

## Cranial neuropathies in sarcoidosis

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to sarcoidosis can be challenging, particularly in the setting of normal imaging studies. In this review, cranial neuropathies in sarcoidosis are discussed in detail.

**Key words:** Sarcoidosis; Neurosarcoidosis; Cranial neuropathy; Central nervous system

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**Core tip:** Sarcoidosis is a multisystem, chronic inflammatory disease that is characterized by the development of non-caseating granulomas in multiple body tissues and organ systems. Neurological complications occur in 5%-15% of the cases. Because sarcoidosis has a predilection to involve the basilar meninges, cranial neuropathy is the most prevalent neurological deficit seen when the nervous system is involved. Several review papers on neurosarcoidosis have been published, but none has elaborated on cranial neuropathies. In this review, cranial neuropathies in sarcoidosis are discussed in detail, with elaboration on each cranial nerve individually and a representation of case reports from the literature.

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### Abstract

Sarcoidosis is a multisystem, chronic inflammatory disease that is characterized by the development of non-caseating granulomas in multiple body tissues and organ systems. Neurological complications of systemic sarcoidosis include peripheral and cranial neuropathies, myopathies, seizures, gait dysfunction, and cognitive decline. Because sarcoidosis has a predilection to involve the basilar meninges, cranial neuropathy is the most prevalent neurological deficit seen when the nervous system is involved. Sarcoidosis cranial neuropathy may occur at different stages of the disease and even as the initial clinical manifestation of central nervous system involvement. Attributing a cranial neuropathy

### INTRODUCTION

Sarcoidosis is a multisystem, chronic inflammatory disease that is characterized by development of non-caseating granulomas in multiple body tissues and organ systems. Sarcoidosis affects more women than men and more adults than children. In the United States, the disease affects more African Americans than Caucasians. Neurological complications occur in 5%-15% of individuals diagnosed with systemic sarcoidosis<sup>[1-4]</sup>, imaging studies reveal neurological disease in 10% of all patients<sup>[5]</sup>, and postmortem

**Table 1** Frequencies of clinical signs and symptoms associated with neurosarcoidosis

Symptoms	%
Cranial nerve palsies	50-75
Overall parenchymal disease	50
Headache	30
Meningeal signs	10-20
Endocrinopathies	10-15
Hydrocephalus	10
Mass lesion(s)	5-10
Seizures	5-10
Encephalopathy/vasculopathy	5-10

Source: Stern *et al.*<sup>[39]</sup>.

studies report that ante-mortem diagnosis is made in only half of the cases with nervous system involvement<sup>[6]</sup>. The exact site of involvement and pathogenesis are difficult to establish, as biopsy and autopsy material is not commonly obtained. Neurological manifestations of sarcoidosis include peripheral and cranial neuropathies, myopathies, seizures, gait dysfunction, and cognitive decline. The presenting symptoms of intracranial sarcoidosis are typically related to meningeal, cranial nerve, hypothalamus, and pituitary involvement<sup>[7-9]</sup>. Common imaging findings include hydrocephalus, mass lesion(s), and leptomeningeal enhancement.

Because sarcoidosis has a predilection to involve the basilar meninges, cranial neuropathy is the most prevalent neurological deficit seen when the nervous system is involved<sup>[10]</sup>, and has been reported in as many as 50%-75% of patients with neurosarcoidosis<sup>[7]</sup>. Table 1 outlines the frequency of some of the most common neurological signs and symptoms associated with neurosarcoidosis. Granulomatous basal meningitis, direct infiltration of cranial nerve(s), and increased intracranial pressure are all potential mechanisms causing cranial neuropathies. Attributing a cranial neuropathy to sarcoidosis can be challenging, especially in the event of normal brain imaging and the often poor correlation between abnormal imaging and clinical findings. For example, in 13 patients with central nervous system (CNS) sarcoidosis and cranial neuropathies, only 9 had correlating brain imaging findings<sup>[11]</sup>. Several explanations of negative brain imaging in patients with cranial neuropathies related to sarcoidosis have been proposed, including extra-cranial nerve involvement, minimal infiltration of the involved cranial nerve by the disease, and small size granulomas.

