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Clinical Reasoning: An Unusual Cause of Diplopia and Ptosis in a 67-year-old Woman

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Abstract

Diplopia is a relatively common chief complaint encountered in an outpatient neurology clinic, and carries a broad differential diagnosis. In this case, a 67-year-old woman presented with new horizontal, binocular diplopia and ptosis of eight-month duration, which persisted without significant progression. This case highlights the need for a comprehensive list of differential diagnoses for patients with acquired ophthalmoplegia and ptosis. Key learning points include an illustration of the stepwise diagnostic approach to evaluate for common etiologies, the importance of interpreting test results in the appropriate clinical setting, and the significance of recognizing specific signs and symptoms in achieving the correct diagnosis.

Section 1

A 67-year-old woman presented with eight months of horizontal, binocular diplopia. The diplopia was constant, without fluctuation or diurnal variation, present in primary gaze, and worsened when looking left. Associated symptoms included right upper eyelid drooping, pressure sensation behind the right orbit, redness of both eyes, and increased lacrimation. There was no associated vision loss, photophobia, pain with eye movement, tinnitus, vertigo, headache, dysarthria, dysphagia, weakness, or numbness.

Her past medical history included hypertension, prediabetes, and remote endometrial adenocarcinoma status post hysterectomy and radiation. Neurologic examination showed a best corrected visual acuity of 20/25 bilaterally, and equal, round, and reactive pupils. Humphrey visual fields (24-2 SITA fast protocol) were unremarkable. There was no exophthalmos, orbital bruit, or papilledema. There was mild, right-sided, non-fatigable ptosis and limited abduction of the left eye with a left esotropia that ranged from 16-40 prism-diopters, maximal in left gaze. Notably, ophthalmic evaluation eight months prior documented a right esotropia. There was no facial sensory loss or facial muscle weakness. The remainder of the neurologic exam was normal.

Questions for consideration:

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

Section 2

The limitation in abduction of the left eye noted in this case suggested a left abducens nerve palsy, within or outside the brainstem. Ptosis may result from an oculomotor nerve palsy or disruption of the oculosympathetic chain leading to Horner syndrome. A single lesion in the cavernous sinus or at the superior orbital fissure, where several critical neurovascular structures controlling orbital function and cerebral blood flow are located, may explain the patient's full constellation of symptoms. Specific pathologies affecting the cavernous sinus include space-occupying lesions (e.g. meningioma), thrombosis, aneurysm, carotid cavernous fistula (CCF), and Tolosa-Hunt syndrome. Traumatic fracture, retro-orbital hematoma, neoplasm (e.g. lymphoma, rhabdomyosarcoma), orbital pseudotumor, systemic lupus erythematosus, and infection (e.g. syphilis, herpes zoster) are known to involve the superior orbital fissure. Outside of these specific locales, pathology involving multiple sites simultaneously, including sarcoidosis, ocular myasthenia gravis (OMG), and Miller-Fisher syndrome may also be considered.

Questions for consideration:

1. Which investigations narrow the differential?

Section 3

Serum testing at initial ophthalmic evaluation revealed a positive acetylcholine receptor (AChR) binding antibody (by radioimmunoassay [RIA]) at a titer of 0.63 nmol/L (normal <0.21 nmol/L). AChR blocking (RIA) and modulating (semi-quantitative flow cytometry) antibodies were negative. This finding initially raised suspicion for OMG.

OMG is a disorder of the neuromuscular junction characterized by extraocular muscle weakness, leading to diplopia and ptosis, both of which were noted in this patient¹. Muscle weakness and ptosis in OMG typically fluctuate in severity, with more pronounced symptoms later in the day or after exercise^{1,2}. New onset diplopia and ptosis in an older individual with an elevated AChR binding antibody would normally be diagnostic of OMG. Despite these findings, the absence of fatigability and diurnal variation in her symptoms, and presence of local ocular symptoms including eye pressure, redness, and tearing argued against OMG. Treatment with pyridostigmine 60 mg three times daily was trialed and failed to lead to significant improvement.

AChR binding, blocking, and modulating antibody testing was repeated four months later and resulted negative. AChR antibodies detected by RIA are about 85% sensitive and 99% specific in generalized MG but sensitivity falls to 50% in patients with OMG³. False positive AChR antibody testing has been observed in other disease states including autoimmune liver disorders, multiple sclerosis, neuromyelitis optica spectrum disorder, celiac disease, systemic lupus erythematosus, amyotrophic lateral sclerosis, and as an idiopathic finding⁴. Recent work suggests that diagnostic accuracy in MG may be improved in the right clinical setting with an AChR binding antibody titer exceeding 0.5 nmol/L and the addition of an abnormal AChR modulating

antibody⁴. No further evaluation for MG was pursued in this case due to the presence of atypical clinical features, negative repeat serologies, and lack of treatment response.

