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Khushi Saigal,
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Neurosarcoidosis: overview of management and differentiation from fungal aetiologies

Shawn Khan[1], Khushi Saigal[1], Juan Varela[1], Gabriel Flambert[1], Parth Patel[1], Arman Mahmood[1], Brandon Lucke-Wold[2]

[1] University of Florida College of Medicine, Gainesville, Florida, USA
[2] Department of Neurosurgery, University of Florida, Gainesville, Florida, USA

Keywords
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Abstract

Neurosarcoidosis, a rare inflammatory condition, poses a diagnostic challenge due to its various clinical presentations and potential mimics. This comprehensive review delves into the complexities of neurosarcoidosis, emphasizing the importance of a thorough diagnostic workup and the consideration of alternative conditions, such as fungal mimics. The study explores the intricacies of the diagnostic process, particularly the role of histopathology, imaging, and laboratory tests. The current state of neurosarcoidosis management is examined, such as the use of corticosteroids as well as novel therapies including Rituximab and JAK-STAT inhibitors. The clinical spectrum is described in detail for both the peripheral and central nervous systems, offering insights into the many presentations, which include ocular manifestations and syndromes like Heerfordt's syndrome. The complexities of neurosarcoidosis necessitate further research in its diagnosis, pharmacotherapy, and management. The inclusion of information on ongoing research and clinical trials underscores the need for tailored therapeutic approaches.

Introduction

Sarcoidosis is an inflammatory condition that affects multiple systems and is identified by the development of granulomas, which can emerge in various organs. Neurosarcoidosis, which involves the nervous system, impacts 5–10% of individuals and has the potential to result in severe consequences [1-5].

Typical manifestations of neurosarcoidosis encompass cranial neuropathies, leptomeningeal disease, intraparenchymal lesions, and myelitis. Nevertheless, there have been documented instances of initial presentations involving stroke, seizures, cerebral vasculopathy, intracranial masses, hypopituitarism, neuropsychiatric symptoms, and encephalopathy [1,2]. Neurosarcoidosis frequently impacts the pulmonary system, lymph nodes, eyes, and skin as the most common systemic sites affected in patients [1].

Corresponding author:
Brandon Lucke-Wold

University of Florida, Gainesville, Florida, USA

Brandon.Luck-Wolde@neurosurgery.ufl.edu

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Diagnosing the condition can be challenging because of the diverse range of clinical symptoms, the fluctuating nature of concurrent systemic ailments, and the difficulties in obtaining a central nervous system (CNS) biopsy for a conclusive diagnosis. To diagnose neurosarcoidosis, according to existing guidelines, the patient should exhibit a neurological clinical presentation consistent with the condition, and other potential causes must be ruled out. Patients meeting these criteria can be categorized as having a "possible" diagnosis of neurosarcoidosis[6].

A biopsy revealing granulomatous inflammation is required to diagnose definite neurosarcoidosis (via nervous system biopsy) and probable neurosarcoidosis (via biopsy of a systemic site). However, this alone is not conclusive for diagnosis, as various granulomatous diseases, including infections, autoimmune conditions, and neoplastic disorders, can mimic sarcoidosis and initially respond to corticosteroid treatment. In cases where patients with a confirmed diagnosis of systemic sarcoidosis undergo cranial neuropathies or exhibit leptomeningeal disease indicative of neurosarcoidosis, there is a potential risk of overlooking other possible causes. It is crucial to recognize that these patients do not automatically fulfill the criteria for "probable" neurosarcoidosis without considering mimicking conditions. Other potential diagnoses, such as atypical infection and malignancy, especially in light of treatment-related complications, should be taken into account. Common mimics of neurosarcoidosis include tuberculosis, cryptococcus, primary angiitis, granulomatosis with polyangiitis, IgG4-related disease, and primary central nervous system lymphoma. Fundamentally, any granulomatous infections infiltrating the central nervous system can imitate neurosarcoidosis. These infections encompass atypical bacteria (such as mycobacterial, syphilis, Whipple's disease, brucellosis, nocardiosis, and actinomycosis), fungi (including aspergillosis, cryptococcosis, and endemic mycoses), and parasites (such as toxoplasmosis, schistosomiasis, neurocysticercosis, and toxocariasis)[7,8].