Cranial neuropathy of neurosarcoidosis can involve one or multiple cranial nerves simultaneously. Table 2 shows the frequency of occurrence of cranial nerve involvement. Cranial nerves can be affected by direct infiltration of the nerve at any anatomical location, extra- or intra-cranially, or by other processes such as increased intracranial pressure and mass lesions.

## THE PATHOGENESIS OF NEUROSARCOIDOSIS

Several mechanisms have been proposed to explain the

**Table 2** Frequencies of occurrence of cranial neuropathies in sarcoidosis

Cranial nerve	Frequency of occurrence
CN-I	Rare
CN-II	5% of all patients with sarcoidosis
CN-III, -IV, -VI	Rare
CN-V	Rare
CN-VII	25%-50% of all patients with sarcoidosis
CN-VIII	1%-7% of all patients with sarcoidosis
CN-IX, -X, -XI	Common
CN-XI	Rare
CN-XII	Rare

CN: Cranial nerve.

pathogenesis of sarcoidosis, but none are conclusive. Several studies suggest a particular role of T-lymphocytes, triggered by an antigen of an unknown origin, in amplifying a local cellular immune response that is crucial for the development of sarcoidosis<sup>[12,13]</sup>. Non-necrotizing granulomas of sarcoidosis are composed of epithelioid macrophages, lymphocytes, and monocytes, and the consequential inflammation is often perivascular. Thickening of the vascular intima and media, along with fibrosis, may lead to ischemic injury.

CNS sarcoidosis has a predilection to involve the leptomeninges, with a granulomatous inflammatory exudate that infiltrates brain parenchyma through the Virchow-Robin spaces<sup>[14,15]</sup>. This pattern of infiltration may explain the predilection of neurosarcoidosis to the base of the brain where the Virchow-Robin spaces are particularly large and, consequently, the high incidence of cranial neuropathies<sup>[16-18]</sup>.

## OLFACTORY NERVE, OR CRANIAL NERVE-I

Involvement of the olfactory nerve, cranial nerve- I (CN-I), in sarcoidosis is considered rare<sup>[19]</sup>. Clinical signs and symptoms include anosmia and hyposmia. Isolated involvement of CN- I in patients with neurosarcoidosis is rare, and anosmia is an extremely infrequent isolated clinical presentation<sup>[20]</sup>. In a series published by Delaney<sup>[2]</sup>, 17% of patients with neurosarcoidosis had anosmia, whereas Colover *et al.*<sup>[20]</sup> reported this symptom in only 2 of 118 cases (< 0.2%). CN- I can be affected by direct infiltration of the nasal mucosa, intracranial disease, basal granulomatous meningitis, or a combination of these mechanisms. Kieff *et al.*<sup>[21]</sup> reported a case of a 51-year-old man who presented with a 6-wk history of anosmia and visual difficulty. Magnetic resonance imaging (MRI) of the brain showed an enhancing subfrontal, extra-axial mass with accompanying edema. Tissue biopsy demonstrated non-caseating granulomas, consistent with the diagnosis of neurosarcoidosis.

## OPTIC NERVE, OR CRANIAL NERVE-II

Following the facial nerve, the optic nerve, or cranial nerve- II (CN- II), is the second most commonly involved

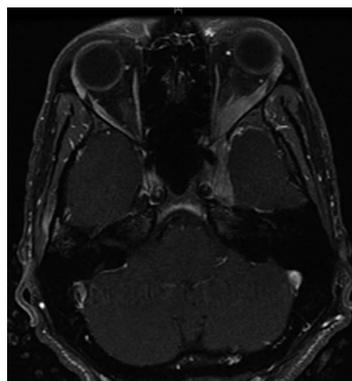
nerve in patients with neurosarcoidosis<sup>[7]</sup>. Approximately 5% of patients with sarcoidosis experience some type of optic neuropathy during the course of the disease, and about 30% of those will have other signs of neurosarcoidosis. Granulomatous infiltration of the optic nerves, chiasm, or tracts has been reported in autopsy studies<sup>[22]</sup>.

