A comprehensive imaging review of neurosarcoidosis

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Learning objectives

To provide a comprehensive pictorial review of the imaging features of neurosarcoidosis.
To describe the imaging features that help distinguish neurosarcoidosis from the important differential diagnoses.

Background

Neurosarcoidosis is a central nervous system manifestation of sarcoidosis, a multisystem disease process of unknown cause which commonly affects lungs and lymph nodes. Central nervous system (CNS) involvement (brain and spinal cord) is seen in 5%-25% of patients and can be severe or even life threatening. Up to 70% of patients developing neurosarcoidosis do so within the first two years of their systemic illness, however CNS involvement may also be the first and only manifestation of sarcoidosis.

Histologically, neurosarcoidosis is characterised by the formation of granulomas in the CNS consisting of lymphocytes and mononuclear phagocytes surrounding a non caseating epithelioid cell granuloma. These granulomas represent an autoimmune response to CNS tissues. The most typical imaging appearance is thickening and enhancement of the leptomeninges (with accompanying cellular changes in the cerebrospinal fluid (CSF)), especially around the bases of the brain. Sarcoidosis may individually or in combination involve the bone, dura mater, nerve roots, leptomeninges and parenchyma (periventricular regions, white matter and grey matter, hypothalamus, pituitary gland).

No part of the CNS is protected from sarcoidosis, therefore clinical and neuroradiological manifestations vary greatly. There is a favourable prognosis for the disease in the acute phases with systemic/oral steroid therapy. Chronic courses may respond poorly to medical treatment and cerebral irradiation has been used as a possible effective treatment modality.

Clinical symptoms of neurosarcoïdosis are headache, cranial nerve palsy, seizures, paresis, paresthesias and features of aseptic meningitis, features that are also seen in other common disorders such as multiple sclerosis, tumours or myelopathy. Neurosarcoïdosis is a great ‘mimicker’ of other CNS disorders, therefore histological confirmation of non caseating granulomas is often required. In the absence of histological proof of systemic sarcoïdosis, the diagnosis can be supported by typical chest radiography, whole body gallium (Ga) scanning or elevated serum angiotensin converting enzyme (ACE) levels (produced by the epithelioid cells of granulomatous
lesions). Patients with neurosarcoidosis have been reported to have elevated serum ACE in 5-50% of cases. Non specific CSF abnormalities may be a feature such elevated protein levels, lymphocytosis or rarely elevated ACE levels.

**Imaging findings OR Procedure details**

We analyse the neurological clinical features in relation to radiological findings of neurosarcoid and provide an imaging review of the CNS manifestations of sarcoidosis.

This includes: **Brain;** cranial nerves, lacrimal glands, hydrocephalus, leptomeningeal enhancement, enhancing brain parenchymal lesions/masses, vasculitis/infarct. **Spinal cord lesions;** enhancing leptomeningeal and intramedullary lesions.

**Brain:**

**Cranial Nerves:** There is a poor correlation between imaging evidence of cranial nerve involvement and clinical neuropathy with patients exhibiting clinical signs and symptoms without imaging findings and vice versa. Cranial nerve involvement is the most prevalent in patients with neurosarcoidosis (50-75%). It commonly affects the facial nerve and optic nerve. Features may or may not occur with other lesions such as leptomeningeal involvement. Clinically, the facial nerve is the commonest of the cranial nerves to be affected (only two reported MRI cases in the literature), whereas radiographically, it is the optic nerve which is more commonly seen.

The differential for facial nerve lesions includes metastases (consider primary lesion and involvement of multiple nerves), schwannomas (neurofibromatosis 2 and its' features) and multiple sclerosis (e.g. optic neuritis and other parenchymal lesions). Bells palsy (usually infratemporal facial nerve) and Ramsay Hunt syndrome (Herpes Zoster, e.g. vesicular rash over pinna) tend to be isolated but one may not see facial nerve enlargement and the T1W post contrast nerve enhancement may persist long after symptoms resolve or treatment is completed.

