A 69-year-old black man with vascular risk factors, including hypertension, hyperlipidemia, and poorly controlled diabetes mellitus, who was treated with the vascular endothelial growth factor inhibitor, bevacizumab, for macular degeneration, experienced sudden onset horizontal diplopia associated with fatigue. His deficits did not prevent him from driving. The next morning he noticed right eye ptosis obscuring his vision. Because of worsening symptoms, the patient presented to the emergency department where he was found to have bilateral ptosis, right greater than left, and left internuclear ophthalmoplegia (INO). Pupils were equal and reactive to light. General neurological examination revealed peripheral neuropathy with decreased pinprick/light touch and vibration/joint position sense distally in the lower extremities with associated difficulty with tandem walk and positive Romberg sign. Initial National Institutes of Health Stroke Scale was 2 for partial gaze palsy and sensory deficits. He did not qualify for thrombolysis because of minor deficits and symptoms lasting longer than 4.5 hours.

The patient was admitted to the neurology service with suspected stroke. MRI of the brain revealed a midbrain midline diffusion restriction with apparent diffusion coefficient correlated in the aqueduct of Sylvius slightly more extended to the right consistent with subacute ischemic stroke involving the nucleus of oculomotor nerve and adjacent medial longitudinal fasciculus (MLF) likely secondary to small-vessel disease. MR angiography of the head and neck did not show significant intracranial or extracranial vascular disease. Transthoracic echocardiogram revealed normal heart function and no patent foramen ovale.

The patient was started on aspirin and a statin and provided an eye patch for comfort. His diplopia improved, and he was eventually discharged with follow-up with ophthalmology, balance rehabilitation clinic, and his primary care physician for management of his risk factors.

This patient presented with acute onset painless horizontal diplopia and was found on examination to have bilateral ptosis and a left INO in the setting of poorly controlled vascular risk factors and ongoing bevacizumab injections. Here, we will consider the localizing value of our clinical findings and comment briefly on bevacizumab and stroke.

Anatomy of Oculomotor Nerve

The oculomotor nerve innervates all extraocular muscles, except the lateral rectus (cranial nerve [CN] VI) and superior oblique (CN IV); it also innervates the levator palpebrae, the ciliary body, and pupillary constrictors. Varying degrees of ptosis, gaze palsy, pupillary defects, sometimes with involvement of nearby structures, can be observed with involvement of the oculomotor nerve (CN III) and help identify the exact location of the lesion along the course of the nerve (eg, nuclear, fascicular, and subarachnoidal). The oculomotor nucleus is a paired structure located in the ventral border of the periaqueductal gray of the midbrain and extends rostrally to the posterior commissure and caudally to the nucleus of the CN IV. The oculomotor nucleus comprises several subnuclei involved in control of different ocular functions. Fascicles of CN III exit from the rostral/caudal aspect of the nuclear complex and pass through the MLF, red nucleus, substantia nigra, and medial aspect of the cerebral peduncle before exiting the midbrain at the interpeduncular fossa. The nerve then runs between the posterior cerebral artery and the superior cerebellar artery to pass through the basal cisterns. The nerve courses along the posterior communicating artery and pierces the dura to enter the cavernous sinuses with CN IV, V1, and V2, and VI. It then passes through the superior orbital fissure where it divides into a superior and inferior ramus. The superior division supplies motor fibers to the superior rectus and levator palpebrae. The inferior ramus innervates the inferior oblique, inferior rectus, and medial rectus and provides parasympathetic input to the pupillary constrictors.

Of particular interest and localizing value to our case is the central caudal nucleus (CCN) within the oculomotor nuclear complex. This subnucleus, which controls the motor function of bilateral levator palpebrae, is a single midline structure just ventral to the aqueduct of Sylvius. The Edinger–Westphal nucleus is another midline subnucleus of the oculomotor

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nuclear complex, found rostral to the CCN, controlling parasympathetic input to the bilateral pupillary constrictors and lens ciliary muscles (Table). Oculomotor nuclear lesions may involve the other oculomotor subnuclei, namely the dorsal, intermediate, and medial subnuclei innervating ipsilateral and contralateral superior rectus, and ipsilateral inferior rectus, inferior oblique, and medial rectus. The traditional scheme for the organization of the oculomotor nuclear complex has been recently revised based on radiotracer labeling studies, which show that motor neurons receiving input from the MLF and providing output to the medial rectus are scattered throughout the oculomotor nuclear complex, including a region adjacent to the central CCN. In close proximity of the oculomotor nucleus, slightly caudal and inferior, lies the CN IV nucleus and laterally lies the MLF. Involvement of these structures can contribute to diplopia. Careful examination of eye movements can help localize the origin of diplopia. In our patient, proximity of the MLF-related neurons to the CCN explained the clinical presentation.