MRI of the brain and orbits without contrast was performed four months after symptom onset. This revealed symmetric STIR hyperintensity in the bilateral lateral rectus muscles with myotendinous junction sparing and normal muscle bulk. No abnormality was noted in the brainstem or remaining brain parenchyma. An MRI of the orbits with and without contrast four months after that showed prominence of the inferior and medial rectus muscles bilaterally as well as the right superior and lateral rectus muscles and left superior oblique muscle, without contrast enhancement. These imaging results along with the patient's retro-orbital eye discomfort and lacrimation raised suspicion for thyroid eye disease, although there was no exophthalmos on examination and systemic findings suggesting hyper- or hypothyroidism were absent. Serum thyroid stimulating hormone (TSH), T3, T4, thyroglobulin, thyroid stimulating immunoglobulin antibodies, and creatine kinase were normal.

Thyroid eye disease is typically seen in patients with Graves' hyperthyroidism, and rarely in hypothyroid or euthyroid patients⁵. The most commonly affected muscles are the inferior and medial recti^{1,5}. Imaging shows enlargement of the muscle bellies with relative tendon sparing^{1,5}. The lateral recti and obliques are the least commonly involved muscles⁵. The atypical pattern of extraocular muscle involvement and lack of serologic evidence of thyroid dysfunction argued against thyroid eye disease in this case.

Other diagnoses to consider that can present with ophthalmoplegia, ptosis, and local ocular symptoms include orbital pseudotumor and Tolosa-Hunt syndrome^{1,6}. Both involve idiopathic granulomatous inflammation of multiple tissue types in and around the orbit, and typically present with unilateral acute/subacute onset periorbital pain, cranial nerve palsy (III, IV, V1/2, VI), and exophthalmos in the case of orbital pseudotumor⁶. MRI may show inflamed, gadolinium-enhancing tissue that is T1 hypointense relative to fat and isointense with muscle, and T2 isointense with fat⁶. Mild retro-orbital pressure was reported in this case without significant pain. The lack of pain, exophthalmos, and typical MRI findings made both of these diagnoses unlikely.

Neuro-ophthalmology subsequently assessed the patient and found prominent corkscrew vessels (Figure 1) bilaterally on slit lamp exam, suggestive of elevated episcleral venous pressure. Digital subtraction angiography was performed, revealing a direct, high-flow, right CCF with indirect external carotid artery (ECA) dural branches on the right and small meningeal branches originating from the posterior wall of the ophthalmic internal carotid artery (ICA) segment on the left (mixed Barrow type A/D; Figure 2)⁷. Obliteration of the fistula was achieved with transvenous coiling and onyx-18 embolization. Follow-up at four months showed a significant decrease in residual corkscrew vessels (Figure 1) and improvement of her esotropia.

Discussion

CCF is an abnormal communication between the carotid arterial system and the cavernous sinus. CCFs can be classified as direct (Barrow type A) and indirect, or dural, fistulas (Barrow types B, C, and D)^{7,8}. Direct fistulas involve a connection between the ICA and the cavernous sinus, and are typically of high flow⁷. Causes include trauma, rupture of an ICA aneurysm within the cavernous sinus, or are iatrogenic from prior invasive procedures⁸. Indirect CCFs are abnormal connections between the cavernous sinus and cavernous arterial branches, are usually of low flow, and may be caused by hypertension, connective tissue disorders, ICA dissection, or occur spontaneously^{7,8}. The CCF in this case was classified as mixed Barrow type A/D due to the presence of both direct and indirect fistulas.

Typical clinical signs and symptoms of CCF include ophthalmoplegia, proptosis, lagophthalmos, ptosis, lacrimation, headache, increased intraocular pressure, and injection (arterialization of conjunctival and episcleral blood vessels from elevated episcleral venous pressure leading to the development of corkscrew vessels)⁸⁻¹⁰. Anteriorly draining fistulas are more likely to cause ocular symptoms, while posteriorly draining fistulas often result in isolated ocular motor nerve paresis and ensuing diplopia⁸. Corkscrew vessels may be observed in other pathologies that elevate episcleral venous pressure including thyroid eye disease, Sturge-Weber syndrome, orbital tumor or varices, and venous sinus thrombosis¹¹. In one retrospective study of 80 patients with CCF, corkscrew vessels were found in 93% of cases¹². Ophthalmoplegia in CCF may be myogenic due to engorged, enlarged extraocular muscles, or neurogenic from ocular motor cranial nerve dysfunction². Abducens nerve involvement occurs more frequently due to its central location adjacent to the ICA within the cavernous sinus^{2,8}.

