Pictorial Review

Imaging of neurosarcoidosis: common, uncommon, and rare

G. Bathla a,*, A.K. Singh b, B. Policeni a, A. Agarwal c, B. Case d

a Department of Radiology, University of Iowa Hospitals and Clinics, IA, USA
b Department of Radiology, UT Health Science Center, San Antonio, TX, USA
c Department of Radiology, Penn State University College of Medicine, Hershey, PA, USA
d Carver College of Medicine, University of Iowa, IA, USA

Sarcoidosis is an idiopathic inflammatory disease that may affect any organ system and have protean manifestations. Neurosarcoidosis refers to involvement of the central nervous system and may occur in patients with known sarcoidosis, or be the initial manifestation of the disease. In the latter, it can be a source of considerable confusion, given the non-specific imaging appearance. The aim of this review is to describe the imaging spectrum of neurosarcoidosis, including follow-up imaging and superimposed infections, which may occur secondary to immunosuppression. An increased awareness of this great mimicker could potentially expedite diagnosis and reduce morbidity.

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Introduction

Sarcoidosis is an idiopathic, non-infectious inflammatory disorder characterised by formation of non-caseating granulomas. 1–4 It may affect any organ system, although the involvement of the lungs, skin, and lymph nodes is most frequently observed. 1,3 The disease most commonly affects African-Americans and persons of Scandinavian descent, and is often seen in the third and fourth decades. 2,3,5 The underlying aetiology has been variously attributed to infection, genetic predisposition, and environmental toxins, but continues to remain elusive. 4–6 It is felt that the disease likely reflects an exaggerated response to a specific but unidentified antigen. 4,8

Neurosarcoidosis (NS) refers to the involvement of the central nervous system (CNS) and is seen on imaging in approximately 10% of patients with systemic sarcoidosis, even though pathological CNS involvement is observed in about 15–25% of patients on post-mortem studies. 1–3 Clinical involvement is even less common, occurring in about 5% of patients. 1,3,7 The disease can have protean neurological manifestations, although patients most frequently present with cranial nerve dysfunction or aseptic meningitis; 4,5 however, based on the site of involvement, other presentations may include hypopituitarism or diencephalic syndromes (hypophyseal involvement), seizures, cognitive decline (parenchymal disease), or myelopathic symptoms (spinal involvement). 1,4,6–8

Histopathologically, sarcoidosis is characterised by formation of non-caseating granulomas, primarily composed of epitheloid cells, helper T-cells and Langerhans’ giant
Figure 1 Photomicrographs (H&E 20×) in a patient with NS reveal leptomeningeal inflammation (arrowheads) and granuloma formation (arrows) (a) along with perivascular spread of the disease (arrowheads) (b).

Table 1
Differential diagnosis of neurosarcoidosis based on pattern of involvement.

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<th>Intraparenchymal lesions</th>
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<td>Acute disseminated encephalomyelitis</td>
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<td>Osseous involvement</td>
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Within the CNS, the disease has a propensity to involve the basal meninges. The process often spreads to the nearby structures; commonly involving the pituitary—hypothalamic axis and optic chiasm. Preferential spread of inflammation along the perivascular Virchow–Robin spaces at the base of the brain leads to perivascular inflammation and parenchymal granulomas (Fig. 1).

Clinically, the diagnosis of NS relies on Zajicek criteria wherein the diagnosis is considered definite if there is biopsy confirmation from neural tissue, probable if there is evidence of neurological inflammation with systemic disease and possible when the presentation is typical and other potential causes have been excluded. 

Figure 3: Contrast-enhanced axial T1WI shows the presence of extensive leptomeningeal enhancement (arrowheads) involving the right temporal and occipital lobes with associated numerous enhancing parenchymal granulomas (arrows).

Figure 4: Axial T2WI in a patient with solitary sarcoid granuloma in the left frontal lobe shows T2 shortening secondary to intralesional haemorrhage (arrow).

Figure 5: Axial fluid-attenuated inversion recovery (FLAIR) image at the level of the corona radiata reveals multiple areas of T2 prolongation involving the periventricular and deep white matter (arrowheads).

