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Definition and Consensus Diagnostic Criteria for Neurosarcoidosis

From the Neurosarcoidosis Consortium Consensus Group

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IMPORTANCE The Neurosarcoidosis Consortium Consensus Group, an expert panel of physicians experienced in the management of patients with sarcoidosis and neurosarcoidosis, engaged in an iterative process to define neurosarcoidosis and develop a practical diagnostic approach to patients with suspected neurosarcoidosis. This panel aimed to develop a consensus clinical definition of neurosarcoidosis to enhance the clinical care of patients with suspected neurosarcoidosis and to encourage standardization of research initiatives that address this disease.

OBSERVATIONS The work of this collaboration included a review of the manifestations of neurosarcoidosis and the establishment of an approach to the diagnosis of this disorder. The proposed consensus diagnostic criteria, which reflect current knowledge, provide definitions for possible, probable, and definite central and peripheral nervous system sarcoidosis. The definitions emphasize the need to evaluate patients with findings suggestive of neurosarcoidosis for alternate causal factors, including infection and malignant neoplasm. Also emphasized is the need for biopsy, whenever feasible and advisable according to clinical context and affected anatomy, of nonneural tissue to document the presence of systemic sarcoidosis and support a diagnosis of probable neurosarcoidosis or of neural tissue to support a diagnosis of definite neurosarcoidosis.

CONCLUSIONS AND RELEVANCE Diverse disease presentations and lack of specificity of relevant diagnostic tests contribute to diagnostic uncertainty. This uncertainty is compounded by the absence of a pathognomonic histologic tissue examination. The diagnostic criteria we propose are designed to focus investigations on NS as accurately as possible, recognizing that multiple pathophysiologic pathways may lead to the clinical manifestations we currently term NS. Research recognizing the clinical heterogeneity of this diagnosis may open the door to identifying meaningful biologic factors that may ultimately contribute to better treatments.

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Supplemental content

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Typical presentations of sarcoidosis permit ready diagnosis in a substantial proportion of individuals with this disease; however, the diagnosis is often rendered difficult by unusual clinical manifestations or diagnostic mimics, which can be organ specific. This difficulty is particularly evident in neurosarcoidosis (NS).[1] Despite numerous publications on NS, no consensus definition of the entity exists and no consensus perspective addresses the prerequisites for establishing a diagnosis. Development of criteria for diagnosis is essential for the design of clinical trials for NS and is valuable to the patient and clinician. A consortium of physicians with expertise in NS has developed consensus criteria for the diagnosis of NS. Because sarcoidosis can affect the central nervous system (CNS) and peripheral nervous system (PNS), occasionally in the absence of other organ involvement, we propose harmonized diagnostic criteria for both the CNS and PNS.

Methods

The Neurosarcoidosis Consortium Consensus Group consisted of 14 members: 10 neurologists and 4 pulmonologists. The group met 5 times in person and conducted additional work via electronic communication. The group started with the premise that a need existed for consensus diagnostic criteria for NS to improve clinical care and support research. The group agreed that diagnostic labels about NS should be based on level of certainty and provide specific guid-

ance about exclusion of potential mimics. The group reviewed the available literature, including performing 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 criteria.

The proposed criteria were submitted to the World Association of Sarcoidosis and Other Granulomatous Disorders executive committee for review and comment. This executive committee endorsed the content of the criteria.

Background

In 1999, the American Thoracic Society, the European Respiratory Society, and the World Association of Sarcoidosis and Other Granulomatous Disorders published a Joint Statement on Sarcoidosis.[2] Sarcoidosis was defined as a "multisystem disorder of unknown cause (s).... The diagnosis is established when clinicoradiological findings are supported by histologic evidence of noncaseating epithelioid cell granulomas. Granulomas of known causes and local sarcoid reactions must be excluded."[3(p736)] There was no specific mention of criteria for the diagnosis of NS.

Given the pivotal role of histologic tissue examination for the diagnosis of sarcoidosis, the joint statement emphasizes that the "characteristic lesion of sarcoidosis is a discrete, compact, noncaseating epithelioid cell granuloma. The epithelioid cell granulomas consist of highly differentiated mononuclear phagocytes (epithelioid cells and giant cells) and lymphocytes. Giant cells may contain cytoplasmic inclusions such as asteroid bodies and Schaumann bodies.... The central portion of the granuloma consists of predominantly CD4+ lymphocytes, whereas CD8+ lymphocytes are present in the peripheral zone. ... Granulomas may occasionally exhibit focal coagulative [fibrinoid] necrosis."[3(p740)]