Although many of these infections are uncommon and demand a heightened suspicion for diagnosis, it is crucial to rule them out before initiating immunosuppressive therapies. A comprehensive exposure history and examination can guide diagnostic testing. Notably, mycobacterial and fungal infections frequently mimic sarcoidosis and should be assessed in all individuals suspected of having neurosarcoidosis.

Several current randomized controlled trials (RCTs) are assessing novel therapeutic compounds, innovative targets for treatment, and alternative regimens to steroids in sarcoidosis, and several of them have shown positive results in early phases[8,9].

Clinical presentation

The presentation of neurosarcoidosis is known to be quite variable and non-specific, which may make diagnosing this disease difficult. Firstly, neurosarcoidosis can affect either the central nervous system (CNS), the peripheral nervous system (PNS), or both[10]. The most frequent manifestations are onset of cranial nerve-palsies and neuropathies; however, other manifestations include aseptic meningitis, parenchymal brain lesions, hydrocephalus, headache, seizure, neuropsychiatric abnormalities, neuroendocrine dysfunction, myelopathy, and peripheral neuropathy[10-17]. Fritz et al. reported that, in a meta-analysis and systematic review, 55% (572/1047) of patients with neurosarcoidosis presented with cranial neuropathy, and of the cranial nerves, the facial nerve (24%) and optic nerve (21%) were involved the most frequently[1]. It was similarly reported that sensory and motor abnormalities (hemiparesis, paraparesis), spinal cord abnormalities, and PNS involvement (polyneuropathy, myopathy) are other common presenting features. Sarcoidosis-associated facial nerve palsy may be unilateral or bilateral[6,10,18]. Other studies have reported that approximately 50% of cohorts reported CNS involvement and that potentially affected areas include brain parenchyma with multiple masses as well meninges with hypertrophic pachymeningitis; vascular disease with associated stroke also may be an affect area but is rare[19-40]. Clinical symptoms may manifest in an acute fashion or progress chronically; however, spontaneous regression is more common than progressive neurological deterioration[41-44].

The main CNS clinical manifestations of neurosarcoidosis can be further divided into the various systems affected: brain, spinal cord, and meningeal disease[19]. Brain involvement can be differentiated into parenchyma manifestations,

which may result in the symptoms such as headaches, hormonal disturbances, SIADH, focal deficits, behavioral/cognitive changes, seizures, visual changes, and vascular manifestations, which may result in the symptoms such as strokes, confusion, and cognitive impairment. Meningeal disease can similarly present with symptoms such as headaches, cognitive changes, gait dysfunction, and hydrocephalus; spinal cord manifestations can also similarly present with symptoms such as gait changes, sensory changes, weakness, and bowel/bladder disturbances.

Conversely, the main PNS clinical manifestations can be further divided into various neuropathies, namely, cranial neuropathy, small fiber neuropathy, and large fiber neuropathy[19]. Cranial neuropathy may present as symptoms such as anosmia, decreased visual acuity, facial numbness, hearing loss, dysarthria, dysphagia, and hiccups[45,46]. Small fiber neuropathy may cause painful paresthesia and dysautonomia (GI, orthostasis), whereas large fiber neuropathy may cause polyneuropathy, mononeuritis multiplex, radiculopathy, plexopathy, paresthesia, weakness, and gait disturbance. Figure 1 depicts the various clinical manifestations of neurosarcoidosis.

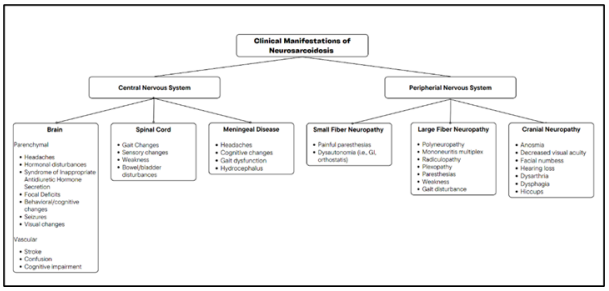

Figure 1. Clinical Manifestations of Neurosarcoidosis.