Figure 6: Contrast-enhanced sagittal T1WI in a patient with NS reveals diffuse thickening and enhancement involving the pituitary–infundibulum–hypothalamus axis (arrow), extending posteriorly along the clivus (arrowhead).
Histopathological tissue confirmation forms the basis of diagnosis as there is paucity of reliable laboratory tests. The Kveim test has fallen out of favour due to risk of infection and is not approved by the US Food and Drug Administration.\(^5\) Values of serum/cerebrospinal fluid (CSF) angiotensin converting enzyme are variably abnormal and neither sensitive nor specific.\(^3,6\) Similarly, the CSF is often abnormal but lacks specificity.\(^3,5,8\) Positive gallium-67 scintigraphy, showing both the lambda (uptake in bilateral hilar and right paratracheal nodes) and panda signs (symmetric uptake in bilateral lacrimal and parotid glands) is considered specific for sarcoidosis, but is not very sensitive, occurring in only about 60% of cases.\(^11\) In these cases, histopathological demonstration of systemic involvement in a patient with neural inflammation (as shown on contrast-enhanced craniospinal magnetic resonance imaging [MRI]) is a reasonable option if neural tissue biopsy is not feasible. 2-[\(^{18}\)F]-fluoro-2-deoxy-D-glucose (FDG) positron-emission tomography (PET) can be especially useful in such cases to search for occult systemic involvement to detect extra CNS involvement and are being used more frequently.\(^2\)

Often, the patients already carry the diagnosis of sarcoidosis by the time CNS involvement is discovered; however, neurological involvement may be the first or the only manifestation and can be a source of considerable confusion. The following sections discuss the protean imaging manifestations of NS. It should be noted, however, that as the imaging findings are often non-specific, the differential considerations in any given case tend to be broad, based on the predominant pattern of involvement (Table 1) and a detailed discussion about the various conditions that may mimic NS is beyond the scope of this text. A quick glance at the patient’s demographics, history of presenting illness, past medical history, and clinical and biochemical findings could help narrow down the imaging-based diagnostic possibilities and is desirable, although not always available. Nevertheless, isolated NS remains a diagnosis of exclusion.

**Brain**

Within the CNS, the involvement of neuroparenchymal proper may manifest as multiple or solitary supra/infratentorial lesions, seen in about 35% and 10% of patients with NS, respectively.\(^6,7\) The involvement is felt to be secondary to the spread of inflammation from the leptomeninges along the Virchow–Robin spaces.\(^2,7\) Smaller parenchymal granulomas may be seen only after intravenous contrast medium administration\(^9\) (Fig 3). Larger masses are often iso-intense on T1-weighted images (T1WI) and show T2 prolongation, although intralesional haemorrhage may change the appearance\(^3,6,7\) (Fig 4). Necrosis and calcification are rare.\(^2,7\) Contrast-enhanced images often reveal diffuse or rim enhancement, although non-enhancing lesions may rarely occur.\(^3,6\) The presence of multiple lesions and additional meningeal/CN involvement would argue against a primary glial tumour, although differentiation from primary CNS lymphoma in some cases may eventually require tissue confirmation.

Other parenchymal manifestations include the presence of periventricular and white matter T2 hyper intense lesions, which have been variably described in 12.5–54% of patients and are felt to be the most common manifestation of NS by some authors\(^3,4–8\) (Fig 5). These lesions may mimic multiple sclerosis on imaging, although presence of associated parenchymal granulomas and meningeal involvement would favour NS\(^6,8\); however, their pathogenesis is unclear.\(^4\) These are often asymptomatic and do not change with therapy.\(^2\)

Involvement of the hypothalamic–pituitary axis is seen in approximately 18% of cases and may present clinically with symptoms of hypopituitarism.\(^7\) This relatively high incidence is felt to be secondary to proximity to basal meninges, which are often involved.\(^8\) Imaging reveals non-specific thickening and enhancement of the pituitary–infundibulum–hypothalamus, which may extend in to...