The presence of granulomas is critical in establishing the diagnosis of sarcoidosis, but granulomas can also be observed in a wide variety of other disorders that may mimic sarcoidosis, such as infectious and inflammatory diseases, immunodeficiency states, malignant neoplasms, and reactions to foreign bodies and certain elements (silicosis). Because granulomas may be a pathologic hallmark of infection, evaluating the patient for infectious causes is critical. If granulomas in biopsy specimens from patients with suspected NS reveal caseous necrosis, every effort should be made to identify an infectious cause, although necrosis can rarely be seen in bona fide NS, especially as a relatively rare finding in a relatively large sample. Stains for acid-fast bacilli and fungi should be used for histologic examination, and tissue samples should be sent for culture and other molecular diagnostics for potential infectious agents. In countries where tuberculosis is endemic, quantitative polymerase chain reaction (PCR) or new nucleic acid amplification assays, such as GeneXpert MTB (Cepheid), may be useful in distinguishing patients with pulmonary sarcoidosis and latent tuberculosis from patients with active tuberculosis.[4] Furthermore, noncaseating epithelioid granulomas may occasionally occur proximate to malignant neoplasms, including CNS malignant neoplasms, or in regional lymph nodes near a carcinoma or lymphoma.[5] Although we emphasize the need to obtain histologic confirmation of systemic sarcoidosis, we understand that, occasionally, the clinical presentation is virtually pathognomonic, such as occurs with Lofgren syndrome; in this circumstance, no histologic tissue examination is required.

A major challenge regarding NS is the difficulty of obtaining neural tissue for histologic and microbiologic analyses. If a patient has clinical evidence of nervous system inflammation consistent with NS and pathologic proof of sarcoidosis in another organ system, nervous system involvement representative of the same pathologic process is typically assumed. This assumption may or may not be true, as 2 or more diseases may coexist.[6] Furthermore, for the subset (approximately 10% to 19%) of patients[7] with presumptive NS and no evidence of systemic extraneural inflammation, the diagnosis can be confirmed only with nervous system biopsy.[8] These patients are believed to have isolated neurosarcoidosis. The questions pertinent for these patients are whether (1) a single-organ inflammatory illness represents sarcoidosis, which characteristically involves multiple organs; (2) extraneural tissues are subclinically involved[9] or the disorder spontaneously resolved; or (3) a neurological organ-specific granulomatous disorder distinct from sarcoidosis exists. In addition, NS may herald systemic sarcoidosis, and immunosuppressive treatment for NS may render the subsequent demonstration of systemic disease difficult.[10]

Because of the aforementioned challenges, we propose a pragmatic approach to the diagnosis of NS that emphasizes the degree of diagnostic certainty. A lower level of diagnostic certainty does not necessarily preclude starting treatment for presumptive NS, as there may be clinical contexts, such as a patient with suspected sarcoidosis myelitis or optic neuritis for whom a spinal cord or optic nerve biopsy is unrealistic. Defining the degree of diagnostic certainty can serve as an important reminder to reconsider the diagnosis at regular intervals, particularly in the absence of an anticipated therapeutic response. Furthermore, refining diagnostic certainty allows for purer research-based phenotypic analysis. The possibility of unrecognized infections, malignant neoplasms, or other treatable diagnoses should always be considered in the patient.