Symptoms can be unilateral or bilateral, despite a CCF on one side, due to the communicating nature of the cavernous sinus via the anterior and posterior intercavernous sinuses. Changes in flow rate through the CCF, pattern of venous drainage, and pressure variation within this communicating system likely explain the observed change in laterality of the patient's esotropia over months, from right to left. Although rare, regression of symptoms ipsilateral to the side of the CCF and development of contralateral symptoms has been described previously¹³. Right-sided ptosis may be accounted for by involvement of the right oculomotor nerve within the cavernous sinus. Lack of pupillary abnormality argues against a Horner's phenomenon.

Despite the presenting symptoms and results of AChR binding antibody testing, this case illustrates the importance of considering the entire clinical picture and broadening the differential when atypical features are present. Recognition of unique physical examination findings, such as corkscrew vessels, can alter the diagnostic approach, facilitate timely diagnosis, and allow early treatment.

Figures

Figure 1. Pre- and post-operative slit lamp photos of corkscrew vessels

A: Picture from slit lamp exam of the tortuous conjunctival vessels (corkscrew vessels) in the right eye of the patient presented in this case. Prior to surgical intervention.

B: Picture from slit lamp exam of the tortuous conjunctival vessels (corkscrew vessels) in the left eye of the patient presented in this case. Prior to surgical intervention.

C: Improvement in tortuous conjunctival vessels on slit lamp exam in the right eye four months after surgical intervention.

D: Improvement in tortuous conjunctival vessels on slit lamp exam in the left eye four months after surgical intervention.



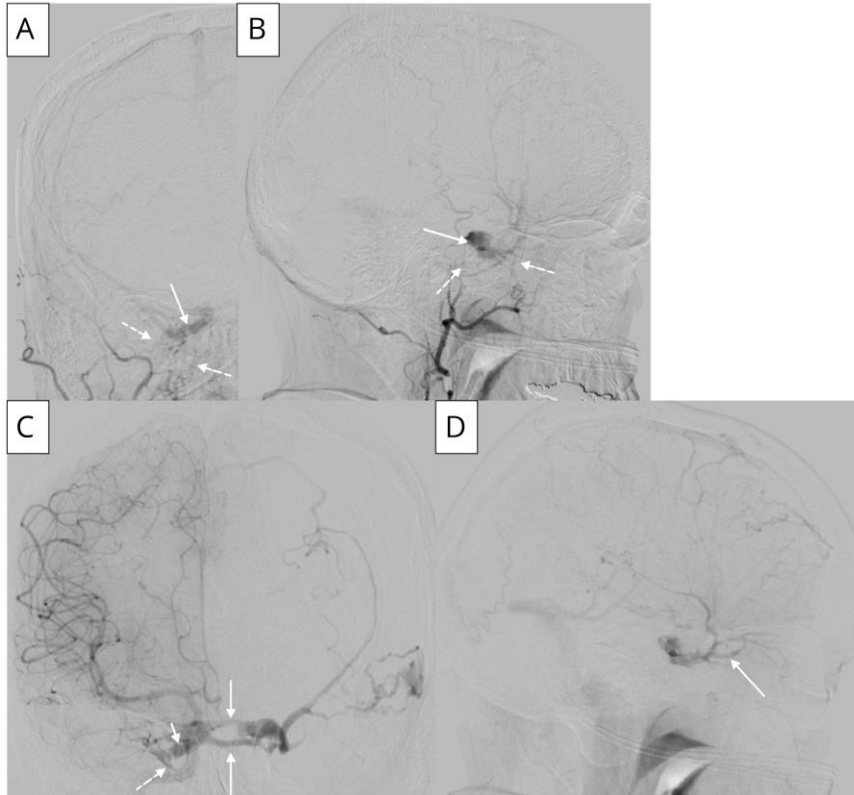
Figure 2. Digital subtraction angiography of carotid cavernous fistula

A: Anterior view of right external carotid artery (ECA) injection, dashed lines pointing to arterial feeders from ECA, solid arrow pointing to the carotid cavernous fistula (CCF).

B: Lateral view of right ECA injection, dashed lines pointing to arterial feeders from ECA, solid arrow pointing to CCF.

C: Anterior view of right internal carotid artery (ICA) injection, dashed line pointing to arterial feeders from ICA, solid arrow pointing to cross filling of contralateral cavernous sinus via anterior and posterior channels of the intercavernous sinus, short solid arrow pointing to CCF.

D: Lateral view of right ECA injection, solid arrow pointing to venous drainage via the superior ophthalmic vein.



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