One syndrome highly suggestive of sarcoidosis is Heerfordt's syndrome, a cranial neuropathy (primarily facial nerve) with uveitis, parotid-gland enlargement, and fever[47,48]. Additionally, Horner syndrome, Argyll-Robertson pupil, and Adie's pupil has been described in sarcoidosis[42,49-52]. Another common ocular manifestation of neurosarcoidosis is optic neuritis which typically presents with blurred vision, a change of color vision, or visual field deficit[10,11]. Optic neuritis related to neurosarcoidosis is a neuro-ophthalmic emergency because it may result in permanent vision loss if there is no immediate intervention. Additionally, common findings indicating neurosarcoidosis on ophthalmologic examination include papilledema or optic nerve head edema[11].

Fungal Mimickers

Rare in non-immunodeficient individuals and more present in immunocompromised patients, central nervous system (CNS) fungal infections have the following main etiologies: mucormycosis, endemic mycoses, *Aspergillus* meningitis (Aspergillosis), and Cryptococcal meningitis *(C. gattii, C. neoformans*)[53]. Manifestations of CNS fungal infections involve intracranial granuloma formation, a central clinical finding in neurosarcoidosis presentation[54]. In that regard, it is essential to rule out fungal mimics when a patient presents with neurosarcoidosis symptoms for effective treatment.

Mucormycosis (*Apophysomyces*)

Mucormycosis is an infrequent fungal infection that occurs in individuals with compromised immune systems, with the rhinocerebral variant being the most prevalent form of presentation[55]. Patients with rhinocerebral mucormycosis exhibit symptoms such as fever, lethargy, black nasal secretions, headache, orbital pain, orbital cellulitis, proptosis, and may experience sudden vision loss, often accompanied by a characteristic necrotic ulcer in the palate or nasal mucosa. Additionally, they may display signs of palsies involving cranial nerves III, IV, V, and VI, such as ptosis, mydriasis, diplopia, and loss of sensation on the ipsilateral side of the face due to local infiltration into the cavernous sinus. While facial paralysis is a rare occurrence, it has been reported in the past[56]. Sarcoidosis, which can manifest as basal meningitis, brainstem and hypothalamus parenchymal involvement, cranial neuropathies, and is associated with systemic features like erythema nodosum and pulmonary symptoms, can mimic mucormycosis[57].

Endemic Mycoses

Coccidioides species belong to the dimorphic fungi category within the Ascomycete division[58]. The two species identified as causing human disease are *Coccidioides immitis* and *Coccidioides posadasii*[59,60]. While most individuals infected with coccidioidomycosis do not show symptoms, those who do experience symptoms typically exhibit mild

flu-like manifestations, muscle and joint pain, rash, and pulmonary symptoms[60,61]. Disseminated coccidioidomycosis is observed in around 1% of infected individuals, and its most severe manifestation is meningitis[60]. Central nervous system (CNS) involvement can happen in as many as 50% of individuals experiencing disseminated coccidioidomycosis, typically emerging within weeks to months after the primary infection[62]. The prevalent manifestation is basilar meningitis, which might be accompanied by complications like hydrocephalus and vascular infarcts[61,63]. Failure to recognize CNS coccidioidomycosis promptly can have severe consequences; hence, early identification and treatment are crucial to minimize mortality and morbidity[61].

After analyzing 71 cases of coccidioidal meningitis, it was observed that 42% were immunocompromised, and 45% reported a prior illness indicative of pulmonary coccidioidomycosis[63]. The primary symptom of CM is typically a headache, accompanied by other symptoms such as fever, neck stiffness, nausea, and vomiting[60,62]. In rare instances, patients may undergo changes in personality, cognitive abnormalities, decreased consciousness levels, and focal neurologic symptoms. Notably, in 50% of cases, an MRI may reveal no abnormalities[59,60,64]. A positive cerebrospinal fluid (CSF) culture for *Coccidioides* or the presence of CSF coccidioidal IgG antibodies is nearly confirmatory for coccidioidal meningitis. The most dependable diagnostic tests include serology using ELISA for initial screening, followed by immunodiffusion tests for IgM and IgG, and complement fixation for IgG[59,60]. In cases where results are inconclusive, but suspicion remains high, polymerase chain reaction (PCR) of CSF can assist in confirming the diagnosis of coccidioidomycosis[65,66]. Additionally, the utilization of 1,3-Beta-D-Glucan testing in CSF may serve as a valuable tool for excluding CM, particularly in immunocompromised patients with potential delays in antibody production[67,68].

