Definition and Consensus Diagnostic Criteria for Neurosarcoidosis: From the Neurosarcoidosis Consortium Consensus Group

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The main question at hand was how to define neurosarcoidosis (NS). At the time of this study, there was no real, consensus definition. As such, the goal of this report was to provide guidance on how to determine the level of diagnostic certainty of neurosarcoidosis (while also excluding potential mimics of NS), for the purpose of also guiding appropriate treatment.

Sarcodiosis was defined in 1999 as a multisystem disorder of unknown cause, though with histologic evidence of noncaseating epithelioid cell granulomas, excluding granulomas of known causes and local sarcoid. However, granulomas can be observed in a wide variety of other disorders that may mimic sarcoidosis; such conditions include infectious etiologies, inflammatory diseases, immunodeficiency states, malignant neoplasms, and reactions to foreign bodies and certain elements (silicosis). In terms of the neurologic complications of sarcoidosis, these occur in 5-10% of patients with sarcoidosis, with an ~8.3/100,000 incidence for all-inclusive sarcoidosis diagnoses. Race (rather than age) seemed to be a significant factor in the prevalence and mortality of sarcoidosis, worst in black American women in the US. Historically, neurosarcoidosis has been difficult to define, as 1) it is often difficult to obtain neural tissue to confirm true, nervous system involvement, and 2) 10-19% of presumed NS patients may not demonstrate evidence of extraneural inflammation. The latter was typically needed for a diagnosis of sarcoidosis, though could also be representative of isolated NS. Other questions and concerns that were raised regarding an NS diagnosis included:

- Can a single organ inflammatory illness represent sarcoidosis?
- Is the extraneural tissue for suspected, isolated NS patients sub clinically involved or did it resolve? If starting on immunosuppressive treatment, would this delay a true diagnosis by suppressing extraneural manifestations?
- Is presumed, isolated NS actually a neurological granulomatous disorders other than NS (e.g. chronic granulomatosis disease, vasculitis)?
- Caseous necrosis may be seen as a rare finding in other infections, such as TB (if not NS).

Study design: In response to the above concerns, the Neurosarcoidosis Consortium Consensus reviewed the available literature related to NS diagnostics. They performed a PubMed search on the broad diagnostic term *neurosarcoidosis* from January 1, 2007, to October 1, 2017, and used the best available evidence and clinical experience to develop the proposed criteria. The group voted (at a predefined threshold of >80%) to support each statement presented here as the proposed diagnostic criteria.

Results: In terms of the agreed-upon, histopathologic characteristics of NS, these are noted below:

- Noncaseating granuloma (histopathological hallmark), rarely with limited necrosis **(Fig 1A).** Such locations often include the base of the brain, perivascular regions, and tumefactive masses in the brain parenchyma or dura (often mimicking a tumor).
- Within neural tissue, collections of grouped epithelioid histiocytes with multinuclear giant cells are often surrounded by non-neoplastic lymphocytes, at times plasma cells **(Fig 1B).**
- Meningeal NS demonstrates a combination of granulomatous and nonspecific lymphoplasmacytic inflammatory reactions. Chronic meningeal NS may result in collagen deposition and fibrosis, leading to a pachymeningeal inflammatory reaction and dense fibrosis.
- Meningeal NS has high frequency of histiocytes, foamy macrophages (CD68+), and infiltration of the granuloma with T lymphocytes (CD4 and CD8+) and B lymphocytes **(Fig 1C – E)**
- In non-NS inflammatory diseases, there is lower frequency of giant cells or granuloma
- Asteroid bodies (stellate-like inclusion within central vacuole of giant cell) may be present

In terms of the clinical manifestations of NS, these are also noted below:

Anatomical location	Clinical Manifestations
Broad CNS disease	Mass lesion, encephalopathy, microvasculopathy, stroke, seizure, brain fog, fatigue. NS also has a predilection for the hypophysis/hypothalamus resulting in endocrinopathies (e.g. hypothyroid, hypogonadism, SIADH)
CN neuropathy	Any CN may be involved. Unilateral or bilateral lower facial nerve palsy is most common. Frequently optic neuropathy or VIII nerve palsy may occur. If vision loss occurs, it is 2/2 extrinsic compression of optic nerve.
Meninges	Aseptic meningitis vs chronic meningitis; mass lesions in meninges (mimicking meningioma)
Hydrocephalus	Communicating vs Noncommunicating
Spinal cord	Subpial intramedullary lesions and meningeal involvement is present in up to ½. Longitudinally extensive myelitis may occur
Autonomics	Vegetative dysfunction, dysautonomia, small fiber neuropathy
Neuropathy	Mononeuropathy, axonal or demyelination, Sensory/Motor/Sensorimotor
Myopathy	Polymyositis, nodules

