

Clinical Reasoning: Woman With Acute Bilateral Ophthalmoplegia

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Abstract

This is a case of a 75-year-old woman who presented with severe headache, left eye ptosis, and binocular diplopia and was found to have multiple cranial neuropathies on examination. This case reviews the localization and workup of multiple cranial neuropathies and emphasizes the importance of not prematurely narrowing the differential diagnosis.

Section 1

A 75-year-old woman with a history of hypothyroidism presented to her primary care provider with sudden-onset holicephalic headache. A CT head scan was negative for acute intracranial abnormality, and conservative treatment of headache was recommended. Eight days after symptom onset, she presented to the hospital with severe throbbing headache, new left-sided ptosis, and binocular diplopia. She also endorsed mild pain with eye movements and nausea. She had no vision loss, dysphagia, dysarthria, cognitive changes, fluctuating symptoms, weight loss, jaw claudication, fevers, or signs of infection on review of systems. She was afebrile and hemodynamically stable. Her initial neurologic examination was notable for

left-sided ptosis and incomplete abduction of her left eye. The rest of her cranial nerve examination was normal including pupillary reaction. She had no signs of meningismus. Her sensory, motor, coordination, reflexes, and gait examination were normal. Over the next 6 days, she developed near bilateral ophthalmoplegia (Figure 1), vision loss (finger counting at 2 feet) in her left eye with a left relative afferent pupillary defect, and scalp tenderness. Fundoscopic examination revealed slightly blurred disc margins bilaterally and a left branch retinal artery occlusion (BRAO).

Questions for Consideration:

1. What is the localization for her presentation?
2. What are the differential diagnoses?

Figure 1 Extraocular Movements During Initial Hospitalization and at 5-Month Follow-up



Extraocular movements show left ptosis and complete ophthalmoplegia with eye movements (A) at rest, (B) leftward gaze, (C) rightward gaze, (D) upward gaze, and (E) downward gaze. Improvement in extraocular movements and left ptosis 5 months after initial diagnosis and treatment with high-dose methylprednisolone followed by prolonged prednisone taper (F) at rest, (G) leftward gaze, (H) rightward gaze, (I) upward gaze, and (J) downward gaze.

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Section 2

The patient initially presented with unilateral pupil-sparing ptosis and impaired left eye abduction. This localized to the left lateral rectus and levator palpebrae muscles, cranial nerves (partial left III and left VI), brainstem (midbrain and pons), partial left cavernous sinus, or superior orbital fissure. The orbital apex was considered less likely given the sparing of vision. Ptosis and impaired abduction can indicate neuromuscular junction pathology; however, this was thought to be less likely given the lack of fatigability or fluctuation in symptoms and the presence of headache. When she progressed to have left vision loss and near complete bilateral ophthalmoplegia, multiple cranial neuropathies (left II, III, and VI; right III and VI), extensive cranial meningeal involvement, or a bilateral extending cavernous sinus with left orbital apex involvement were considered. Diffuse brainstem localization was thought to be less likely given the lack of long-tract signs.

A wide variety of pathologic processes may cause cranial nerve dysfunction within the brainstem or along their extramedullary course as they traverse the meninges, subarachnoid space, bony structures of the skull, and the superficial soft tissues. The differential includes, but is not limited to, infectious processes including bacterial meningitis, Lyme disease, *Mycoplasma*

infection, or syphilis; viruses such as human immunodeficiency virus or varicella-zoster virus; and fungal infections including aspergillus and cryptococcus. Inflammatory diseases (sarcoidosis, neuro-Behcet syndrome, immunoglobulin G4-related disease, myelin oligodendrocyte glycoprotein antibody-associated disease, and idiopathic), in addition to vasculitic processes (granulomatosis with polyangiitis and giant cell arteritis [GCA]), and connective tissue diseases (Sjogren disease, systemic lupus erythematosus, and rheumatoid arthritis) can cause cranial neuropathies. Neoplastic (lymphoma, carcinomatosis, and primary or metastatic skull-base tumors), vascular (diabetes mellitus and cerebral venous sinus thrombosis [CVST]), vertebrobasilar (dolichoectasia, carotid aneurysms, and fistulas), and peripheral nervous system disorders (Guillain-Barre syndrome, myasthenia gravis, and myopathies) should also be considered.