Aspergillosis

The increased concern for CNS Aspergillosis infection is present in both immunocompromised and immunocompetent individuals. Like Cryptococcal meningitis, *Aspergillus* meningitis is recognized as one of the most common CNS fungal infections. More prevalent in immunocompetent patients than immunocompromised, the infection can be detected through PCR methodology of collected CSF[69]. Although fungal cultures of collected CSF can be used, they are not the most effective detection method as they tend to be negative in 70% of *Aspergillus* meningitis infections[70].

Cryptococcal meningitis

Cryptococcal meningitis is a cerebral infection resulting from the presence of the fungus cryptococcus, either in the form of *Cryptococcus neoformans* or *Cryptococcus gattii*. It stands out as one of the common causes of meningitis, especially in individuals with compromised immune systems, particularly those affected by Human Immunodeficiency Virus/Acquired Immune Deficiency Syndrome (HIV/AIDS)[71].

Typical meningeal symptoms like headaches and neck stiffness are commonly observed in classic cryptococcal meningitis. However, additional systemic indications of widespread infection, such as pneumonia and dermatological symptoms, may also manifest[71]. Consequently, it is crucial to assess immunocompetent patients with subacute to chronic meningitis for the presence of *Cryptococcus neoformans*. While serum cryptococcal antigen and radiographic imaging aid in identifying CM, a lumbar puncture is indispensable for a definitive diagnosis[71,72]. Elevated opening pressure during the lumbar puncture, predominantly mononuclear cells, the visualization of encapsulated yeast using India ink, and a positive CSF culture of the organism are characteristic findings that confirm the diagnosis[72].

Invasive cryptococcosis involves two fungi, *C. neoformans* and *C. gatti*, both of which are encapsulated yeasts. Notably, *C. neoformans* is linked to immunocompromised hosts, while *C. gatti* is known to occur in individuals with intact immune systems[73,74]. Cryptococcus species tend to affect the central nervous system, especially in individuals with compromised immune systems, owing to their numerous virulence factors. Nevertheless, the occurrence of cryptococcal meningitis in immunocompetent patients remains challenging to elucidate. Potential reasons for this occurrence may include exposure to a highly pathogenic strain of Cryptococcus, a significant level of exposure to the pathogen, or subtle and undetectable immune deficiencies. These deficiencies could be linked to factors such as alcoholism, diabetes mellitus, or

autoimmune conditions. In immunocompetent individuals, the cryptococcus species are more inclined to lead to pulmonary cryptococcosis compared to immunocompromised individuals. Likewise, neuroimaging results are more confined and may involve hydrocephalus in immunocompetent patients[73,74].

The clinical presentation of cryptococcal meningitis in immunocompetent patients typically exhibits characteristic features like fever, stiff neck, headache, vomiting, or altered mental status. This contrasts with immunocompromised individuals, who typically display only subtle clinical features[75]. Imaging may reveal observations such as cerebral infarction, granulomas, and pseudocysts. One case report described a case involving a 29-year-old immunocompetent woman with no known comorbidities, experiencing intermittent headache and vomiting. Ultimately, she was diagnosed with cryptococcal meningitis. Despite her neuroimaging results deviating from the typical findings in CM cases, the diagnosis was confirmed through a cryptococcal antigen test. The neuroimaging results did not indicate the presence of hydrocephalus; instead, they revealed a ring-enhancing lesion resembling the characteristics observed in the colloidal vesicular stage of neurocysticercosis. However, contrary to the favorable prognosis indicated in the literature, she passed away during her hospitalization[75].

Table 1 lists the fungal mimics of neurosarcoidosis including similarities to neurosarcoidosis and distinct features.