**Localization of Ptosis**

Bilateral ptosis present on admission is a critical piece of history for localization and diagnosis. Causes of ptosis range from neuromuscular disorders to lesions of the brain stem or cortex. Unilateral ptosis caused by loss of sympathetic innervation to the superior tarsal muscle can be associated with Horner syndrome and, because of levator palpebrae weakness, is found with involvement of CN III, which also supplies the superior rectus, inferior rectus, inferior oblique, and medial rectus, with or without abnormal pupillary function. Bilateral ptosis is more suggestive of myasthenia gravis, bilateral lesions of the sympathetic chain, or bilateral involvement of CN III peripherally. However, sudden onset bilateral ptosis can be explained with a single lesion localizing to the CCN of CN III. The midline and unpaired anatomy of the CCN and lateralization of these structures can contribute to diplopia. Careful examination of eye movements and pupillary reflexes can help localize the origin of diplopia. In our patient, proximity of the MLF-related neurons to the CCN explained the clinical presentation.

**Localization and Considerations for Diplopia**

Diplopia can be caused by a variety of pathologies. Polyopia (triple or quadruple vision) and diplopia can be seen with intraocular abnormalities and are classically present in monocular viewing conditions. Binocular diplopia resolving with covering one eye suggests peripheral weakness of the extraocular muscles or a central process. In our case, the patient had no pain and this and his ocular weakness provide significant clues to the cause. Posterior communicating artery/internal carotid artery junction aneurysm rupture often presents with acute pain in the setting of oculomotor nerve palsy with pupillary involvement. Aneurysms of the superior cerebellar artery can also cause oculomotor nerve palsy. Patients with painful oculomotor nerve palsy without pupillary involvement usually have experienced a nerve infarct because of diabetes mellitus or hypertension. In the elderly, giant cell arteritis should be considered as well. Migraine may cause transient painful oculomotor nerve palsy. Medial temporal lobe herniation is another cause of oculomotor nerve palsy, usually associated with coma and motor deficits. Inflammation, thrombosis, or trauma anywhere along the path of the oculomotor nerve may cause both pain and nerve palsy as illustrated by cavernous sinus syndrome and superior orbital syndromes.

In our patient, diplopia was likely secondary to a left INO because of a lesion of the MLF neurons, which are adjacent to the CCN responsible for the bilateral ptosis. The MLF is a paired fasciculus that spans the brain stem, traveling ventrally to the cerebral aqueduct in the midbrain, continuing along the midline ventral to the fourth ventricle, and extending into the medulla. This white matter tract is essential in the circuitry required for horizontal conjugate gaze with smooth pursuit movements, voluntary saccades, and vestibulo-ocular and oculocephalic reflexes. INO is characterized by slowed adduction during horizontal eye movements (adduction lag) and frequently the contralateral eye exhibits horizontal gaze-evoked dissociated nystagmus in abduction. The affected eye is ipsilateral to the side of the MLF lesion. Convergence is usually unaffected with an MLF lesion, which helps distinguish it from a third nerve palsy.

The most common cause of INO in patients ≥60 years is infarction, almost always unilateral. INO has been associated with ischemic and hemorrhagic stroke, vertebral artery dissections, and vasculitis. Multiple sclerosis is the most common cause of INO in patients <45 years and commonly presents bilaterally. In one case series of 410 patients, INO was caused by infarction in 38% of patients, multiple sclerosis in 34%, and unusual causes (trauma, infection, tumor, herniation, surgical procedures, and vasculitis) in 28% of cases. Unilateral INO was seen in 87% of patients with infarcts and 27% of patients with multiple sclerosis.

**Role of Bevacizumab**

There have been several cases of ocular ischemic syndromes and stroke in patients receiving bevacizumab. Many patients have other stroke risk factors, such as diabetes mellitus and causality is hard to prove. Macular degeneration itself is considered a possible risk factor for stroke. Given that the safety of bevacizumab after stroke has not been studied, the current recommendation is to discontinue bevacizumab after a severe arterial thromboembolic event.

**Conclusions**

Careful examination of eye movements and pupillary reflexes at bedside provides valuable insights into localization of
oculomotor nerve lesions, which may be due to central causes, such as stroke, later confirmed by neuroimaging.

**TAKE-HOME POINTS**

- Complete peripheral cranial nerve III palsy: eye down and out, ptosis, unreactive blown pupil.
- Lesions of CN III nuclear complex typically cause bilateral ptosis because the central caudate nucleus is a single median structure that innervates both levator palpebrae and bilateral superior rectus palsy because each CN III nucleus projects to these muscles ipsilaterally and contralaterally; everything else is innervated ipsilaterally.
- Painful palsies should raise a red flag for emergent intracranial events, notably aneurysm.
- Common causes of painful palsy: aneurysm, subarachnoid hemorrhage, herniation (transtentorial or uncal), third nerve infarct (diabetic and giant cell arteritis), migraine, cavernous sinus syndrome, superior orbital fissure syndrome, shearing trauma, and Guillain–Barre.
- Bevacizumab may predispose to the occurrence of ocular ischemic syndrome and stroke.

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**Disclosures**

None.

**References**


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Value of Eye Movement Examination in Aiding Precise Localization in Stroke
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