Our top diagnosis was a vasculitic process given her history of hypothyroidism and risk for other autoimmune conditions. Once she developed scalp tenderness, GCA was at the top of the differential. Infectious etiologies were felt to be less likely given the lack of systemic symptoms and immunocompetent state.

Question for Consideration:

1. What additional workup would you do to help narrow the differential diagnosis?

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Section 3

A directed but comprehensive approach guided by clinical history and examination is warranted to minimize unnecessary testing but ensure an adequate investigation for a wide differential.

Blood Tests

Initial workup included serum studies for infectious and inflammatory causes of multiple cranial neuropathies, including complete blood count, comprehensive metabolic panel, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), antinuclear antibody, Sjogren antibodies, Lyme, rapid plasma reagin, thyroid-stimulating hormone, and hemoglobin A1C. Workup revealed elevated ESR (81 mm/h) and CRP (9.1 mg/dL) which was consistent with GCA. Second tier testing including serum antineutrophil cytoplasmic antibodies (ANCA) for an ANCA-associated vasculitis, acetylcholine receptor antibodies for myasthenia gravis, and anti-GQ1B for Miller-Fisher syndrome eventually returned negative.

Imaging

MRI of the brain with contrast did not show any brainstem lesions or abnormal meningeal or cranial nerve enhancement. Initial magnetic resonance venogram (MRV) showed filling defects within the right and left transverse sinuses concerning for CVST, and she was started on heparin. Repeat imaging with CT venogram (CTV) was obtained after patient continued to worsen despite treatment with 6 days of anticoagulation. The CTV did not confirm evidence of CVST seen on MRV; therefore, heparin was stopped. CT of the chest with contrast did not show any lymphadenopathy suspicious for sarcoidosis or lymphoma.

Lumbar Puncture

CSF studies revealed normal cell counts (1 white blood cell and 1 red blood cell) and mildly elevated protein (58 mg/dL) and glucose (96 mg/dL). Meningoencephalitis panel (including viral studies), cultures, and cryptococcal antigen returned negative. Opening pressure was normal.

Treatment

Given her scalp tenderness, headaches, left BRAO, and elevated inflammatory markers, she was started on methylprednisolone

1 g IV daily for treatment of GCA after her CSF did not show a pleocytosis consistent with infection or elevated intracranial pressure attributable to CVST.

Pathology

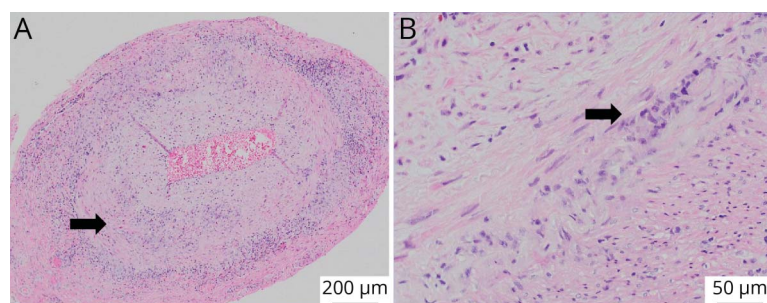
Temporal artery biopsy (Figure 2) revealed granulomatous inflammation, giant cells, and destruction of the internal elastic lamina of the temporal artery, consistent with diagnosis of GCA.

Discussion

GCA, also referred to as temporal arteritis, is a systemic vasculitis affecting large and medium sized arteries, with predilection for the cranial branches of carotid arteries. Based on the American College of Rheumatology 1990 criteria, GCA is diagnosed in patients who have 3 or more of the following: age ≥ 50 years, new onset of localized headache, temporal artery tenderness or decreased temporal artery pulse, elevated ESR ≥ 50 mm/h, and artery biopsy showing necrotizing arteritis, characterized by a predominance of mononuclear cell infiltrates or granulomatous process with multinuclear giant cells.¹ Our patient met 5 of 5 for these criteria, confirming the diagnosis of GCA.