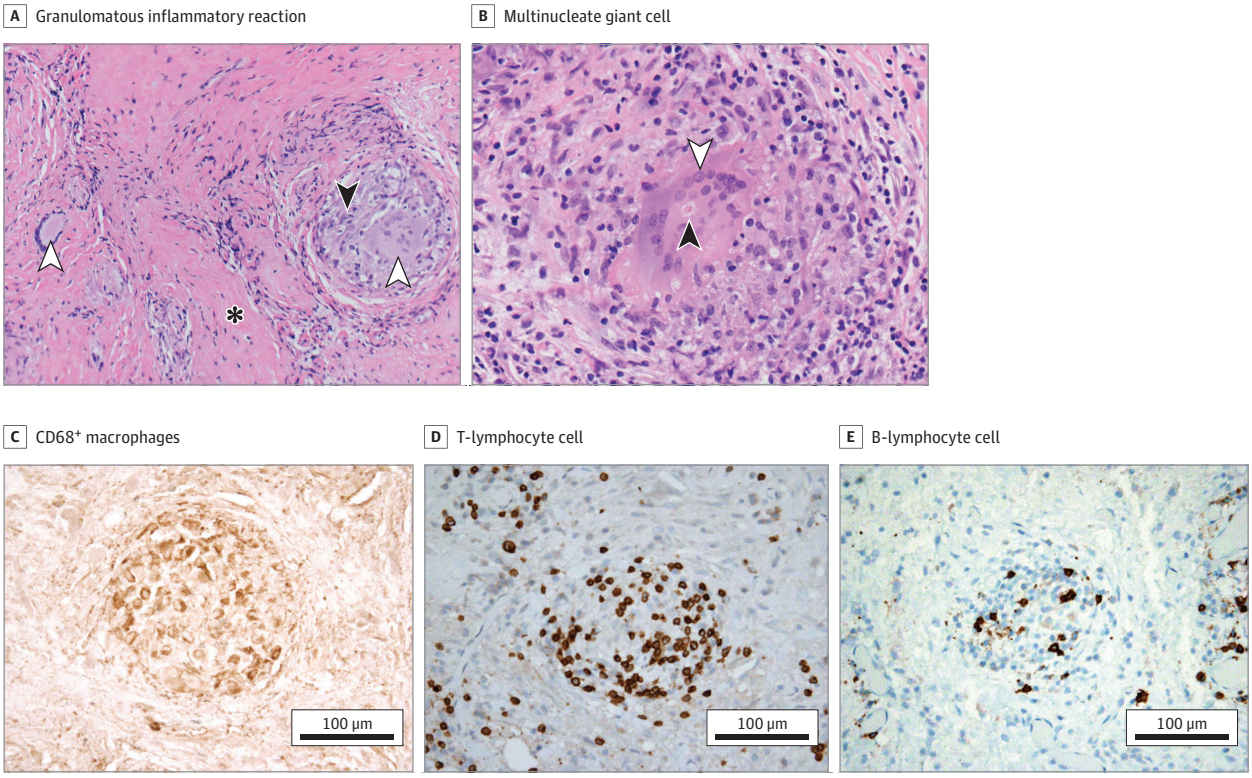
Neuropathologic Features of Sarcoidosis

Central Nervous System

The pathologic hallmark in NS is the presence of a noncaseating granulomatous inflammatory reaction. Granulomas at the surface of the brain, particularly at the base of the brain, have long been known as a prominent feature.[11] When the parenchyma is involved, the granulomas and inflammation tend to be in a perivascular distribution.[12] In the extreme, NS can manifest as a tumefactive mass in the brain parenchyma or dura, mimicking a tumor.[13]

Within neural tissue, collections of grouped epithelioid histiocytes, often with multinucleate giant cells, are surrounded by nonneoplastic lymphocytes and plasma cells (**Figure 1A**).[12] Characteristically, the granulomas of NS are nonnecrotizing but can rarely display limited necrosis. In the meninges, as the process becomes chronic, fibroblasts lay down collagen and fibrosis occurs, a process that may lead to a chronic pachymeningeal inflammatory reaction and dense fibrosis. These same features can occur with chronic infections; thus, comprehensive histologic examination and microbiologic cultures to investigate infection should be

Figure 1. Pathology of Neurosarcoidosis Dural Biopsy Specimen From a Patient With Neurosarcoidosis



A, Granulomatous inflammatory reaction with multinucleate giant cells (white arrowheads), epithelioid histiocytes (black arrowhead), and fibrosis (asterisk), using hematoxylin-eosin (H&E) (magnification ×200). B, Multinucleate giant cell (white arrowhead) with a central asteroid body (black arrowhead), using H&E (magnification ×400). Immunophenotyping of a nonnecrotizing granuloma in a neurosarcoidosis lesion shows the granuloma comprising an accumulation of CD68+ macrophages (C), infiltrating CD3+ (T lymphocytes) (D), and CD20+ (B lymphocytes) (E). Scale bar: 100 µm. Courtesy of Drs Allen Aksamit and Carlos A. Pardo.

completed, and, if possible, molecular diagnostic studies (eg, PCR) should be obtained. Another characteristic, but not required, histologic feature is asteroid bodies, stellatelike inclusions often within a central vacuole of the giant cell (Figure 1B).

Meningeal sarcoidosis shows a combination of granulomatous and nonspecific lymphoplasmocytic inflammatory reactions. In brain biopsy specimens, these changes are also characteristic, but a low frequency of giant cells or classic granulomas may be the main feature of some encephalitic or leukoencephalitic presentations as well as some optic neuropathies, in which marked mononuclear infiltration and lymphocyte infiltration predominate. Immunocytologic phenotyping of brain lesions frequently shows a mixed inflammatory cellular profile with increased numbers of histiocytes, foamy macrophages (CD68+), and infiltration of the granuloma with both CD4 and CD8 T lymphocytes and B lymphocytes (Figure 1C, D, and E).