Clinical signs of optic neuropathy occur as a result of increased intracranial pressure and papilledema, intracranial compression leading to optic atrophy, and/or direct invasion of the nerve by the forming granulomas. Optic nerve involvement is associated with papilledema, disc edema, or optic nerve head granulomas. Disc edema is the most common optic nerve abnormality in patients with neurosarcoidosis, with optic atrophy and neuritis being much less frequent<sup>[23]</sup>. Retrobulbar involvement of the optic nerve may mimic the clinical picture of optic neuritis, with acute loss of vision, with or without optic disc edema<sup>[24,25]</sup>. Pituitary granulomatous disease may also extend to affect the optic chiasm, with a correlating clinical picture of bi-temporal visual field loss and pituitary dysfunction<sup>[26,27]</sup>. Infiltration of the optic tract or the visual cortex is much less common.

### OCULOMOTOR, TROCHLEAR, AND ABDUCENS NERVES (CN-III, -IV, AND -VI)

External ophthalmoplegia is an infrequent manifestation of CNS sarcoidosis<sup>[2]</sup>. Involvement of CN-III, -IV and -VI is rare<sup>[20]</sup>. Potential pathological mechanisms leading to ophthalmoplegia include direct invasion of a cranial nerve or extraocular muscles by granuloma, increased intracranial pressure, leptomeningeal disease, or orbital mass effect. Ischemia to the involved cranial nerve as a result of perivasculitis has also been suggested as a mechanism contributing to ophthalmoplegia in a patient with neurosarcoidosis<sup>[28]</sup>. Overall, the frequency of extraocular muscles and/or innervating cranial nerve involvement in neurosarcoidosis is felt to be under-reported, as biopsy of these structures is rarely performed. Clinical signs and symptoms include double vision, ptosis, pupillary involvement, and ophthalmoplegia.

There are several reports of CN-III palsy as a manifestation of CNS sarcoidosis, typically as a result of aseptic meningitis causing multiple cranial neuropathies<sup>[29-31]</sup>. Ueyama *et al.*<sup>[30]</sup> reported a patient with isolated CN-III palsy as an initial manifestation of sarcoidosis. The case was of a 28-year-old man who presented with sudden onset of complete CN-III palsy. A conventional cerebral angiogram was unremarkable. Cerebrospinal fluid analysis revealed elevated lymphocytes and protein, but negative cytologic analysis. Brain MRI showed enhanced thickening of CN-II at the level of the ponto-midbrain junction. A chest radiograph revealed bilateral hilar lymphadenopathy, and lymph node biopsy showed non-caseating granulomas confirming sarcoidosis<sup>[30]</sup>. Velazquez *et al.*<sup>[31]</sup> reported a case of a 53-year-old woman who presented with bilateral CN-III palsy and was subsequently found



**Figure 1** Brain magnetic resonance imaging with gadolinium showing diffuse thickening and enhancement of the dura involving the left cavernous sinus, with mild mass effect on the left temporal lobe, and soft tissue enhancement extending anteriorly through the foramen rotundum and left orbital apex.

to have biopsy-proven sarcoidosis. The majority of other cases reported on CN-III palsy related to sarcoidosis were associated with multiple cranial neuropathies<sup>[11,28]</sup>.

As stated previously, involvement of CN-IV or -VI is rare<sup>[2,20]</sup>. In the series published by Wiederholt *et al.*<sup>[19]</sup>, 18 of 807 patients with sarcoidosis had cranial nerve lesions. No trochlear or abducens nerve involvement was reported, whether in isolation or in combination with other cranial neuropathies.

We evaluated a 23-year-old African American man who presented to our institution with painless bulging of the left eye of three months duration, associated with diplopia. On the day of admission, he had a first-event witnessed generalized tonic-clonic seizure. The patient had a normal neurological examination except for left CN-VI palsy. Brain MRI revealed diffuse thickening and enhancement of the dura involving the left cavernous sinus (Figure 1). A computed tomography of the chest, abdomen, and pelvis with and without contrast was unremarkable for any sarcoidosis lymphadenopathy or malignancy. A left cavernous sinus dural biopsy revealed extensive chronic inflammation containing non-necrotizing granulomas, consistent with sarcoidosis.