Various neuro-ophthalmologic complications of GCA have been recognized. Arteritic anterior ischemic optic neuropathy is the most common ocular manifestation resulting in monocular vision loss, although central, branch, and cilio-retinal artery occlusions have also been described. In addition, transient ischemic phenomena, pupillary autonomic dysfunction, postchiasmal field defects and cortical blindness from occipital lobe infarction, visual hallucinations, and ophthalmoparesis have been reported.^{2,3} Concomitant optic nerve head and retinal ischemia in an elderly patient, as seen in our case, is very specific to GCA.³ In a 2018 review article describing visual complications of GCA, 1%–19% of cases presented with diplopia and ophthalmoplegia.³ Since then, there have been a handful of other case reports of bilateral ophthalmoplegia related to GCA.^{4–8} Only 1 of the 5 cases involved bilateral cranial nerves III and VI.⁵ One case presented with bilateral oculomotor nerve plegia,⁴ and all other cases involved bilateral internuclear ophthalmoplegia.^{6–8} The mechanism of ophthalmoplegia in GCA is from ophthalmic artery and

Figure 2 Pathology From Temporal Artery Biopsy Confirming the Diagnosis of GCA



(A) The black arrow points to intramural inflammation within the temporal artery cross section. (B) Giant cells destroying internal elastic lamina. The black arrow points to a giant cell. GCA = giant cell arteritis.

vasa nervorum ischemia, which supply the extraocular muscles and the oculomotor nerves, respectively.³

This case represents an atypical presentation of GCA. It is important to consider GCA in the differential diagnosis of ophthalmoplegia to initiate timely treatment. This case was challenging owing to a broad differential for multiple cranial neuropathies, which was prematurely narrowed by a false-positive MRV suggestive of CVST. The sensitivity and specificity of MRV vary by technique, ranging between 71.4%/55.6%, respectively, for 2-dimensional time-of-flight MR venography (MRV) imaging to 85.7%/97.2%, respectively, for elliptic centric ordered 3-dimensional MRV.⁹ False-positive diagnoses can occur because of congenital hypoplasia of veins, slow flow because of downstream compression of the brachiocephalic or internal jugular veins, direction of venous flow, and idiopathic intracranial hypertension.¹⁰ In comparison, CTV is not affected by flow-related artifacts.¹¹ A CVST could explain the patient's initial presentation of headache and cranial nerve VI palsy. Left eye ptosis is more commonly caused by left-sided Horner syndrome in cases of CVST, although cranial nerve III palsies due to increased intracranial pressure are also possible.¹² It is also possible that the patient initially had a CVST which resolved on repeat imaging with treatment; however, the patient continued to have progression despite therapeutic anticoagulation, and her opening pressure was normal. In addition, the degree to which the patient's ESR and CRP were elevated should prompt early consideration of vasculitis. ESR and CRP can be mildly elevated in CVST¹³; however, this may be less prominent than seen in GCA where the median ESR and CRP was elevated at 62.0 and 52.0, respectively, in a group of 177 patients.¹⁴

In all previously reported cases, patients had good response to prednisone therapy with complete resolution of ophthalmoplegia after 2–3 weeks of treatment^{6,7} or only mild residual deficits.^{4,8} In our case, the patient's headaches resolved with IV methylprednisolone, and she had mild improvement in ophthalmoplegia. On follow-up examination 1 month later, the patient's visual acuity in her left eye had improved to 20/40. Her extra ocular movements were still restricted for the first several months but had significantly improved on follow-up examination 5 months later (Figure 1).

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Disclosure

The authors report no relevant disclosures. Go to [Neurology.org/N](https://www.neurology.org/N) for full disclosures.

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Mathura Ravishankar, MD, MS	Department of Neurology, UPMC, Pittsburgh, PA	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design
Leana Doherty, MD	Department of Neurology, UPMC, Pittsburgh, PA	Drafting/revision of the manuscript for content, including medical writing for content; study concept or design

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