Clinical Reasoning:

A 37-year-old man with multiple cranial neuropathies

Sean O’Loghlen, MD*
Brent Guy, MD*
John P. Rossiter, MB,
BCh, PhD, FRCPC
John Gordon Boyd, MD,
PhD, FRCPC

Correspondence to
Dr. O’Loghlen:
sean.b.ologhlen@gmail.com

SECTION 1

A 37-year-old man presented with a 7-month history of vertigo, nausea, dysphagia, right-sided tinnitus, and hearing loss. He denied headache, paresthesias, change in vision, or problems with cognition. He endorsed a history of progressive fatigue, generalized weakness, and poor libido. His symptoms left him functionally impaired and bedridden.

His medical history was remarkable for dyslipidemia, obesity hypoventilation syndrome, nephrolithiasis, and an episode of bilateral anterior uveitis 6 years prior. In addition, he had been in a motor vehicle collision that caused a facial degloving injury requiring multiple operations, leaving the patient with vision loss in his left eye.

On examination, the patient was morbidly obese with extensive scarring on the left side of his face. There was decreased visual acuity and left exotropia. The right pupil was dilated with a sluggish response to light. The left pupil could not be reliably examined

due to the changes from his prior facial degloving injury. There was also lower lid scarring on the left with lagophthalmos, again secondary to his prior injury. The right lid was normal. There was a mild left-sided facial weakness in a lower motor neuron pattern. His speech was dysarthric. Examination of the remaining cranial nerves (CNs) was normal. Strength was 5/5 in the upper extremities bilaterally and 4+/5 in the lower extremities bilaterally. Muscle bulk and tone were normal, as were coordination and fine motor movements. Sensation and reflexes were intact. Romberg test was negative. Bilateral sensorineural hearing loss, mild to moderate on the left and moderate to severe on the right, was confirmed objectively with audiometry.

Question for consideration:

1. Can you localize the lesion based on the patient’s constellation of findings?

[GO TO SECTION 2](#)

*These authors contributed equally to this work.

From the Divisions of General Internal Medicine (S.O., B.G.) and Neurology (J.G.B.), Department of Medicine, and the Department of Critical Care Medicine (J.G.B.), Queen’s University, Kingston; and the Department of Pathology and Molecular Medicine (J.P.R.), Queen’s University and Kingston General Hospital, Canada.

Go to Neurology.org for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

Figure 1 Images from CT and MRI head

Contrast-enhanced CT (A, B) and T1-weighted MRI (C, D) axial sections demonstrate multiple enhancing lesions throughout the brain parenchyma. The right frontal lesion shown in (B) is the lesion that was biopsied. The leptomeningeal enhancement is most apparent on the gadolinium-enhanced MRI sequences (white arrowheads).

SECTION 2

CT of the head (figure 1, A and B) demonstrated multiple enhancing intra-axial lesions. The largest measured up to $12 \times 15 \times 12$ mm and was located in the lentiform nucleus. There were multiple other lesions involving the anterior parasagittal region of the right frontal lobe, the rostrum of the corpus callosum, and the hypothalamus. There were also findings suspicious for leptomeningeal enhancement, particularly in the basal cisterns. There was no evidence of hydrocephalus or herniation. MRI (figure 1, C and D) confirmed the presence of multiple enhancing parenchymal lesions and leptomeningeal enhancement in the posterior fossa.

Questions for consideration:

1. What is your differential diagnosis at this point?
2. What further investigations would you order at this point?

[GO TO SECTION 3](#)

SECTION 3

The differential diagnosis for multiple cranial neuropathies with evidence of several intracranial lesions is extensive. This presentation is particularly worrisome for an underlying neoplastic process, particularly primary CNS lymphoma. Leptomeningeal carcinomatosis or metastatic disease are also possibilities. Alternatively, granulomatous disease, and infections such as tuberculosis, histoplasmosis, toxoplasmosis, blastomycosis, and HIV, are diagnostic considerations.

Further imaging tests were performed to identify a possible primary malignancy or other sites of disease involvement. CT chest demonstrated mediastinal and hilar lymphadenopathy with scattered small pulmonary nodules. CT abdomen showed retroperitoneal lymphadenopathy, with normal liver and skeletal structures.

Blood cultures were persistently negative, as were serologies sent for HIV, histoplasmosis, toxoplasmosis,

and blastomycosis. CSF examination showed lymphocytic predominance with low glucose (0.6 mmol/L) and high protein (3.15 g/L). CSF flow cytometry was negative. Serum and CSF angiotensin-converting enzyme (ACE) levels were not elevated (22 U/L and 18 U/L, respectively). CSF was sent for acid-fast bacilli stain, which was negative, as were mycobacterial cultures. Tuberculin skin test and interferon-gamma release assays were negative.