### TRIGEMINAL NERVE, OR CRANIAL NERVE-V

Involvement of the trigeminal nerve (CN-V) is exceedingly uncommon in patients with sarcoidosis<sup>[7]</sup>. Sarcoidosis can infiltrate any of the three divisions of CN-V, with or without eye involvement. Involvement of CN-V is usually sensory and unilateral, and commonly accompanied by other cranial neuropathies<sup>[20]</sup>. Clinical signs and symptoms include facial numbness, hypesthesia, and/or corneal ulcers. Biopsy of CN-V is not a common practice, and the physician must thus rely on the clinical presentation and neurological examination.

Three cases of isolated unilateral trigeminal nerve involvement in patients with sarcoidosis have been reported<sup>[32]</sup>. The first was of a patient with pulmonary

sarcoidosis who presented with complete unilateral ophthalmoplegia and cavernous sinus syndrome involving CN-V<sup>[33]</sup>. A case of another patient with mediastinal and parotid sarcoidosis and bilateral Gasser's ganglion cistern involvement has been reported with no ocular findings<sup>[34]</sup>.

Absence of corneal sensation can result from impairment of trigeminal corneal innervation, a condition known as neurotrophic keratopathy. Gupta *et al*<sup>[35]</sup> reported a particularly rare case of isolated bilateral CN-V neuropathy in a patient with sarcoidosis who presented with neurotrophic corneal ulcers and was diagnosed with biopsy-proven cutaneous sarcoidosis. The patient also had decreased sensation to light touch involving all divisions of the trigeminal nerve bilaterally, with no other cranial neuropathies. After all potential causes of CN-V neuropathy were ruled out, isolated bilateral trigeminal neuropathy as a result of sarcoidosis was the confirmed diagnosis<sup>[35]</sup>.

## FACIAL NERVE, OR CRANIAL NERVE-VII

Of all the cranial nerve syndromes associated with sarcoidosis, peripheral cranial nerve-VII (CN-VII) palsy is the most common and is the single most frequent neurologic manifestation<sup>[36,37]</sup>. Facial neuropathy makes up 25%-50% of neurological manifestations of sarcoidosis<sup>[7,28]</sup>. Although usually unilateral, bilateral CN-VII involvement can occur, presenting with either simultaneous or sequential paralysis<sup>[37,38]</sup>. CN-VII can therefore be affected unilaterally, bilaterally, or simultaneously with other cranial nerves<sup>[39]</sup>. Sarcoidosis affects CN-VII either secondary to meningitic reaction or parotid gland inflammation, and may precede or follow parotitis. Clinical signs and symptoms include facial diplegia, peripheral facial palsy, and/or hemiageusia. Other potential etiologies including Lyme disease, human immunodeficiency virus, syphilis, brain stem lesions, leukemia, meningitis, Guillain-Barré syndrome, and diabetes mellitus need to be considered and investigated<sup>[40-42]</sup>.

Facial nerve infiltration can occur at different anatomical locations. Rarely is the facial palsy caused by parotid inflammation<sup>[43]</sup> or part of uveoparotid fever (Heerfordt's syndrome), which includes fever, enlarged parotid glands, uveitis, and unilateral or bilateral facial neuropathy. In patients with sarcoidosis, CN-VII is more commonly affected as it traverses the meninges and subarachnoid space. Facial nerve paresis could also be due to intra-axial sarcoidosis-induced inflammation<sup>[43]</sup>. Necrotizing nerve ischemia and granulomatous infiltration of the epineurium are suggested mechanisms of facial neuropathy<sup>[44]</sup>. CN-VII involvement can be part of multiple cranial neuropathies, especially with meningeal infiltration<sup>[36,45]</sup>. In general, the prognosis for CN-VII is good, with over 80% of patients having a favorable outcome if treated early<sup>[46]</sup>.