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**Figure 7** Axial contrast-enhanced image reveals asymmetric dilatation of the right lateral ventricle (arrowhead) secondary to adhesions. There is associated periventricular seepage (curved arrows) and midline shift. Associated leptomeningeal (small arrows) and pachymeningeal (large arrows) enhancement is also noted.
the surrounding meninges\(^3\) (Fig. 6). Involvement of the cavernous sinus is rare, mostly described as isolated case reports.\(^{12,13}\) Lesions may show T2 prolongation and post-contrast enhancement with or without a dural tail. Approximately 5–12% of NS patients may develop hydrocephalus, which is often communicating and felt to be secondary to impaired CSF absorption.\(^{7,14}\) Less commonly, patients may show focal ventricular dilatation, usually

Figure 8 Axial DWI image (a) in a patient with NS reveals the presence of acute infarcts in the right periventricular white matter and left external capsule, which shows corresponding apparent diffusion coefficient (ADC) (b) hypo-intensity (arrowheads). (c) Contrast-enhanced axial image reveals subtle perivascular enhancement involving the basal ganglia bilaterally (arrows). The patient went on to develop multiple small infarcts over time (not shown) with a negative work-up for cardioembolic phenomenon or atherosclerotic disease. This was presumed to be secondary to NS in the absence of any other cause.
Figure 9 (a) Axial susceptibility weighted image [SWI] in a patient with vasculitic NS shows multiple scattered areas of susceptibility scattered over bilateral cerebral hemispheres in a predominantly peripheral distribution. (b) Contrast-enhanced axial image through the posterior fossa reveals subtle leptomeningeal enhancement (arrowheads).

Figure 10 Contrast-enhanced axial T1WIs in a patient with NS reveals diffuse thickening and enhancement of bilateral optic (arrowheads in a) and trigeminal nerves (arrows in b).
resulting from entrapment secondary to inflammation\textsuperscript{3,14} (Fig 7).

Cerebrovascular manifestations are rare, but may manifest as small vessel vasculitis, ischaemic or haemorrhagic strokes.\textsuperscript{1,15} Punctate ischaemic strokes have been described and are attributed to small vessel involvement\textsuperscript{15} (Fig 8). Rarely, single or multiple parenchymal haemorrhagic lesions may occur and are best seen on susceptibility-weighted imaging (Fig 9). Parenchymal bleeds in patients with NS are more likely to be multiple, punctate, supratentorial, and in atypical location.\textsuperscript{1} Vascular involvement manifesting as moyamoya pattern, subarachnoid haemorrhage, or dural sinus thrombosis have also been described, but are extremely rare.\textsuperscript{10,14,16}

Cranial nerve involvement occurs in up to 50\% of cases; either when they traverse the subarachnoid space, or rarely from peri-neural extension of sinonasal sarcoidosis.\textsuperscript{2,3} Almost any cranial nerve may be affected, though cranial nerve II is most frequently involved on imaging\textsuperscript{2} (Fig 10). Clinically, however, facial nerve palsy is more common and may be bilateral in about 30\textendash 40\% of cases.\textsuperscript{5,8} Involved cranial nerve may appear thickened and show smooth or nodular post-contrast enhancement, which may occur over a background of leptomeningeal involvement and mimic meningitis, lymphoma or carcinomatosis.\textsuperscript{2,3,7}

Leptomeningeal involvement occurs in about 40\% of cases and is frequently basal.\textsuperscript{2,7} On contrast-enhanced images, it manifests as abnormal meningeal enhancement, which may be smooth or nodular.\textsuperscript{5,7} It may be associated

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\caption{Contrast-enhanced coronal image in a patient with NS reveals the presence of extensive perivascular inflammation involving the pons (arrowheads). Supratentorial leptomeningeal enhancement is also noted (arrows).}
\end{figure}

\begin{figure}[h]
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\caption{(a) Axial T2WI reveals presence of a dural-based hypo-intense lesion in the right frontal region anteriorly (arrowhead). (b) There is diffuse post-contrast enhancement.}
\end{figure}
with perivascular enhancement due to spread of the inflammatory process along the Virchow–Robin spaces (Fig 11). Pachymeningeal involvement occurs in about 34% of cases and most commonly involves the posterior fossa.²,⁷ Lesions often show T2 shortening, a non-specific but sometimes helpful clue.³,⁷ On contrast-enhanced images, lesions uniformly enhance and may show a dural tail⁴ (Fig 12). Interestingly, dural and leptomeningeal involvement seldom affect the same region, a finding attributed to the arachnoid barrier cells, which prevent spread of disease through the arachnoid membrane.³,⁴