Optic nerve involvement can be uni or bilateral. Intra or extraorbital parts of the nerve may be involved, to include the optic chiasm and the meninges of the nerve. MR imaging features of optic dural sheath neurosarcoidosis are non specific and include thickening of the affected optic nerve and enhancing perineural encasement. Sarcoidosis may involve the orbital fat, muscles, lacrimal glands (Fig 3) or the globe with a diffuse infiltrative mass radiographically indistinguishable from orbital pseudotumor. Differential diagnosis of optic nerve lesions includes optic neuritis, optic nerve glioma and optic meningioma. The differential for lacrimal gland lesions includes benign mixed...
tumour, lymphoma, Idiopathic orbital inflammatory disease, Adenoid cystic carcinoma and Sjogren's syndrome.

Hydrocephalus:

uncommon finding reported in approximately 10% of the neurosarcoid cases (Fig 4) and is generally considered as one of the serious neurological complications. There are two theories postulated in the pathophysiology of hydrocephalus in neurosarcoidosis. Several reports support the non-communicating or obstructing type as the aetiology, due to obstruction of the IVth ventricle outlets or granulomatous lesions compressing the aqueduct. Other reports support the communicating type, where there is an alteration in CSF dynamics from infiltration of granulomas into the ependyma, choroid plexus, leptomeninges and dura.

Leptomeningeal involvement:

Dural and pial meningeal involvement can be focal or diffuse and are commonly seen in neurosarcoidosis (10-20% prevalence) (Fig 5 and 6). With neurosarcoidosis there is often associated parenchymal mass/nodular disease or cranial nerve involvement. Dural thickening in neurosarcoaidosis is characteristically low on T2, has a predilection for the basal cisterns and displays avid enhancement on T1W images after contrast. The differential includes; post surgical changes, meningeal metastases (smooth or nodular enhancement, adjacent skull lesions), chronic subdural haematoma (MR GRE sequences reveal blood products), meningitis (dura/arachnoid pattern less common than pia/subarachnoid), Intracranial hypotension (look for characteristic 'slumping brain'), lymphoma, meningiomas (focal or diffuse dural enhancement +/- adjacent bony changes) and idiopathic hypertrophic pachymeningitis. The latter can be confused pathologically with sarcoidosis as it also displays a granulomatous process.

Pia mater is the innermost layer of the leptomeninges which covers the brain and invaginates into the sulci. Enhancement patterns include conditions that cause inflammation/infection (e.g. TB or fungal meningitis), vascular process (subacute cerebral infarction, usually along vascular territory), vasculitis, Sturg Weber syndrome, Moya Moya disease and neoplastic processes (e.g. primary glioblastoma multiforme or secondary metastases-lung, breast, melanoma and lymphoma). The patterns of ependymal enhancement are usually basal, hypothalamic and periventricular.

Parenchymal lesions/masses:
Space occupying sarcoid parenchymal lesions of the brain are less common, occurring in less than 1% of patients with neurosarcoidosis. There is usually a gradual onset of symptoms suggestive of a neoplastic or infiltrative process as the aetiology. The appearance of single or multiple intra-axial masses may be a result of extension of granulomatous disease from the leptomeningeal or ventricular surfaces into the perivascular spaces (Virchow-Robin) to accompany the arteries up to the capillaries and subsequently into the brain parenchyma. Mass like lesions with associated contrast enhancement and perilesional oedema can 'mimic' infiltrating neoplasm's such as gliomas, lymphomas or metastases. Other differentials include; infectious aetiologies (including encephalitis or tuberculosis) and inflammatory causes (e.g. demyelinating disorders). Pathologically, sarcoidosis is an inflammatory disease with localised lymphocytic infiltrations. It is not a neoplastic process with neovascularisation. Therefore CT angiography or MR angiography may not show abnormalities within the lesions. If other biochemical or radiological examinations fail to reveal the diagnosis, a definitive diagnosis can only be made after a biopsy. *Fig 7, 8 and 9* show an array of parenchymal lesions in two different patients.

Cerebral vasculitis:

This is a well known vasculitic pathological component of neurosarcoidosis. Granulomatous invasion of blood vessel walls is frequent with vasculitic disruption of the media and internal elastic lamina (mainly small perforating and medium sized arteries) causing stenosis or occlusion. These lesions have been associated with small cerebral/lacunar infarcts or ischaemic gliosis. Non enhancing white matter lesions seen as areas of high T2 signal intensity on MRI (*Fig 10*), have been attributed to possible vascular involvement. However, some of these white matter lesions may also represent granulomatous masses. Other white matter lesions are closely associated with local perivascular enhancement (*Fig 10*). There can be a diagnostic conundrum with similar white matter lesions seen in multiple sclerosis, age related cerebral vascular disease and primary vasculitis of the CNS.