## VESTIBULOCOCHLEAR NERVE, OR CRANIAL NERVE-VIII

Involvement of cranial nerve-VIII (CN-VIII) has been reported

as a neurological manifestation in 1%-7% of patients with sarcoidosis<sup>[7,45,47-50]</sup>. Clinical signs and symptoms include vertigo, tinnitus, deafness, and sensorineural hearing loss. Neurosarcoidosis should be entertained as a diagnosis in a patient with sensorineural hearing loss of an unknown source, especially if a diagnosis of systemic sarcoidosis is known. Several cases of sensorineural hearing loss have been reported in patients with sarcoidosis<sup>[51-54]</sup>. In a report by Babin *et al*<sup>[55]</sup>, autopsy findings in a patient with a known diagnosis of sarcoidosis and deafness included perivascular granulomatous inflammation within the internal auditory meatus. The authors attributed the vestibulocochlear impairment to vascular occlusion, as the severity of cochlear destruction did not correlate with the degree of cochlear infiltration<sup>[55]</sup>.

Cama *et al*<sup>[56]</sup> reported two patients with sudden hearing loss that was attributed to sarcoidosis, with different findings on brain imaging studies. The first reported case was of a 29-year-old man who presented with left-sided hearing loss and facial nerve paralysis. Initial evaluation revealed bilateral sensorineural hearing loss and right anterior uveitis. Brain MRI with gadolinium was normal. Further imaging studies revealed multiple small pulmonary cavities and abdominal lymphadenopathy. Percutaneous hepatic biopsy revealed giant-cell granulomas. The initial presenting symptom of hearing loss was attributed to systemic sarcoidosis with CNS involvement<sup>[56]</sup>.

The second case was of a 44-year-old man with a known diagnosis of systemic sarcoidosis who presented with diplopia and unsteadiness, followed by sudden right-sided hearing loss a few weeks later. Initial evaluation revealed sensorineural hearing loss of a cochlear origin. Contrast-enhanced brain MRI was negative. One month later he had worsening of the right-sided and new left-sided hearing loss. Brain MRI with gadolinium showed bilateral enhancement of the internal auditory meatus. A follow-up MRI two months later showed diffuse enhancement of basal leptomeninges, myelinic sheath of both optic nerves, trigeminal nerves, and pial surfaces of the cerebellar folia. The patient's hearing impairment, secondary to CNS involvement of systemic sarcoidosis, remained stable on oral corticosteroids<sup>[56]</sup>.

## GLOSSOPHARYNGEAL NERVE, OR CRANIAL NERVE-IX

Isolated glossopharyngeal neuropathy associated with sarcoidosis is extremely rare<sup>[57]</sup>. Combined involvement of cranial nerves IX, X, and XI is the third most common cranial neuropathy after facial and optic nerves involvement<sup>[58]</sup>. The most common site of involvement is in the lateral medulla or subarachnoid space<sup>[57]</sup>. The main presenting symptoms are dysphagia and hoarseness of voice<sup>[57,58]</sup>.

## VAGUS NERVE, OR CRANIAL NERVE-X

Cranial nerve-X (CN-X) involvement in neurosarcoidosis

is rare, with only a few cases reported in the literature<sup>[59]</sup>. Vagal neuropathy can occur in isolation as a manifestation of neurosarcoidosis or in combination with other cranial neuropathies. Neurosarcoidosis should be considered in a patient with vocal fold paresis of no apparent etiology. Two cases of CN-X involvement were reported in a retrospective review of 35 cases of confirmed neurosarcoidosis<sup>[3]</sup>. Additionally, Alon *et al*<sup>[60]</sup> conducted a retrospective study of a small cohort of 53 patients who presented with neurosarcoidosis and found only four with clinical or radiological findings suggestive of CN-X involvement. None of the four patients had a known diagnosis of systemic sarcoidosis. All four patients had vocal fold motion impairment. In one patient, a retropharyngeal mass was identified with biopsy-proven noncaseating granulomas, which extended to the jugular foramen several months later. The patient was found to have unilateral vocal fold paralysis and palatal weakness. Another patient with a history of chronic cough presented with right vocal fold paralysis and decreased gag reflex. A mediastinal lymph node biopsy revealed non-caseating granulomas. A third reported patient initially presented with unilateral throat and tongue burning sensation as well as vocal cord and tongue paresis. An MRI of the brain showed an enhancing mass in the jugular foramen extending into the right hypoglossal canal and second division of CN-V. Finally, a case of bilateral vagus and glossopharyngeal nerve enhancement was reported in a patient with biopsy-proven sarcoidosis who presented with palatal weakness and vocal folds paralysis<sup>[60]</sup>.

