An 80-Year-Old Woman With Left-Sided Headache and Diplopia

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The Neurohospitalist
3(3) 170-172
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DOI: 10.1177/1941874413483755
nhos.sagepub.com

An 80-year-old white woman with a history of hyperthyroidism treated with radioactive iodine ablation, gastroesophageal reflux disease complicated by Barrett esophagus, osteoarthritis, breast cancer status post-bilateral mastectomy, and diverticulosis presented with severe left-sided headache and diplopia. Three weeks prior to presentation, she developed a sharp pain located over the left temporal, parietal, and occipital regions. It was associated with exquisite scalp tenderness. Over the next few days, the pain progressed, involving the left side of the face, including the periorbital region. There was no radiation of the pain, and she had little relief with over-the-counter acetaminophen. She also experienced earache, sore throat, and left jaw pain with mastication.

The patient saw a dentist for these symptoms, and she was diagnosed with temporomandibular joint disorder. She was prescribed a mouth guard; however, despite its use, her symptoms progressed to a point where she was unable to open her mouth at times, and her jaw felt swollen. Diplopia started 4 days prior to presentation. She experienced this intermittently for 24 hours before it became constant. She saw an ophthalmologist who diagnosed her with a right eye abduction deficit presumed to be a cranial nerve 6 (CN6) palsy. The patient then went to the emergency department for further evaluation.

Review of systems was notable for fatigue, recent 10-pound weight loss, and intermittent myalgias, but there were no fevers, chills, dizziness, dysphagia, dysarthria, weakness, or numbness. Family history included coronary artery disease, diabetes, and various cancers. She was a 40-pack-year smoker, but quit 12 years ago. Her general physical examination was only notable for a blood pressure of 164/77 mm Hg. Neurological examination was notable for the inability to fully abduct the right eye. Fundoscopic examination was negative for papilledema. Strength was 5/5 throughout with normal tone.

Serum laboratory analysis showed mild leukocytosis ($12\,200/\text{mm}^3$), normocytic anemia (hematocrit of 32.9% and mean corpuscular volume of 80.6 fL compared to hematocrit 40.2% 2 months prior), and thrombocytosis ($675\,000/\text{mm}^3$). Erythrocyte sedimentation rate (ESR) was 76 mm/h (reference range 0-30) and C-reactive protein (CRP) was 73.65 mg/L

(reference range 0.30-8.00). A lumbar puncture (LP) was performed with a normal opening pressure of 15 cm H₂O. The white blood cell count was 1 in tube 1 and 2 in tube 4. The red blood cell count was 9 in tube 1 and 1 in tube 4. The glucose was slightly elevated at 79 mg/dL (reference range 40-70), and the protein was normal at 41 mg/dL. The viral and bacterial studies of the cerebrospinal fluid (CSF) were unremarkable. Magnetic resonance imaging (MRI) of the brain and orbits with and without contrast was unremarkable except for moderate supratentorial white matter changes. Magnetic resonance angiogram of the head and neck with and without contrast was normal.

Differential Diagnosis

Discussant: Beau B. Bruce, MD, MS. The main physical finding was limited abduction of the right eye. Although it is a natural response, particularly for neurologists, to presume that an abduction deficit results from a CN6 palsy, it is very important to consider the entire anatomical pathway responsible for abducting an eye from brain stem to the muscle itself. The presence or absence of certain associated features can help refine the differential diagnosis by limiting the anatomical region under consideration. The CN6 nerve nucleus is located in the medial pons. However, a lesion of the nucleus is likely to have an associated seventh nerve palsy (due to the close

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proximity of the seventh nerve fascicle) and will produce horizontal gaze palsy, not an isolated abduction deficit.

The exiting neuronal axons converge to form the fascicle, and then the nerve traverses the prepontine cistern in the subarachnoid space. It courses superiorly along the ventral pons, passing the anterior–inferior cerebellar artery in close proximity.¹ It continues along the clivus and over the ridge of the petrous temporal bone, where the nerve penetrates the dura. Lesions of the fascicle are usually accompanied by other neurologic signs attributable to the brain stem and causes include pontine infarction, hemorrhage, mass lesions, infectious encephalitis (eg, *Listeria monocytogenes*), or inflammation (eg, multiple sclerosis).¹ If bilateral papilledema or meningitis is present, a subarachnoid process would be very likely, but their absence does not exclude it. Processes in the subarachnoid space include microvascular ischemia (hypertension, diabetes, or vasculitis), meningitides (infectious, inflammatory, neoplastic), severe head trauma, aberrations of intracranial pressure (either high or low), infections of the petrous apex, and compression by masses or aneurysms.

The nerve then enters the cavernous sinus and runs laterally to the internal carotid artery and in close association with the sympathetic fibers. Cavernous sinus lesions resulting in CN6 palsy include cavernous carotid aneurysm and dissection, carotid-cavernous fistulas, masses (eg, meningioma), inflammation, and infection (usually associated with thrombosis). Lesions in this region are usually associated with other cranial nerve palsies or oculosympathetic dysfunction, and pain is often prominent.