Cerebral infarction:

Although a rare presentation, many authors have studied patients with known neurosarcoidosis and stroke like symptoms with a variety of modalities and have found hyperintensities on T2-weighted images and gadolinium enhancement. Only one report has mentioned the use of DWI and the presence of restricted diffusion in a young patient who presented with isolated focal neurological deficit and no previous history. We illustrate stroke like MR features in *Fig 11*. The method of infarction is not completely understood but is thought to result from small-vessel vasculitis, embolus, or large-vessel inflammation.
Spinal cord lesions:

A relatively uncommon manifestation of sarcoidosis occurring in ~10% with CNS sarcoid. There are an array of spinal cord lesions which can be classified as intramedullary, extramedullary intradural, extradural and can manifest also as cauda equina syndrome and arachnoiditis. Clinical features include myelopathy with paraparesis, quadriparesis and bladder and bowel dysfunction.[27]

In terms of imaging characteristics, intramedullary lesions (Fig 12) are non specific with a broad differential which includes; multiple sclerosis, infections and neoplasms. Common MR features are leptomeningeal lesions with subsequent infiltration of inflammatory granulomata into the intramedullary region. Often there is a broad base on the cord surface and the enhancement does not involve the full cord thickness[26,28]. Cervical and thoracic cord are usually involved displaying initial fusiform enlargement, high T2W signal intensity, low signal intensity on T1W and patchy enhancing lesions after contrast administration, accompanied by nearby thin linear and nodular enhancing leptomeningeal lesions.

Four possible histological phases of the disease have been hypothesised by Jugar et al: Phase 1, early inflammation showing linear leptomeningeal enhancement after gadolinium administration along spinal cord surface; phase 2, secondary centripetal spread of the leptomeningeal inflammatory process through the Virchow-Robin spaces, showing parenchymal involvement with faint enhancement and diffuse swelling; phase 3, less prominent swelling and possible normal sized spinal cord, associated with focal or multiple enhancement; phase 4, resolution of the inflammatory process with normal size or atrophy of the spinal cord and no enhancement.

The MRI characteristics of spinal neurosarcoid lesions depend on the stage of the illness and the degree of cord damage/involvement. Other features such as calcifications, cyst formation, and extradural involvement have also been described.

Extramedullary intradural lesions include diffuse or multifocal leptomeningeal involvement (60% of spinal cord sarcoidosis), which enhance on post contrast T1W MR imaging. Even rarer are extramedullary sarcoid masses which may also have a dural base and a have a predilection for any part of the cord. The lesions are shown on MRI as hypointense or isointense signal on T1W images, hyperintense signal on T2W images and marked contrast enhancement with a dural tail described in some reports[4]. The differential for these features include; meningioma, nerve sheath tumors, lymphoma, carcinomatous metastasis, hemangiopericytoma, and other granulomatous depositions[4].
Fig. 1: 53yr old lady with known pulmonary sarcoid presenting with right facial nerve palsy. T1 axial and coronal post contrast images showing enhancement and enlargement of horizontal (short arrows) and lesser extent vertical part (long arrows) of facial nerve within the right internal auditory canal and ganglion respectively.
Fig. 2: 30 year old with known pulmonary sarcoid presenting with 6 month history of recurrent headache, gradual loss of vision in both eyes, nausea, vomiting and dizziness. T1 coronal fat sat and T1 axial post contrast images demonstrate diffuse enhancement of the dura and leptomeninges mainly on the right side with intense enhancement of the chiasm and optic nerves (arrows), hypo-thalamus and basal cisterns.