### SPINAL ACCESSORY NERVE, OR CRANIAL NERVE-XI

Isolated spinal accessory neuropathy has not been reported as a clinical manifestation of neurosarcoidosis. However, cranial nerve-XI neuropathy has been reported in combination with other cranial neuropathies. Clinical manifestations include ipsilateral sternocleidomastoid and trapezius muscle weakness.

### HYPOGLOSSAL NERVE, OR CRANIAL NERVE-XII

Hypoglossal nerve involvement commonly occurs with other cranial neuropathies. As with CN-IX, -X, and -XI, the medulla and subarachnoid space are the most common sites of cranial nerve-XII involvement. The nerve is commonly affected as a result of a meningeal process, such as pachi meningitis, or focal granulomatous disease involving the medial medulla. The main presenting symptom is dysarthria<sup>[61,62]</sup>, but patients can also have tongue deviation and atrophy.

#### **Multiple cranial neuropathies of sarcoidosis**

In most patients with neurosarcoidosis, more than one cranial nerve is involved<sup>[59]</sup>. Loor *et al*<sup>[45]</sup> reported a 26-year-old woman with an initial presentation of left-sided facial

palsy and sensorineural hearing loss. MRI of the brain with gadolinium revealed enhancement of the left CN-VII and bilateral CN-VIII. A chest X-ray demonstrated hilar lymphadenopathy. The patient later developed anosmia, and all her symptoms resolved after a course of steroid treatment<sup>[45]</sup>.

Chapelon *et al*<sup>[3]</sup> reported a case of a woman with bilateral vestibular symptoms, as well as CN-VII, -IX, -X, and -XI involvement. Another case reported by Chapelon *et al*<sup>[3]</sup> was of a 21-year-old man with a history of confirmed sarcoidosis who presented with multiple cranial neuropathies (CN-VII, -X, -XI, -XII). As discussed earlier, the predilection of sarcoidosis to the base of the brain is a plausible explanation of multiple cranial neuropathies.

### TREATMENT OF NEUROSARCOIDOSIS

Corticosteroids remain the gold standard treatment of patients with neurosarcoidosis, and patients with symptoms should be treated initially with pulse corticosteroid therapy<sup>[63]</sup>. If the use of steroids is limited secondary to resistance or adverse reactions, immunosuppression therapy is recommended.

According to recent recommendations made by Nozaki *et al*<sup>[64]</sup> in 2013, prednisone is the first-line of therapy in patients with cranial neuropathy secondary to neurosarcoidosis, particularly if CN-VII is involved, at a daily dose of 20-40 mg. If prednisone cannot be tapered to less than 10 mg per day within 3-6 mo, a higher dose or an alternative agent should be considered. Recurrence of symptoms has been reported when prednisone was tapered to less than 20-25 mg daily<sup>[64]</sup>.

Immunomodulating agents include methotrexate, considered the first agent of choice that allows tapering the prednisone to 10-20 mg per day in one third of neurosarcoidosis patients<sup>[64]</sup>. Other immunosuppressant agents to be considered include azathioprine, cyclophosphamide, and cyclosporine.

### CONCLUSION

Neurosarcoidosis is a rare manifestation of sarcoidosis. The diagnosis can be challenging, as many conditions can mimic neurosarcoidosis both clinically and radiographically. Sarcoidosis mononeuropathy may occur at different stages of the disease and even as the initial clinical manifestation of CNS involvement. Cranial neuropathy can present as an isolated entity of sarcoidosis in the absence of systemic involvement, which makes the diagnosis challenging and dependent on tissue biopsy. In these patients, extensive work-up is warranted to rule out infections and demyelinating conditions, as well as inflammatory and autoimmune diseases.

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