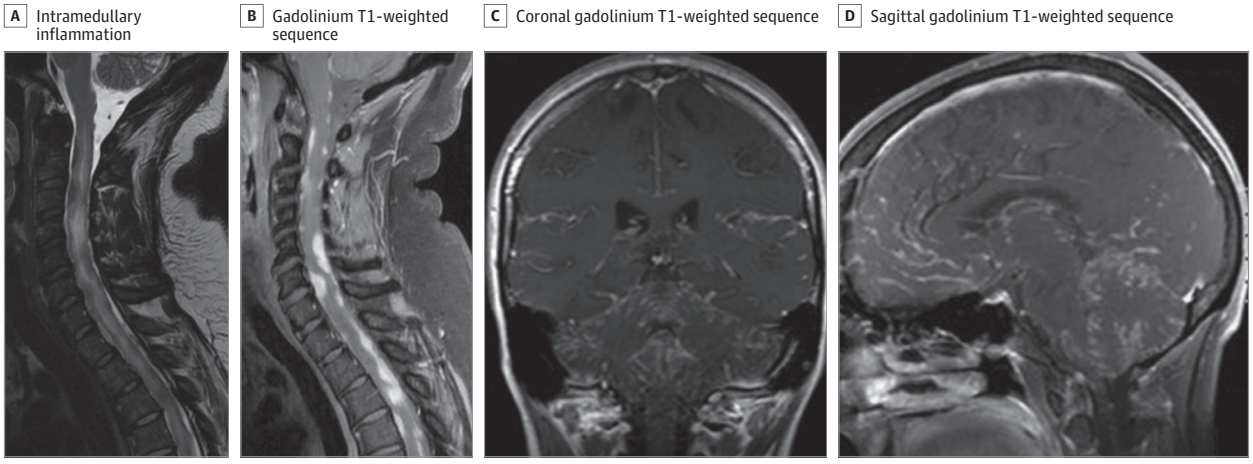
Peripheral Nervous System

Knowledge of neuropathic involvement in sarcoidosis is derived mostly from studies of large fiber neuropathies, in which granulomatous inflammatory infiltration of the nerves, vasculitis, or necrotizing vasculitic changes are observed. In patients with clinical evidence of a myopathy or features characteristic of muscle involvement on magnetic resonance imaging or fluorodeoxyglucose positron emission tomographic scans, muscle biopsies are valuable for the demonstration of a granulomatous inflammatory reaction. Concurrent muscle and nerve biopsies may be valuable, as some patients with sarcoidosis involving large fiber nerves have subclinical muscle involvement.[14]

Clinical Presentations

The clinical manifestations of NS are heterogeneous, as granulomatous inflammation may affect any anatomic substrate pertaining to the meninges, cranial nerves, brain, spinal cord, and peripheral nerves associated with diverse clinical forms of the disease. Manifestations of NS and their frequency are highlighted in eTable 1 in the Supplement, and select manifestations of NS and comments on relevant diagnostic studies are highlighted in eTable 2 in the Supplement. Included in these tables are paraneurosarcoidosis manifestations, entities for which no discernible evidence of nervous system inflammation exists and the origin may be multifactorial.[15] Fatigue,[16,17] *brain fog* (a colloquial term that patients may use to describe cognitive difficulties, such as impaired memory, slowed thinking, and diminished attention and concentration[18]), and small fiber neuropathy fall within this construct. The clinician must not attribute every new neurologic symptom and sign to NS but rather must evaluate the patient's presentation thoroughly for alternative explanations.

Figure 2. Magnetic Resonance Imaging (MRI) of Spinal Cord and Brain Neurosarcoidosis



Enlarged cervical spinal cord with T2-weighted MRI sequence demonstrating intramedullary inflammation (A) and gadolinium T1-weighted sequence demonstrating dural enhancement (B). Coronal (C) and sagittal (D) gadolinium T1-weighted sequences demonstrating leptomeningeal enhancement. Courtesy of Dr Siddharama Pawate.