Multiple attempts at biopsy of the mediastinal lymphadenopathy yielded nondiagnostic results. A biopsy of the most accessible intracranial lesion located in the right frontal lobe showed necrotizing granulomatous inflammation (figure 2). Stains for infection were negative. There was no evidence of neoplasia.

Question for consideration:

1. What is the final diagnosis?

GO TO SECTION 4

Figure 2 Histopathology from brain biopsy

(A) Low-power photomicrograph of brain biopsy shows multiple granulomas (black asterisks on representative examples). (B) Higher power view of one granuloma, with multinucleated giant cells (arrows) and a central necrotic area (white asterisk). Hematoxylin-phloxine saffron (HPS) stain. A, $\times 40$; B, $\times 185$.

SECTION 4

Given the history of prior anterior uveitis, multiple cranial neuropathies, and bilateral hilar and mediastinal lymphadenopathy, the patient's presentation is most compatible with neurosarcoidosis. The necrosis seen on biopsy, though unusual with sarcoidosis, is consistent with necrotizing sarcoid granulomatosis, a rare subtype.¹ Though serum and CSF ACE levels were normal, both tests have poor sensitivity and specificity.²

DISCUSSION Sarcoidosis is an uncommon disease with protean manifestations characterized by the appearance of noncaseating granulomas in involved organs.³ The etiology is poorly understood, but thought to be related to an exaggerated immune response to unidentified antigens, occurring in genetically predisposed individuals.³ The most common site of disease involvement is the pulmonary parenchyma and mediastinal and hilar lymph nodes (90%). However, up to 50% of patients will have extrapulmonary manifestations, including the anterior uvea (10%–30%), peripheral lymph nodes (10%–20%), and skin (15%).^{3–5} The CNS is an unusual site of granuloma formation, affecting only 5% of patients, but carries significant morbidity.^{3–5} Our patient had evidence of neurologic and pulmonary involvement, based upon his radiologic findings.

Neurosarcoidosis is challenging to identify and is rarely a definitive diagnosis.² The most common manifestation is cranial neuropathies, observed in 50%–75% of cases.^{2,5} The CN dysfunction is a result of multiple mechanisms, including increased intracranial pressure, mass effect from granulomas, and basal meningitis causing compression of CNs traversing the subarachnoid space.^{2,5} CN VII is the most commonly affected, followed by CN II.^{2,5} Our patient's facial droop, lateral gaze deviation, and hearing loss were indicative of CN VII and CN VIII dysfunction and a partial CN III palsy. Aseptic meningitis is observed in 10%–20% of cases, manifesting as a lymphocytic pleocytosis with elevated protein and low glucose.^{2,5} Our patient's CSF analysis exhibited this pattern. Mass lesions are present in 50% of patients on imaging.² These lesions preferentially involve the hypothalamus and pituitary gland, and up to 15% of patients will develop neuroendocrine manifestations.^{2,5} Our patient demonstrated elevated prolactin, presumably secondary to granulomatous involvement of the pituitary stalk. Additionally, our patient endorsed a history of poor libido and fatigue, and subsequent investigations were compatible with hypogonadotropic hypogonadism. Psychiatric symptoms, cerebellar ataxia, and peripheral neuropathy each represent other potential manifestations of neurosarcoidosis.^{2,5}

The imaging modality of choice for neurosarcoidosis is MRI with gadolinium.^{2,5} Typical findings include periventricular white matter lesions and leptomeningeal enhancement, both present in our patient. However,

numerous other processes can have an identical radiographic appearance, including lymphoma or leukemia and infectious and other inflammatory etiologies.⁵ Serum and CSF ACE levels are of limited diagnostic utility. Previous studies demonstrated that serum ACE levels are only elevated in 50% of patients with proven neurosarcoidosis.⁵ Similarly, CSF ACE levels are elevated in 55% of patients with known disease, and can be elevated in 5% of patients where disease is absent.⁵ Our patient's serum and CSF ACE levels were both within normal limits.