	Shared CNS features	Shared systemic features	Distinguishing features	Diagnostic testing
Tuberculosis	• Predilection for the skull base (basilar meningitis) • Leptomeningeal enhancement • Cranial neuropathies • Dural masses • Initial steroid response	• Pulmonary disease • Lymphadenopathy • Ocular inflammation • Constitutional symptoms • Arthropathy	• More likely to cause clinical meningitis, basilar exudates on neuroimaging, caseating granulomas on biopsy	• CSF AFB smear, culture and PCR
Cryptococcus	• Leptomeningeal enhancement • Cranial neuropathies • Dural masses • Initial steroid response	• Pulmonary disease • Lymphadenopathy • Ocular inflammation • Constitutional symptoms	• More likely to cause meningitis and hydrocephalus • Pulmonary presentation can cause acute pneumonia or ARDS	• Serum cryptococcal antigen testing by LAF CSF culture
PACNS	• White matter lesions • Leptomeningeal enhancement • Vasculitis with noncaseating granulomas on biopsy • Steroid response	• No systemic features	• No systemic features • More likely than neurosarcoidosis to cause CNS vasculitis	• CNS biopsy
GPA	• White matter lesions • Steroid response • Pachymeningeal enhancement • Ocular inflammation	• Pulmonary disease • Lymphadenopathy • Ocular inflammation • Sinusitis • Constitutional symptoms • Arthropathy	• More likely to cause diffuse alveolar hemorrhage, rapidly progressive glomerulonephritis, vasculitic skin rashes	• Biopsy of CNS or other systemic organ • ANCA, anti-MPO, anti-PR3
IgG4-RD	• Pachymeningeal enhancement • Intraparenchymal mass • Cranial neuropathies • Steroid response	• Lymphadenopathy • Ocular inflammation with or without pseudotumor • Sinusitis • Constitutional symptoms	• More likely to cause pancreatitis, retroperitoneal fibrosis, and kidney infiltration • Vasculitis more frequently seen	• CNS biopsy, staining for IgG4 plasma cells, looking for evidence of storiform fibrosis and obliterative phlebitis

Table 1. Fungal mimics of neurosarcoidosis with shared and distinguishing features.

Overview of management

Diagnostic workup

Neurosarcoidosis is an inflammatory disorder that clinically manifests in multiple body systems, identified by the presence of non-caseating granulomatous lesions[5]. Retrospective studies and case reviews have demonstrated that approximately half of patients with systemic sarcoidosis likewise have neurological symptoms, demonstrating the distinct need for a full neurosarcoidosis workup when assessing patients in clinical settings[76,77]. Patients with neurosarcoidosis experience lesions and subsequent dysfunction of nerve, brain, spinal cord, meningeal, and muscular tissue, resulting in common findings of frequent headaches, ataxia, visual disturbances, facial nerve palsy, fatigue, and somato-sensory disturbances[77]. Diagnosis is difficult due to the myriad possible causes of granulomatosis, including bacterial CNS infections, inflammatory diseases, and lymphomas[4]. As a result, ruling between differential diagnosis and definite neurosarcoidosis necessitates the identification of accordant clinical scenarios, histological determination of non-caseating granulomas in tissue, and imaging/laboratory testing supporting diagnosis, as noted by Zajicek et al[5].

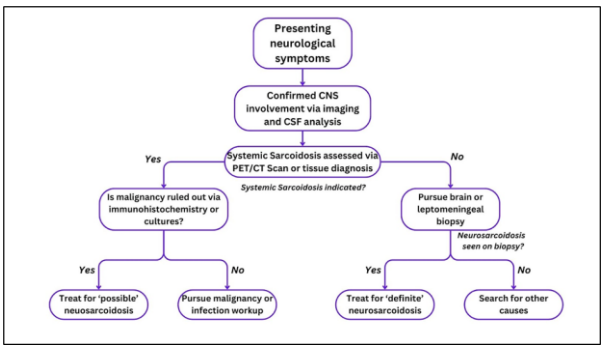

Figure 2. Neurosarcoidosis workup.