Assessment and Diagnosis of Sarcoidosis and NS

The clinician may first suspect the diagnosis of NS on the basis of clinical presentation of the patient and appropriate imaging (**Figure 2**) and cerebrospinal fluid (CSF) findings. The clinical investigation of patients with suspected NS requires a careful assessment of the systemic manifestations of the disease along with a neurologic evaluation (eTable 3 in the Supplement). In many patients with clinical manifestations of NS, evidence of systemic disease is already established. However, in almost 50% of patients with suspected NS, the neurologic symptoms represent the first defining manifestation of sarcoidosis.[19] Furthermore, in a meta-analysis of 1088 patients culled from 29 articles, only 338 patients with NS (31.1%) had evident systemic disease at presentation, although 914 patients (84.0%) eventually developed systemic manifestations.[20] Evidence for extraneural sarcoidosis can be detected in almost 90% of these patients. Therefore, diagnostic strategies should focus on the evaluation of systemic disease in patients with an unknown history of sarcoidosis and neurologic disease suspected to be associated with sarcoidosis as well as on staging the full extent of neurologic involvement to establish a definite or probable diagnosis of NS. Lung, intrathoracic lymphadenopathy, eye, and skin are frequently involved in the inflammatory process; thus, attention should be directed at these sites. Tissue biopsy of a relatively safe and accessible nonneural site is recommended to establish a definite pathologic diagnosis of multiorgan sarcoidosis. This biopsy is especially important for patients for whom long-term immunosuppressive treatment is anticipated.

CSF Findings in CNS

Cerebrospinal fluid findings are not specific for NS, but, if deemed safe, CSF analysis should be considered in cases of suspected NS to (1) establish the presence of intrathecal inflammation and (2) rule out infectious and neoplastic processes. The result of CSF analysis is sometimes abnormal even when magnetic resonance imaging scan results are unremarkable. The CSF opening pressure can be elevated. Frequent CSF abnormalities include a predominantly mononuclear pleocytosis, elevated protein, low glucose, elevated IgG index, and oligoclonal bands, none of which are specific but provide important evidence for active inflammation. As clinically indicated, viral PCRs (herpes simplex virus, varicella zoster virus, cytomegalovirus, Epstein-Barr virus) and associated serologies (eg, CSF varicella zoster virus IgM); mycobacterial PCR; and bacterial, acid-fast bacterial, and fungal cultures should be obtained, along with a venereal disease research laboratory test and Lyme disease serology, as these infectious states can mimic NS. Next-generation metagenomic sequencing of CSF for pathogen detection is a current research tool that has been unrevealing for infectious organisms in NS; it may prove valuable to exclude infection in the future.[21] Cytology and flow cytometry should be obtained, especially if leptomeningeal enhancement or hydrocephalus is detected on magnetic resonance imaging.

Nonspecific CSF markers of CNS inflammation are seen in 50% to 70% of patients with NS. Cerebrospinal fluid abnormalities are most likely in patients with leptomeningeal enhancement.[22] In a study of 54 patients,[23] elevation of CSF protein (26 of 42 patients [62%]) and lymphocyte predominant pleocytosis (24 of 42 patients [57%]) were the most common findings, followed by the presence of oligoclonal bands (8 of 42 patients [19%]). Another study[24] reported similar numbers, with elevated protein in 15 of 25 patients (60%), pleocytosis in 18 of 28 patients (64%), and oligoclonal bands in 4 of 18 patients (22%). This study also reported an elevated IgG index in 8 of 21 patients (38%). Determination of CSF angiotensin-converting enzyme activity is controversial; it has low specificity and sensitivity and adds little to the certainty of the diagnosis.[25] The CSF is normal in approximately 30% of individuals with NS.[26]

Biomarkers

A variety of biomarkers, most commonly angiotensin-converting enzyme, has been used for the diagnosis of sarcoidosis; however, the test is insufficiently specific and sensitive in both serum and CSF to be of use.[27] Serum lysozyme is elevated in patients with pulmonary

sarcoidosis[28] and a subset of patients with NS,[24] but this test also lacks sensitivity and specificity and is not useful for NS diagnosis.

Chest Imaging

The chest imaging results of up to 90% of patients with sarcoidosis will have abnormalities. If suspicion for sarcoidosis is high and the chest x-ray results are normal, a high-resolution chest computed tomographic scan, preferably with contrast, should be performed.

If mediastinal or hilar lymphadenopathy is present, endobronchial ultrasonography–directed transbronchial biopsy, endoscopic ultrasonography–directed biopsy, or mediastinoscopy can be used to obtain tissue for histologic examination. This approach may avoid a transbronchial biopsy and the risks of bleeding and pneumothorax.