Fig. 3: Bilateral lacrimal gland enlargement on CT axial image (arrows) and resolving lacrimal gland enlargement post steroid treatment MRI STIR axial image.
**Fig. 4:** Hydrocephalus with dilatation of the lateral ventricles and temporal horns (arrow). T1 axial fat sat and T1 coronal and axial post contrast images from the patient in fig 2 demonstrating right sided cerebral leptomeningeal and dural enhancement and nodular enhancement along the floor of the IIIrd ventricle. Note old left internal capsular infarct on bottom image.
**Fig. 5:** 64 year old lady with a positive serum ACE with intractable headache. T1 coronal and axial post contrast images demonstrate diffuse pachymeningeal thickening and enhancement which on the T1 axial post contrast image below has reduced post steroid treatment.
**Fig. 6:** 65 year old lady with bilateral hilar adenopathy presented with features of drowsiness and acute neurological disturbance. T1 axial and coronal post contrast images show nodular parenchymal and pial enhancement along right lower midbrain, cerebelli and right superior temporal gyrus (arrows)

![Image of Fig. 6](image1)

**Fig. 7:** Fig 7 and 8. 30 year old man with known pulmonary sarcoid presenting with fevers, worsening facial pain and right eye/orbital swelling. Clinical and radiological features markedly improve 2 years post high dose steroid treatment. CT axial bone window images demonstrate extensive paranasal sinus disease with permeative bone changes in the ethmoid sinuses, cribriform plate and maxillary sinuses (long arrow).

![Image of Fig. 7](image2)

**Fig. 8:** Same patient as images in Fig 7. There is breach of the orbital margins, the anterior cranial fossa through the cribriform plate, with changes consistent with frontal lobe cerebritis (FLAIR sagittal). T1 axial fat sat post contrast images show an enhancing mass lesion centered on the upper nasal cavity and ethmoid air cells which is inseparable from the undersurface of the frontal lobes, with small foci of enhancement in the adjacent parenchyma and extensive medial frontobasal T2/FLAIR hyperintensity consistent with oedema. Note the thick dural enhancement overlying the anterior wall of the right middle cranial fossa and enhancing nodule within the ventral midbrain (short arrow) with surrounding midbrain oedema.

![Image of Fig. 8](image3)
Fig. 9: 48yr old male presented with a 6 month history of gradual left sided limb weakness and facial droop. T2 and FLAIR axial images show a large ill defined heterogeneous signal intensity mass with its epicentere in the right basal ganglia/thalamus. There is involvement of the right cerebral peduncle and surrounding perilesional oedema. T1 post contrast axial and coronal images show micronodular and leptomeningeal enhancement in the basal ganglia (arrow), thalamus and upper brainstem on the right. Enhancing Lesions beyond the meningeal surface are thought to have a propensity for parenchymal extension along the basal perforating arteries. This is where there is a potential for spread of the inflammatory process along the perivascular space which separates two sheets of leptomeninges(22). Stereotactic biopsy confirmed neurosarcoid non caeseating granulomatous inflammation.
Fig. 10: 65 year old lady with known pulmonary sarcoid presented with, poor vocal response, short term memory loss, dyscalculia and poor concentration. FLAIR axial and T1 post contrast axial images (top and bottom left) show periventricular white matter and right superior temporal gyrus subcortical white matter hyperintensities. There is leptomeningeal enhancement along the right superior temporal gyrus reflecting probable vasculitis (normal DWI). T2 axial and T1 axial post contrast images show non enhancing subcortical white matter lesions in the right frontal lobe (arrow, bottom middle) and T2 hyperintensities in the cerebelli and middle cerebellar peduncles (arrow top right). Note similarity to lesions in MS and small vessel disease.

Fig. 11: 26 year old male with known pulmonary sarcoid presented with a 2 day history of gradual left sided upper motor neurone limb weakness which worsened on the day of
admission. T2 axial image shows an ill defined area of hyperintensity in the right upper pons which is high on DWI (middle arrow) and low on ADC. On T1W post contrast sagittal images there is enhancement over the pial surface and within the pons. In a patient of this age a pontine stroke as a complication of neurosarcoidosis is likely.

Fig. 12: 25 year old girl with a history of pulmonary sarcoid presented with a 1 week history of numbness and parasthesia in both legs and difficulty passing urine. STIR sagittal whole spine shows fusiform enlargement of the cord and high signal intensity at T11-T12 level (arrow). T1 post contrast axial and sagittal images show intramedullary (arrow) and patchy anterior and posterior leptomeningeal enhancement.
Conclusion

Neurosarcoidosis has no specific clinical presentation that makes it elusive to diagnose. Early diagnosis of neurosarcoid is important to reduce the morbidity and mortality associated with this disorder. Certain imaging features in the brain and spinal cord can help differentiate neurosarcoidosis from other causes and guide further management. Imaging can also contribute to follow up and review of lesions for those patients on treatment.

Personal Information

References


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