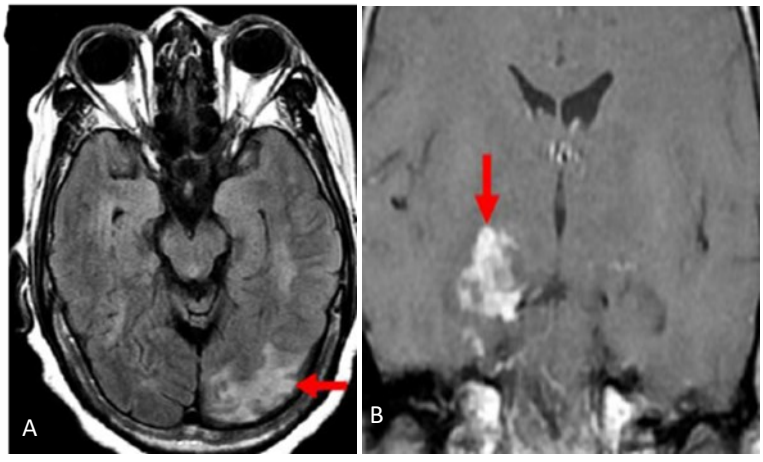


Figure 1: A: *T2/FLAIR; MRI of definite NS demonstrates T2 hyperintensity in the occipital lobe (arrow).*

B. *Mass-like lesion in the right mesial temporal lobe with enhancement (arrow) on post- gadolinium T1 MRI.*

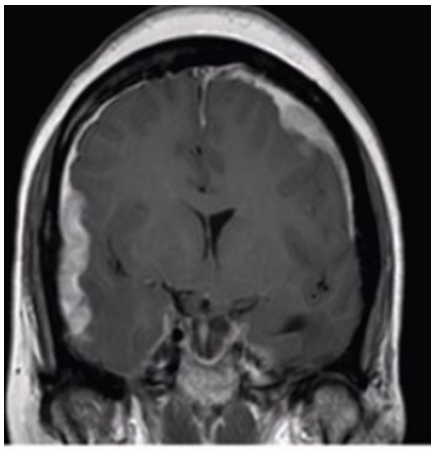
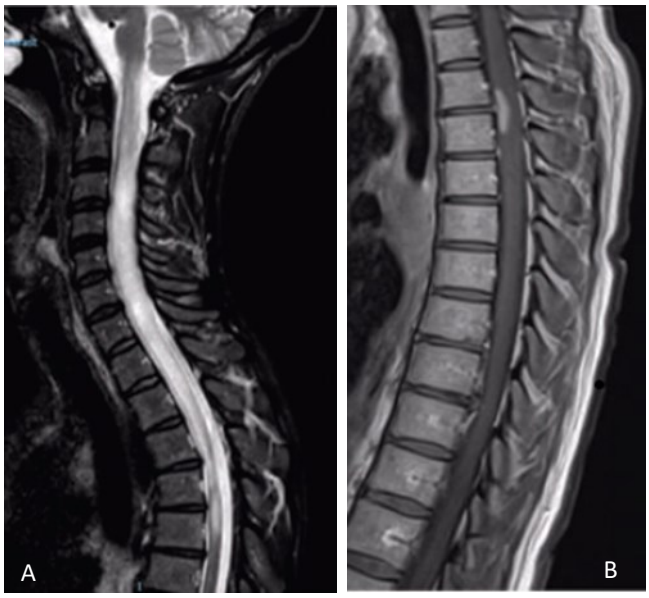


Figure 2: *Pachymeningeal disease in neurosarcoidosis.*

At the spinal level, typical patterns often include longitudinally extensive myelitis, isolated segments with myelitis, perivascular lesions, leptomeningeal enhancement, lesions that mimic masses in the leptomeninges, and lumbosacral radiculitis (Figure 3).

Figure 3: *Spinal Lesions in Neurosarcoidosis.*



A: *Secuencia T2. Longitudinally extensive myelitis.*

B. *Lesion of the thoracic cord.*

Biopsy

If the diagnosis remains uncertain, occasionally meningeal, cerebral, or spinal cord biopsy may be indicated. Biopsy of extraneural tissue from other clinically affected organs is generally preferable when feasible, as it can help avoid significant complications; biopsies of the skin, lymph nodes, and lung (transbronchial) can be quite informative [30].

Biopsy should be considered to establish a diagnosis instead of empirical therapy, particularly when there is no defined systemic disease. Biopsy, as an effort to explore an alternative neurological diagnosis, should also be considered for patients with known systemic sarcoidosis and neurological disease that is progressively deteriorating despite treatment [31].

Treatment

There are no clinical trials specifically focused on treating neurosarcoidosis, but there are recommendations from expert consensus. Sarcoidosis is typically a systemic disease, and treatment should address the disease burden in all affected organs.

Glucocorticoids are the first-line agents for treating neurosarcoidosis, and the dose and duration of therapy should depend on the severity of the disease and the response to treatment.

For severe cases, high-dose methylprednisolone boluses (1 g daily for 3-5 days) followed by a subsequent tapering course of oral corticosteroids can be used. For milder presentations, oral doses between 0.5-1 mg/kg/day may be employed [17].

Patients who worsen despite glucocorticoid treatment, cannot tolerate glucocorticoids, or have a significant contraindication to glucocorticoid therapy may benefit from alternative therapies. Expert opinion suggests considering alternative therapies early in the treatment course for patients on high-dose glucocorticoid treatment and those with manifestations likely to require prolonged treatment. In such cases, mycophenolate mofetil, azathioprine, methotrexate, cyclophosphamide, and leflunomide are often employed [30].

Tumor Necrosis Factor (TNF) inhibitors, especially infliximab, are used in severe cases. Close monitoring for recurrences is necessary when ending treatment with these drugs. Adalimumab has also demonstrated effectiveness for neurosarcoidosis [17].

Through case series, Rituximab has shown benefits in refractory cases of neurosarcoidosis [32].

New therapies like Tofacitinib, Baricitinib, and Tocilizumab have been used for refractory cutaneous and systemic sarcoidosis, but their use in patients with neurosarcoidosis is not well described [17].

Conclusion

Sarcoidosis is a multisystem granulomatous disorder of unknown etiology. Neurologic manifestations occur in more than 5% of sarcoidosis patients and may be the presenting feature. The diagnosis of neurosarcoidosis is usually based on the identification of characteristic neurologic findings in an individual with proven systemic sarcoidosis as established by clinical, imaging, or histologic findings. Even after proper diagnosis, treatment of neurosarcoidosis poses problems. Although corticosteroids are regarded as the foundation of treatment, they are not always successful and have serious side-effects. Moreover, some patients with neurosarcoidosis are refractory to conventional therapy.

Conflict of Interest

The authors declare no conflict of interest.

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