The gold standard for diagnosis is a tissue biopsy of an involved site demonstrating noncaseating granulomas. Typically the most accessible site of disease involvement is biopsied first to minimize morbidity. In our patient, this was the mediastinal lymphadenopathy. Attempts to sample these lymph nodes via endoscopy and mediastinoscopy yielded nondiagnostic results. Ultimately, a brain biopsy was required to arrive at the final pathologic diagnosis of necrotizing sarcoid granulomatosis. The differential diagnosis of necrotizing granulomas involving the CNS is extensive, and includes numerous infectious agents (particularly fungi and mycobacteria) and noninfectious processes, such as Wegener granulomatosis and necrotizing sarcoid granulomatosis.⁶ To the authors' knowledge, there are no clear data in the literature to indicate that the presence or absence of necrosis on histopathology influences the clinical behavior or response to therapy of neurosarcoidosis. Despite the lack of formal randomized controlled trials, corticosteroids are the first-line therapy of choice for neurosarcoidosis.⁷ The initial route of treatment is dictated by disease severity. Mild disease, such as isolated facial nerve palsy, can typically be treated with oral prednisone at a dose of 0.5–1 mg/kg/d. Severe, disabling disease is treated aggressively with IV pulse corticosteroids. A common regimen is methylprednisolone at a dose of 20 mg/kg for 3–5 days, followed by an oral regimen.² A prolonged taper of up to 1 year may be required, but symptom recurrence is common as the corticosteroid dose nears 10–20 mg/d.⁵

Alternative therapies for neurosarcoidosis are typically reserved for cases where corticosteroids have been ineffective or poorly tolerated. Further, some experts have advocated for their use early in the course of treatment for those with disabling symptoms.⁷ These therapies are typically steroid-sparing immunosuppressive agents, such as methotrexate and azathioprine.

In the case of our patient, he was initially treated with prednisone at a dose of 80 mg per day with a prolonged taper, and early in his course azathioprine was added and titrated to a target dose of 2.5 mg/kg/d. The patient's clinical response to treatment has been limited, which is not unusual with neurosarcoidosis. He was subsequently referred to an appropriate rehabilitation program.

AUTHOR CONTRIBUTIONS

Dr. Sean O'Loughlen and Dr. Brent Guy cowrote the manuscript. Dr. Rossiter provided analysis and interpretation of the pathologic specimens and revised the manuscript. Dr. Boyd provided analysis and interpretation of the radiologic specimens and revised the manuscript.

STUDY FUNDING

No targeted funding reported.

DISCLOSURE

The authors report no disclosures relevant to the manuscript. Go to Neurology.org for full disclosures.

REFERENCES

1. Aubry MC. Necrotizing granulomatous inflammation: what does it mean if your special stains are negative? *Mod Pathol* 2012;25:S31–S38.
2. Terushkin V, Stern BJ, Judson MA, et al. Neurosarcoidosis: presentations and management. *Neurologist* 2010;16:1–15.
3. Valeyre D, Prasse A, Nunes H, Uzunhan Y, Brillet PY, Muller-Quernheim J. Sarcoidosis. *Lancet* 2014;383:1155–1167.
4. Criado E, Sanchez M, Ramirez J, et al. Pulmonary sarcoidosis: typical and atypical manifestations at high-resolution CT with pathologic correlation. *Radiographics* 2010;30:1567–1586.
5. Joseph FG, Scolding NJ. Sarcoidosis of the nervous system. *Pract Neurol* 2007;7:234–244.
6. Prayson RA, Kleinschmidt-DeMasters BK. An algorithmic approach to the brain biopsy: part II. *Arch Pathol Lab Med* 2006;130:1639–1648.
7. Scott TF, Yandora K, Valeri A, Chieffe C, Schramke C. Aggressive treatment for neurosarcoidosis: long-term follow-up of 48 treated patients. *Arch Neurol* 2007;64:691–696.

Neurology®

Clinical Reasoning: A 37-year-old man with multiple cranial neuropathies

Sean O'Loghlen, Brent Guy, John P. Rossiter, et al.

Neurology 2016;86:e66-e70

DOI 10.1212/WNL.0000000000002381

This information is current as of February 15, 2016

Updated Information & Services	including high resolution figures, can be found at: http://n.neurology.org/content/86/7/e66.full
References	This article cites 7 articles, 1 of which you can access for free at: http://n.neurology.org/content/86/7/e66.full#ref-list-1
Subspecialty Collections	This article, along with others on similar topics, appears in the following collection(s): All Clinical Neurology http://n.neurology.org/cgi/collection/all_clinical_neurology All Medical/Systemic disease http://n.neurology.org/cgi/collection/all_medical_systemic_disease Clinical neurology examination http://n.neurology.org/cgi/collection/clinical_neurology_examination CT http://n.neurology.org/cgi/collection/ct MRI http://n.neurology.org/cgi/collection/mri
Permissions & Licensing	Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at: http://www.neurology.org/about/about_the_journal#permissions
Reprints	Information about ordering reprints can be found online: http://n.neurology.org/subscribers/advertise

Neurology® is the official journal of the American Academy of Neurology. Published continuously since 1951, it is now a weekly with 48 issues per year. Copyright © 2016 American Academy of Neurology. All rights reserved. Print ISSN: 0028-3878. Online ISSN: 1526-632X.