Finally, in terms of NS mimickers, the most common are listed below:

Category	Examples
Infectious	Lyme, Syphilis, Fungal (coccidiomycosis, histoplasmosis, cryptococcus, spirotrichosis, blastomycosis), TB, meningitis, Whipple's, mycobacterium, PML, HIV, parasitic infection
Neoplastic	Lymphoma, Meningeal carcinomatosis, CNS tumors, Histiocytosis, Cancer-associated granuloma
Neuroinflammatory	MS, MOG, NMO, ADEM, Vasculitis, Lymphocytic hypophysitis, CLIPPERS, Autoimmune astrocytopathy
Rheumatologic (systemic)	SLE, IgG4, Sjogren's, Behcet's, Vogt-Koyanagi-Hanada, CVID
Abnormal CSF Pressure	Syndrome of intracranial hypotension
Vascular	AVM, stroke

Overall, the authors proposed that a diagnosis of NS should take into consideration all of the above clinical features, along with imaging (systemic and neurologic), possible EMG/NCS studies, and appropriate CSF studies. Further, extraneural imaging (CXR, CT chest, FDG-PET or Ga67 scintigraphy imaging to assess for extrapulmonary LN involvement) and tissue biopsy (if available) may be needed. Namely, ~50% of patients with NS will present with neurological symptoms, in the absence of systemic signs, at first presentation. However, the authors noted (via a meta-analysis of 1088 patients), that although only 31% of patients with isolated neurologic symptoms at first presentation had evidence of systemic involvement, 84% of these patients developed systemic manifestations eventually. Typical MRI brain and spine imaging findings are shown in Figure 2, and typical CSF findings are highlighted below:

- Opening pressure may be elevated
- A predominant mononuclear pleocytosis, elevated protein, low glucose, elevated IgG index and OCBs
- (-) results for infectious etiologies (TB, fungal, HSV, lyme, TB, VZV, CMV, EBV) and neoplastic etiologies (flow and cytology)
- NOTE: biomarkers (including ACE) are insufficiently sensitive or specific

With the above features, the authors proposed new diagnostic guidelines for NS, including clinical and histopathological findings that would suggest a possible, probable, or definite diagnosis of NS (see Box, p.E6). These are listed below:

Possible:

1. Clinical presentation and diagnostics suggestive of NS (via MRI, CSF, EMG/NCS), with exclusion of mimickers
2. NO pathologic confirmation of granulomatous disease

Probable:

1) Clinical presentation and diagnostics suggestive of NS with exclusion of mimickers
2) Systemic confirmation of granulomatous disease (though not 100% definitive of a sarcoidosis diagnosis)

Definite:

1) Clinical presentation and diagnostics suggestive of NS with exclusion of mimickers
2) Nervous system pathology is consistent w/neurosarcoidsis

Conclusions: Systemic manifestations of sarcoidosis along with imaging, CSF or EMG/NCS findings all aid in the diagnosis of neurosarcoidosis. There are notable barriers to the direct biopsy and diagnosis of neurological involvement of sarcoidosis, as noted above, and for this reason, alternative sources of tissue (LN or other) may be needed to search for true granulomatous histopathology. In addition, it is imperative to rule out NS mimickers, as these can be numerous. Otherwise, in terms of treatment, there is consensus (per UptoDate) on the use of glucocorticoids as a first line agent. CN palsies or myopathies are treated with prednisone 0.5mg/kg for 2-4wks, meningeal, mass lesions, and vasculopathies with prednisone 1-1.5mg/kg for 4wks, and severe incapacitated or rapid diseases with IVMP 20mg/kg for 3d and then a prednisone taper. Other, non-steroidal treatments include TNFa inhibitors, Methotrexate, Azathioprine, MMF, Leflunomide, and cyclophosphamide, often in combination with low-dose prednisone. Surgically, resection techniques are often not helpful, VPS may be needed to relieve hydrocephalus if present, and radiation therapy may be considered for patients refractory to glucocorticoid and 2 other therapies.

Summary created by Taka Kitani, M.D.