Detection of Extrapulmonary Sarcoidosis

When results of chest computed tomographic scan are normal, gallium citrate Ga 67 scintigraphy or, preferably, fluorodeoxyglucose positron emission tomographic scan may be helpful to detect extrathoracic systemic sarcoidosis. Fluorodeoxyglucose positron emission tomography appears to have higher spatial resolution and better sensitivity than the gallium scan, especially for detecting lymph node involvement, and is the preferred imaging test in this era and clinical context.[29]

Biopsy Results From Other Organs

The diagnosis of sarcoidosis is supported by the identification of granulomas in 1 or more organs. The lung is the most common site, but a substantial proportion of patients are diagnosed by tissue sampling of other organs.[30] The biopsy results should be correlated with the clinical presentation for that particular organ. One can be more confident of the diagnosis of sarcoidosis if a positive biopsy result correlates with a probable or highly probable sarcoidosis manifestation for that organ.[31]

Conjunctival biopsy for diagnosis of sarcoidosis has been suggested since the mid-1950s because of the frequent involvement of the eye, asymptomatic nature, and relative ease of obtaining a biopsy.[32] However, although conjunctival biopsy in carefully selected patients can sometimes be of value, it has an overall low diagnostic yield for NS in patients evaluated for inflammatory nervous system disease of unknown origin.[33]

Approach to the Patient

Patients with suspected CNS sarcoidosis should have brain and/or cervical, thoracic, and lumbar magnetic resonance imaging with and without gadolinium, depending on the clinical presentation. A comprehensive analysis of CSF is usually indicated. If there are contraindications to performing these tests, diagnostic confidence is diminished without pathologic examination of CNS tissue. Patients with suspected PNS sarcoidosis should undergo electromyogram and nerve conduction study. As clinically indicated, nerve or muscle biopsy is recommended.

What constitutes an adequate search for systemic sarcoidosis can be the subject of debate. The diagnostic evaluation should be guided by the patient's symptoms and physical examination findings. If the patient is suspected of having occult disease, we recommend, at a minimum, that the patient undergo a comprehensive ocular examination, a high-resolution chest computed tomographic scan, and a whole-body fluorodeoxyglucose positron emission tomographic scan. The latter 2 scans are particularly helpful in suggesting a biopsy site, but there needs to be a high enough index of suspicion for sarcoidosis as a causative diagnosis to justify the radiation exposure and cost of such testing. Blood tests to be considered include a complete blood count, liver and renal profiles, calcium, and creatine kinase. Serum angiotensin-converting enzyme activity and C-reactive protein and soluble interleukin-2 receptor assays currently have no proven value in the diagnosis or management of NS, although they may be clinically informative in individual circumstances.[27,34] Finally, interpretation of neuro-infectious diagnostics should consider the clinical context, including the history and physical examination, CSF studies with relevant correlations between CSF and serum, and other diagnostics such as CNS and body imaging, as appropriate.

Diagnostic Criteria for Neurosarcoidosis

As outlined in eTable 4 in the Supplement, a variety of diagnostic criteria for NS have been proposed. Most of these criteria originate from a single group of physicians at a single institution and reflect their methodology to accomplish the aims of their study. Considerable variability exists regarding the emphasis on clinical or paraclinical data for establishing a diagnosis. To our knowledge, previously proposed criteria have not been prospectively validated; our perspective is that this is an important future research endeavor. Furthermore, none of the criteria propose what constitutes an adequate evaluation to exclude alternate diagnostic considerations.

The consensus criteria we propose build on earlier efforts and reflect the collective opinion of physicians from different institutions who have expertise in sarcoidosis and NS. In eTable 3 in the Supplement, we indicate differential diagnostic considerations that are encountered in the evaluation of patients with potential NS, and we recommend tests for patients with either CNS or PNS disease.

One can never be 100% certain of the diagnosis of sarcoidosis, even with a brain biopsy, but some general rules can be helpful guides. The more organs that appear to be affected, the higher the assurance of the diagnosis of sarcoidosis. A clinician may become more confident of the diagnosis with time as other conditions, such as lymphoma or tuberculosis, become much less likely.

Complicating matters is the concept of paraneurosarcoidosis. How paraneurosarcoidosis manifestations should be categorized within a disease definition paradigm is open to debate. We propose a rubric for identifying such symptoms as consistent with the sarcoidosis diagnosis but as distinct from the neurologic manifestations of NS originating from granulomatous inflammation and infiltration of the affected part of the nervous system.