The 1999 joint statement on sarcoidosis by the American Thoracic Society (ATS), the European Respiratory Society (ERS), and the World Association of Sarcoidosis and Other Granulomatous Disorders (WASOG) established the primary diagnostic and treatment modalities for sarcoidosis and subsequent neurosarcoidosis[78]. More recently, the Neurosarcoidosis Consortium Consensus Group leveraged novel guidelines for diagnosing neurosarcoidosis, suggesting 'possible,' 'probable,' and 'definite' diagnostic criteria for diagnosis[76]. Stern et al. proposed a 'possible' neurosarcoidosis diagnosis in situations with established clinicoradiological findings but lacking histological evidence; a "probable" diagnosis when existing clinicoradiological results are supported by pathologic indication of granulomatous disease; and 'definite' for instances where nervous system biopsy confirms neurosarcoidosis[76]. Figure 2 illustrates the workup for neurosarcoidosis.

Imaging

Clinical disease manifestations in patients most commonly appear as cranial neuropathies, optic neuropathies, endocrine/hypothalamic dysfunction, seizures, meningitis, myelopathies, myopathy, peripheral neuropathy, and intracranial masses[79]. Subsequent imaging for diagnosing neurosarcoidosis involves the usage of computed tomography (CT) and Gadolinium-enhanced magnetic resonance imaging (MRI), the latter being the current gold standard for assessing the brain parenchyma, meninges, and spinal cord[80]. The most common MRI finding is basilar leptomeningeal involvement, presenting as diffuse thickening of the dural meninges; but focal masses, persistent pseudotumor changes, and involvement of hypothalamus/pituitary and cranial nerves are also noted in neurosarcoidosis[81,82]. CT scans may show hydrocephalus, intracranial calcification, and enhancing nodules, but they lack the sensitivity of MRI modalities[76].

Due to the multi-organ nature of sarcoidosis and subsequent neurosarcoidosis, chest radiography is an indicated tool for ruling out pulmonary disease, as the lungs are the most affected organ, and most frequently present with hilar lymphadenopathy[76,83]. Although the decreased sensitivity of chest radiographs presents an inherent drawback in diagnosing neurosarcoidosis, chest radiography was involved in correct diagnoses 71% of the time in observational cohort studies by Zajicek et al[5]. The use of fluorodeoxyglucose positron emission tomography (FDG-PET) can likewise assist in differentiating granulomatous lesions in neurosarcoidosis from potential malignancy and have been noted as a more useful modality for targeting hypermetabolic lesions for biopsy than CT and MRI[84]. These modalities are seldom used, however, due to their limited availability and cost. To be noted, the use of Gallium-67 scintigraphy and

similar radioisotopic imaging studies have been noted within the literature; these studies can aid in detecting perfusion defects indicative of diminished circulation, as well as sarcoidosis of the lacrimal and parotid glands denoted as the "panda sign"[78,82].

Laboratory and CSF studies

Those who are suspected of neurosarcoidosis should have a cerebral spinal fluid (CSF) analysis. While the CSF analysis is not very specific to diagnosing neurosarcoidosis, the testing could be potentially helpful to determine if there is a malignancy or infection that is mimicking the clinic manifestations of neurosarcoidosis[19,85]. Abnormalities in the CSF are a frequent occurrence in neurosarcoidosis, with one study finding CSF abnormalities in over 80% of cases[5]. Commonly found elevated in the CSF of patients with neurosarcoidosis was an increased ratio of lymphocytes C4/CD8 of greater than 5[82]. Proteins levels, IgG levels, and glucose levels are either normal or low[19,82]. Angiotensin converting enzyme (ACE) is often used in terms of raised protein levels, however the significance of the raised ACE levels in the CSF is yet to be understood[5,19].

Studies have shown that ACE has low specificity and sensitivity for neurosarcoidosis and the levels of ACE in CSF are not likely a key player in diagnosing neurosarcoidosis[86,87]. Another component that may also be taken into account when making a diagnosis is the elevated levels of CSF interleukin 2 receptor. Petereit et al. found that the increase in the levels of interleukin 2 receptor in CSF was associated with the disease activity[85]. Overall CSF analysis could potentially be useful in eliminating other diagnoses, but it does not provide a definitive answer for the diagnosis of neurosarcoidosis. The continued advancement of medical technologies and research have produced novel techniques for improving neurosarcoidosis diagnosis. Future considerations for physicians should include multiplex or broad-range universal PCR and agnostic metagenomic next-generation sequencing for use in specialized laboratory settings; these emerging diagnostic modalities have demonstrated promise in improving diagnosis compared to standard CSF culture[19,88].