**Spine**

Spinal involvement in NS was previously felt to be rare and affect less than 10% of patients.³ This perception is, however, changing with widespread use of MRI for spinal imaging. Currently, intramedullary involvement is reported in up to 25% of patients with NS and most commonly involves the cervical and upper thoracic spine.³,⁵,⁷,⁸ Lesions often extend over multiple segments and show T1/T2 prolongation and patchy post-contrast enhancement, which is often peripheral.³,⁴ There is often fusiform enlargement of the affected cord segment (Fig 13). In up to 60% of these cases, there is overlying leptomeningeal involvement, which is thought to be a precursor of intramedullary lesions by some authors.³ Involvement of the spinal nerves may occur and again presents as non-specific leptomeningeal enhancement. Extramedullary lesions are rare and often show T2 prolongation, unlike intracranial dural-based lesions, which show T2 shortening.³

**Bones**

Osseous involvement occurs in approximately 13% of patients with sarcoidosis and is felt to be underestimated, as most lesions are clinically asymptomatic.³,⁷ It often involves the long tubular bones and appendicular skeleton.³ Involvement of the skull and vertebral column is uncommon, but usually involves the lower thoracic and upper
lumbar spine. Lesions are most commonly lytic, but may appear as mixed or sclerotic on CT (Fig 14). There may be an associated soft-tissue component. At MRI, lesions are often T1 isointense and may show T2 prolongation or shortening based on whether they are predominantly lytic or sclerotic. Lesions may be multiple and enhance post-contrast medium administration (Fig 15). Involvement of the posterior spinal elements and intervertebral disc spaces may occur.

Follow-up imaging

Corticosteroids form the first-line therapy for patients with NS, with steroid-sparing immuno-suppressants reserved for resistant cases or as co-therapy to avoid side effects from long-term steroids. Optimal therapy can achieve clinical remission in about 70% along with variable improvement in imaging findings. Interestingly, the two may not necessarily correlate. This is especially true for spinal lesions.

Rarely, the lesions may paradoxically worsen post-therapy and the possibility of opportunistic infections occurring in a now immunocompromised patient may need to be excluded (Fig 16). A fairly quick clinical deterioration and worsening imaging appearance, not otherwise explained by the primary disease are useful clues. Patients with chronic NS may show generalised parenchymal loss and prominence of ventricles, which likely reflects the smouldering nature of disease (Fig 17).

Conclusion

Sarcoidosis may involve the CNS and have protean clinical manifestations. Assessment of the CNS involvement is best done with contrast-enhanced MRI. Unfortunately, the imaging manifestations are broad and non-specific and sarcoidosis remains a diagnosis of exclusion. Imaging, however, may point towards the correct diagnosis, rule out various other disease entities, which mimic NS clinically, may help select the site for biopsy, and is useful to assess changes on follow-up imaging. Given the non-specific clinical presentation, the diagnosis may be initially suggested on imaging, and awareness of the entity and its imaging appearance may expedite the diagnosis and potentially reduce morbidity.

Figure 14 CT image (bone window) of a patient with NS reveals the presence of a lytic lesion involving the sphenoid on the left side (arrowhead).

Figure 15 Contrast-enhanced sagittal T1WI through the cervical spine in a patient with NS reveals abnormal enhancement of the clivus, multiple vertebral bodies, and few posterior spinal elements (arrowheads) along with anterior pial enhancement (arrows).
Figure 16 (a) Contrast-enhanced axial T1WI through the posterior fossa in a patient with NS reveals prominent enhancement along the cerebellar foliae (arrowheads) and in bilateral internal auditory canals (arrows). The patient was started on corticosteroids and showed clinical improvement initially followed by rapid deterioration. (b) Follow-up MRI image shows interval worsening leptomeningeal enhancement (arrowheads) and attenuated fourth ventricle (arrow). An artefact from the ventricular shunt is noted on the right side (curved arrow). The patient was eventually diagnosed with cryptococcal meningitis, presumably acquired secondary to immunosuppression.

Figure 17 Axial FLAIR images at the same level in a patient with NS at the time of diagnosis (a) and after 3 years (b). There is interval progression of parenchymal volume loss and periventricular white matter signal abnormalities (arrowheads) despite treatment and satisfactory clinical response.
References