The nerve then continues out of the cavernous sinus through the superior orbital fissure where it enters the orbit and innervates the lateral rectus muscle. Lesions of the superior orbital fissure often have similar associated features to cavernous sinus lesions but can also affect visual function via the optic nerve. Neoplasm, inflammation, and infection (particularly fungal infections) commonly affect the orbital apex. A lesion anywhere along the fascicle or nerve can cause an abduction deficit, but it is also important to remember that lesions of the neuromuscular junction (eg, myasthenia gravis) or the muscle itself (eg, thyroid eye disease) can also cause isolated abduction deficits.

Diagnostic Workup

In a patient presenting with an isolated CN6 palsy, the MRI of the brain with and without contrast should be obtained to evaluate for anatomical lesions along the course of the nerve. Since subarachnoid processes are the most common cause of isolated CN6 palsies, particularly in association with headache, an LP is also an important part of the evaluation to exclude abnormal intracranial pressure and abnormal CSF contents. These studies were normal. In a patient older than 50 years, even without other notable vascular risk factors as in our case, a microvascular CN6 is the most likely diagnosis. Although the vast majority of microvascular CN palsies are nonarteritic, it is extremely important to always consider the

possibility of an arteritic etiology, since ischemia of extraocular muscles or the motor nerves that innervate them occur in 2% to 15% of the cases of giant cell arteritis (GCA).² Among patients older than 50 years, GCA is the primary arteritic consideration, and all patients presenting with diplopia aged older than 50 years should be screened for other signs and symptoms of GCA, and complete blood count including platelets, ESR, and CRP should be obtained.

In our patient, the diagnosis of GCA was strongly suspected because of a new, left-sided, temporal headache associated with jaw claudication, scalp tenderness, general fatigue, and polymyalgia. Her laboratory examinations supported the concern for GCA due to elevations in ESR, CRP, and platelets, a normocytic anemia, and slight leukocytosis. Therefore, steroids were immediately initiated to avoid the possibility of devastating visual loss from ischemic optic neuropathy while temporal artery biopsy (TAB) was obtained.

Temporal Artery Biopsy

Discussant: Hans E. Grossniklaus, MD, MBA. The left TAB specimen showed findings typical for GCA. There was marked intimal hyperplasia and inflammation in all layers of the artery. The inflammation was concentrated in the adventitia and around the inner elastic lamina in the media (Figure 1). There was fragmentation and dissolution of the inner elastic lamina surrounded by epithelioid histiocytes and occasional giant cells (Figure 2). These findings reflected the pathophysiology of the disease in which dendritic cell-mediated inflammation is introduced via the adventitia and then extends into the wall of the artery.³ The histopathologic findings in this case would be considered classic for GCA.

Management

Discussant: Christian M. Cabrera Kang, MD, and Beau B. Bruce, MD, MS. Giant cell arteritis is an inflammatory vasculitis involving the medium and large arteries and is the most common primary vasculitis in adults.⁴ Due to the potential complication of rapidly progressive and often devastating visual loss, GCA is considered a neuro-ophthalmic emergency and requires immediate and aggressive initiation of therapy in the setting of high clinical suspicion.⁵ Glucocorticosteroids are the treatment of choice and have substantially decreased the frequency of visual loss to 14% to 20% from 30% to 60%, without treatment.⁶ Particularly in cases affecting the visual system, the currently recommended treatment is a 3-day induction dose of intravenous (IV) methylprednisolone, 15 mg/kg/d, followed by maintenance with oral prednisone, 1 mg/kg/d.⁶ Hospitalization is recommended during induction due to the adverse effects associated with high-dose steroids and the comorbidities present in this older patient population. Histopathologic changes in TAB can be visualized for weeks to months despite being on treatment, and concern about negative biopsies should not delay the initiation of therapy.

Figure 1. Temporal artery biopsy. Hematoxylin and eosin stain at $\times 25$ magnification. Thickened internal lamina with histiocyte infiltration of the muscularis layer surrounding the inner elastic lamina and also in the adventitia.

Figure 2. Temporal artery biopsy. Hematoxylin and eosin stain at $\times 100$ magnification. Histiocytes infiltrating the muscularis layer and surrounding the destroyed inner elastic lamina of the left temporal artery.

Aspirin may be used as an adjunctive treatment in an attempt to prevent ischemic manifestations of GCA; however, its use may be delayed until after TAB to avoid bleeding complications. The typical course of steroid treatment lasts 1 to 3 years, with a very gradual taper and careful monitoring for possible relapse. Close follow-up is essential for monitoring symptoms and inflammatory markers until resolution. Studies evaluating steroid-sparing agents, such as immunosuppressive drugs like methotrexate, are yet to show any clear benefit over steroids and require further investigation.⁶

The patient in this case was treated with IV methylprednisolone 250 mg every 6 hours for 3 days followed by prednisone 60 mg by mouth daily, which was gradually tapered. The patient had improvement in pain and jaw claudication immediately after induction treatment. Both ESR and CRP normalized at 12 mm/h and 4.30 mg/L, respectively, after 2 weeks of treatment. The diplopia slowly improved on the oral corticosteroid, tapering to the point of only manifesting on extreme right gaze at 3 months.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: Beau

Bruce receives support in part by an unrestricted departmental grant (Department of Ophthalmology) from Research to Prevent Blindness, Inc, New York. Dr Bruce receives research support from the NIH/NEI (K23-EY019341).

Keywords

vasculitis, central nervous system, ocular motility disorders, headache disorders, secondary

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