Histopathology

Biopsy of leptomeningeal tissue is pursued when assessing a patient for neurosarcoidosis; however, due to the high-risk and invasive nature of targeting brain and intracranial tissue, it is often not performed[76]. Nevertheless, brain or cerebrospinal meningeal biopsy remains the gold standard for confirming a definite neurosarcoidosis diagnosis[82]. Peripheral nerve biopsies are also used for patients who may have diabetes mellitus to rule out the role of diabetes in the diagnosis, due to the similarity in symptomatology and the possibility of patients without symptoms[19].

Another option that was previously available was the Kveim-Siltzbach test or Kevin skin test. This modality involves inoculating a patient with a sarcoidal spleen tissue intradermally for about 5 to 6 weeks after which a skin biopsy is taken[5]. The test was found to have a high specificity of 95% for neurosarcoidosis and also a sensitivity of 79%[89]. However, the Kveim skin test is not used anymore due to safety concerns over the transmission of diseases and the material used for this test, specifically the inoculation material that was obtained from human spleen specimens that is no longer available[83,90].

Treatment

Much of our understanding of neurosarcoidosis comes from autopsy and retrospective studies assessing neurosarcoidosis investigation, treatment, and disease course[83]. Historically, the treatment of neurosarcoidosis has been subject to similar immunopathogenic targeting as seen in systemic manifestations of the disease[19]. Current first-line treatment indicates the use of corticosteroids, although its usage as a monotherapy has become less indicated due to the increased risk of relapse and the contraindications of high dose corticosteroid use. Second-line treatment includes the use of synthetic disease-modifying antirheumatic drugs (csDMARDs), including methotrexate, azathioprine, mycophenolate, hydroxychloroquine, and leflunomide[19,79,81].

Methotrexate remains the most utilized second-line treatment, due to its associations with decreased disease-relapse in comparison to the less commonly used azathioprine, mycophenolate, and hydroxychloroquine[91]. Third-line treatments like anti-tumor necrosis factor drugs (anti-TNF) and cytotoxic agent have historically been used only after the aforementioned failed, yet recent use of infliximab and adalimumab have shown promise in

clinical cohort studies[91,92]. Third-line cytotoxic agents like cyclophosphamide have decreased in usage in recent years due to their high toxicity, yet observational studies like Joubert et al, retain that it may still be useful in severe neurological presentations for neurosarcoidosis, such as in stroke[20]. Overall, the literature indicates first-line corticosteroid administration benefits from being paired with a second-line treatment like methotrexate, improving the drug response and reducing the drug-toxicity of corticosteroid usage alone[4]. Figure 3 depicts the respective lines of treatment for neurosarcoidosis.

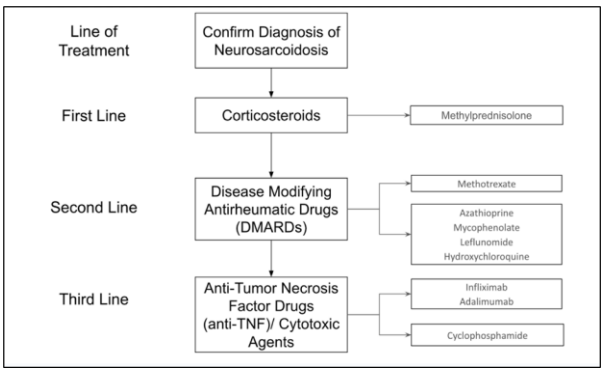

Figure 3. Neurosarcoidosis lines of treatment for neurosarcoidosis.

Emerging Treatment

Neurosarcoidosis, being a relatively rare and understudied manifestation of sarcoidosis, lacks the relevant literature needed to prove the efficacy of pharmacological treatments. Consequently, there are no FDA-approved pharmacotherapies on the market indicated for neurosarcoidosis—only off-label uses of other therapies. On the other hand, the use of prednisone and repository corticosteroid injections (RCI) have been FDA-approved for general sarcoidosis. Current literature regarding the therapy of neurosarcoidosis is composed of retrospective studies and case studies, and thus far, no randomized controlled trials concerning treatment strategies have been completed[93]. Generally, treatment options are derived from studies with regards to the care of pulmonary or general sarcoidosis[94]. Due to the variability of clinical manifestation, severity, and causes, it is imperative that treatments are studied and developed specifically to target neurosarcoidosis, and a few emerging treatments look to do so.