Another consideration in assessing diagnostic certainty is how a patient responds to treatment of clinical and paraclinical manifestations.[17] We have chosen not to include the response of the patient to treatment as a formal component of diagnostic confidence because many inflammatory and even infectious and neoplastic disorders may transiently respond to immunosuppressive treatment. If the patient is responding to treatment as expected, the diagnosis of NS might be considered relatively more secure within the context of our proposed categories of diagnostic certainty. Conversely, if the patient is not responding as anticipated, diagnostic

Box. Proposed Diagnostic Criteria for Central Nervous System and Peripheral Nervous System Neurosarcoidosis

Possible

1. The clinical presentation and diagnostic evaluation suggest neurosarcoidosis, as defined by the clinical manifestations and MRI, CSF, and/or EMG/NCS findings typical of granulomatous inflammation of the nervous system and after rigorous exclusion of other causes.
2. There is no pathologic confirmation of granulomatous disease.

Probable

1. The clinical presentation and diagnostic evaluation suggest neurosarcoidosis, as defined by the clinical manifestations and MRI, CSF, and/or EMG/NCS findings typical of granulomatous inflammation of the nervous system after rigorous exclusion of other causes.
2. There is pathologic confirmation of systemic granulomatous disease consistent with sarcoidosis.

Definite

1. The clinical presentation and diagnostic evaluation suggest neurosarcoidosis, as defined by the clinical manifestations and MRI, CSF, and/or EMG/NCS findings typical of granulomatous inflammation of the nervous system after rigorous exclusion of other causes.
2. The nervous system pathology is consistent with neurosarcoidosis.
   Type a. Extraneural sarcoidosis is evident.
   Type b. No extraneural sarcoidosis is evident (isolated CNS sarcoidosis).

Abbreviations: CSF, cerebrospinal fluid; EMG, electromyogram; MRI, magnetic resonance imaging; NCS, nerve conduction study.

certainty should be questioned, although some individuals may have NS that can be refractory to conventional therapies.

Given the many factors discussed, we propose consensus diagnostic criteria for NS (**Box**). Patients who meet the *probable* or *definite* criteria should be considered to have NS, while those who meet the *possible* criteria may have NS and may respond to treatment directed at sarcoidosis. Pathologic examination increases the level of confidence of the diagnosis of sarcoidosis, but even pathologic identification of granulomas is not 100% definitive. In addition, if inflammation is present in a pathologic specimen but granulomas are absent, the patient does not meet the criteria for definite NS but can be considered to have possible or probable NS if the clinical circumstances otherwise support these assignments (eg, presence or absence of granuloma in systemic biopsy).

Discussion and Conclusions

We present an overview of the clinical manifestations of NS and the challenge of diagnosing this disorder. Diverse disease presentations and lack of specificity of relevant diagnostic tests contribute to diagnostic uncertainty. This uncertainty is compounded by the absence of a pathognomonic histologic tissue examination. The diagnostic criteria we propose are designed to focus investigations on NS as accurately as possible, recognizing that multiple pathophysiologic pathways may lead to the clinical manifestations we currently term NS. Research recognizing the clinical heterogeneity of this diagnosis may open the door to identifying meaningful biologic factors that may ultimately contribute to better treatments.

We present differential diagnostic considerations and potential diagnostic tests to address the diverse alternate possibilities. Suggesting mandatory tests is difficult because of the diverse presentations of NS and the large number of alternative possibilities. However, a key principle is the exclusion of infection and malignant neoplasm before settling on the diagnosis of NS.

We propose possible, probable, and definite definitions of NS on the basis of our targeted review of the literature and our extensive experience. Three categories of diagnostic certainty are proposed to emphasize the need for the clinician to maintain an open mind to alternate diagnoses on the basis of the patient's clinical course and response to treatment. We anticipate that patients who meet the criteria for any of the diagnostic categories will be treated for NS. However, for patients with a predicted progressive or remitting relapsing course, for whom long-term immunosuppressive treatment is projected, we suggest that, at a minimum, extraneural tissue be obtained for pathologic examination whenever possible. Furthermore, for most research purposes, we propose that only patients who meet the criteria for probable and definite NS be included in studies. Investigators may want to stratify enrollment according to diagnostic certainty and reassess diagnostic certainty at the patient's final evaluation.