As mentioned previously, repository corticotropin injections (RCI), marketed as Acthar Gel, is an FDA-approved treatment for sarcoidosis and several other conditions[95]. In patients with both general and pulmonary sarcoidosis, RCI use has been shown to reduce the burden of corticosteroids and displayed therapeutic benefit in several studies[96-98]. A study reviewing the use of RCI in patients with sarcoidosis, including neurosarcoidosis, showed improvements in objective measures after three months of RCI use as well as a reduction in prednisone dosage[97].

A clinical trial by the Cleveland Clinic aimed to assess the use of Acthar therapy for neurosarcoidosis, but was withdrawn due to difficulty of recruitment, reaffirming the rarity of this disease (NCT02920710). Another exploratory therapy is rituximab, a monoclonal antibody that targets and depletes CD20+ B-cells[99]. In refractory cases or when steroid use is contraindicated, case reports have shown the effectiveness of rituximab in the therapy of neurosarcoidosis[100-102].

Single-institution retrospective reviews evaluating the use of rituximab in refractory sarcoidosis demonstrated symptomatic relief in the case of granulomatous disease of the eye and a generally positive prognosis[103,104]. Cibinetide (ARA290) is an amino acid peptide derived from erythropoietin and acts by reducing inflammatory and fibrotic responses. These therapeutic targets make it advantageous in targeting sarcoidosis-associated small nerve fiber loss (SNFL), as a prevalent hypothesis behind its etiology is systemic inflammation[105]. Literature has shown that it is not only effective in reversing SNFL but also increasing the density of corneal nerve fibers[106]. Along with these pathological markers, Dahan et al. noted improved patient-reported outcomes and increased exercise capacity using the 6-minute walk test[106].

Double-blinded, phase 2 studies with regular administration of cibinetide in sarcoidosis patients have established safety and shown significant improvements in neuropathic symptoms and a decrease in pain intensity[107,108]. The use of randomized controlled trials in the studies of cibinetide and their positive results make it promising in the development of neurosarcoidosis-specific therapy regimens. JAK-STAT inhibitors have also shown some potential in the treatment of neurosarcoidosis. Genes associated with the JAK-

STAT signaling pathway were differentially expressed between sarcoidosis patients and healthy controls, indicating that JAK-STAT may be implicated in the pathogenesis of sarcoidosis[109]. Specifically, Rosenbaum et al. revealed that granulomas in the lymph nodes of sarcoidosis patients expressed higher levels of STAT1 compared to control levels. Considering the possible immunologic basis for sarcoidosis, this is a possible therapeutic target. Recent studies have shown that the use of Janus kinase inhibitors have resulted in the clinical remission of lesions associated with sarcoidosis[110,111]. Damsky et al. looked at the use of tofacitinib, a JAK inhibitor, in the treatment of one patient with multiorgan sarcoidosis which resulted in the resolution of inflammation from granulomas and a reduction in disease biomarkers[111]. All in all, a lack of conclusive RCTs and general literature regarding neurosarcoidosis therapy remains a major barrier to developing comprehensive treatment strategies.

Conclusion

In conclusion, neurosarcoidosis stands as a challenging and multifaceted entity within the spectrum of inflammatory disorders. The intricacies of its clinical presentation, diagnostic hurdles, and potential mimics necessitate a meticulous approach to ensure accurate identification and appropriate management. As highlighted in this review, advancements in diagnostic tools, ranging from imaging modalities to laboratory studies, play a pivotal role in differentiating neurosarcoidosis from its fungal etiologies. Treatment strategies, currently anchored in corticosteroids and disease-modifying antirheumatic drugs, are witnessing the emergence of novel therapeutic options, offering hope for more specific and efficacious interventions.

The current understanding of neurosarcoidosis presented in this review highlights the need for controlled trials to further the knowledge base surrounding diagnosis and treatment. As we navigate the evolving landscape of diagnostic and therapeutic approaches, this exploration provides a foundation for continued advancements in the understanding and management of neurosarcoidosis.

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