These criteria need to be validated in various practice settings. In addition, as the pathogenesis of sarcoidosis and NS is better defined and more accurate biomarkers are identified, the diagnostic criteria proposed will need to be updated and modified. We hope that our recommendations spur interest in investigating genetic and other biomarkers for sarcoidosis and NS using state-of-the-art methods.[35]

ARTICLE INFORMATION

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Conflict of Interest Disclosures: Dr Stern reported serving on the Scientific Advisory Board of the Foundation for Sarcoidosis Research, being a co-investigator on a neurosarcoidosis research study funded by Mallinkrodt, being a consultant to Araim Pharmaceuticals, receiving salary support for serving as the Medical Safety Monitor on the National Institutes of Health–funded CREST2 study, receiving royalties for a contribution on neurosarcoidosis to UpToDate, having received

honoraria for lecturing on neurosarcoidosis, and serving as an expert legal witness for legal proceedings concerning neurosarcoidosis. Dr Royal reported receiving research support from the National Institutes of Health and the Veterans Administration as well as research and/or clinical education grant support from Mallinckrodt, Biogen-Idec, Alexion, EMD-Serono, and MedImmune, and serving as associate editor for the *Journal of Neurovirology*. Dr Gelfand reported receiving consulting fees from Biogen; research support (to the University of California, San Francisco) from Genentech, MedDay, and Quest Diagnostics; and personal compensation for medical-legal consulting as an expert witness. Dr. Gelfand's spouse has received consulting fees from Zosano Pharma Corp, Eli Lilly and Company, and Biohaven Pharmaceutical; honoraria from UpToDate (for authorship) and *JAMA Neurology* (as an associate editor); consulting payments for work done through the University of California, San Francisco, Pediatric Headache Program from eNeura, Inc; and personal compensation for medical-legal consulting. Dr Clifford reported serving as a consultant, Data and Safety Monitoring Board member, and/or Progressive Multifocal Leukoencephalopathy (PML) adjudication committee member for Amgen, AstraZeneca, Bristol-Myers Squibb, Pfizer, Takeda, Biogen, Merck, Genentech/Roche, Glaxo Smith Kline, Seattle Genetics, Novartis, Protagonist, Dr Reddy, and Merck Serono. He reported being chair of the Data Safety and Monitoring Board for 2 clinical studies involving Huntington disease funded by Wave Life Sciences; he reported no disclosures related to sarcoidosis. Dr Tavee reported being involved in a clinical trial with Araim Pharmaceuticals and receiving speaking fees from Mallinkrodt. Dr Berger reported serving as a consultant and/or on the PML adjudication committees of Amgen, AstraZeneca, Bristol-Myers Squibb, Eisai, Janssen, Parexel, and Pfizer; serving on the Scientific Advisory Board of NeuVir and ExcisionBio; receiving honoraria from Prime Education and the Multiple Sclerosis Foundation for lectures; serving as an associate editor for the *Journal of Neurovirology* and as an editorial board member of *ISRN Education* journal, *Journal of Neuroscience*, *World Journal of Rheumatology*, and *Multiple Sclerosis and Related Disorders* journal; receiving publishing royalties for *Handbook of Clinical Neurology*, Vol. 85; serving as a consultant to Alcimed, Amgen, AstraZeneca, Bayer, Biogen, Eisai, EMD Serono, Forward Pharmaceuticals, Genentech/Roche, Genzyme, Inhibikase, Millennium/Takeda, Novartis, Johnson and Johnson, Pfizer, and Sanofi Aventis; receiving research support from Biogen; and participating in legal proceedings for Biogen. Dr Moller reported being chairman and chief technical officer of Sarcoidosis Diagnostic Testing, LLC; receiving funding, including past salary support under the National Heart, Lung, and Blood Institute (NHLBI) Small Business Technology Transfer program (grant R41 HL129728); receiving research support from Endocyte; being a consultant to Merck and a past consultant to Novartis and Dicerna; serving on the Scientific Advisory Board of the Foundation for Sarcoidosis Research; receiving royalties from Hodder Education for editing a book on sarcoidosis; expecting future royalties from Taylor & Francis Group for editing a book on interstitial lung disease; receiving research support, including salary support from NHLBI (grant U01HL112708 [GRADS]); receiving honoraria for lecturing on sarcoidosis; and serving as an expert legal consultant/witness for legal proceedings concerning sarcoidosis. Dr Judson reported serving as a consultant to Biogen and receiving grant support (to his institution) from Novartis and Malinckrodt. Dr Baughman reported serving on the Scientific Advisory Board of the Foundation for Sarcoidosis Research; being a principal investigator on studies of clinical trials of nonneurosarcodiosis studies funded by NHLBI, Mallinkrodt, Celgene, Bayer, Gilead, and Novartis; and being a principal investigator of a registry of advanced sarcoidosis, including neurosarcoidosis. Dr. Pawate reported attending an advisory board meeting for Biogen regarding a matter unrelated to sarcoidosis. No other disclosures were reported. Drs Clifford and Stern reported providing modest support, derived from discretionary research funds, for the meetings of the Neurosarcoidosis Consortium Consensus Group.

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