Pearls & Oy-sters: Looking up the anatomy of looking up

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PEARLS

1. A unilaterally dilated pupil would indicate that the lesion is fascicular rather than nuclear as the Edinger-Westphal nucleus is in the midline and causes bilateral mydriasis.
2. The inferior rectus, medial rectus, and inferior oblique muscles are supplied ipsilaterally while the superior rectus is supplied contralaterally.

OY-STERS

1. Parinaud syndrome is classically from a compressive lesion on the dorsal midbrain; however, focal lesions can interrupt the pathways and result in similar features.
2. If the presentation is explainable by a single lesion in the oculomotor complex, investigations for causes such as Miller Fisher syndrome and myasthenia gravis may be avoidable.

A 46-year-old Chinese man with diabetes mellitus, hypertension, and hyperlipidemia, developed sudden onset of vertiginous dizziness and diplopia that was worse on looking up. His symptoms were not preceded by any antecedent infections, neither was there any headache. Blood pressure on arrival in the Emergency Department was 145/95 mm Hg and his neurologic examination revealed bilateral upward gaze restriction (video on the *Neurology*[®] Web site at Neurology.org). There was voluntary lid retraction by the patient. The pupils were 3 mm bilaterally and reactive to light and accommodation, there was no ptosis or nystagmus, and no fatigability could be elicited. Apart from esophoria and pseudo-6th nerve palsy, the rest of the eye movements were normal. Other cranial nerves, motor, sensory, and cerebellar examinations were unremarkable. The vertical optokinetic reflex was intact and there was no tremor of the upper limbs. On forced eye closure, there was upward deviation of his eyes consistent with the Bell phenomenon. ECG did not show any atrial fibrillation or ischemic changes. The basic blood investigations were unremarkable. He was initially diagnosed with myasthenia gravis with frontalis overactivity and

complex ophthalmoplegia by the admitting emergency physicians.

MRI revealed a lesion in the anterior periaqueductal midbrain, eccentrically situated to the left of the midline. The apparent diffusion coefficient characteristics were in keeping with an acute infarct (figure 1, A and B) and magnetic resonance angiogram did not reveal any stenosis. The patient was treated with aspirin, statins, and tight blood pressure control.

DISCUSSION In our patient, abduction, adduction, downgaze, and convergence were preserved, and there was no ptosis, indicating that the respective subnuclei were spared. Apart from esophoria and a pseudo-6th nerve palsy, the only findings were asymmetric upgaze restriction and lid retraction (figure 2A and video). This can be explained by the infarct in the caudal midline region in the posterior commissure location (figures 1C and 2B), which provides regulation to the respective superior rectus subnucleus.

A review of the spatial anatomy of the subnuclei components of the oculomotor complex and its surrounding structures would be useful in understanding this clinical presentation and that of other midbrain lesions. This can help in precise localization of the lesion in nuclear and perinuclear 3rd-nerve palsies¹ (figure 1C).

Presentation of supranuclear lesions. The oculomotor nuclear complex is situated in the midbrain at the level of the superior colliculus, ventral to the periaqueductal gray matter. It is composed of paired and unpaired subnuclei and lesions confined to the nuclear complex are relatively uncommon (figure 1C).² Involvement of the oculomotor nucleus, the supranuclear structures, or the fascicles will produce a symptom complex that involves one or several muscles and presentation of lesions remains largely dependent on the territory involved.³ We will organize our description of these structures along the dorsal-ventral axis for a more structured framework.

Conscious decisions to move the eyes in the vertical plane begins in the cerebral cortex and bilateral projections to the mesencephalic reticular formation

Supplemental data
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Figure 1 (A, B) MRI brain in axial and sagittal cuts with diffusion-weighted restriction show the infarct at the midbrain, rostral extension (arrows); and (C) schematic representation of oculomotor nuclear complex and perinuclear structures in the midbrain

(MRF) are present.⁴⁻⁶ These reach the medial longitudinal fasciculus for downgaze and pretectal plate for upgaze.⁷ Supranuclear paralysis of upgaze results from bilateral lesions of the pretectal area involving the fibers and nuclei of the posterior commissure. A single lesion of the posterior commissure, as seen in our patient, can at times result in upgaze paralysis due to the large decussation of fibers within the commissure.¹ The vertical optokinetic reflex is spared in these patients and it was similarly normal in our patient (figures 1C and e-1 and table e-1).

Parinaud syndrome is a constellation of abnormalities of eye movement and pupillary dysfunction.⁸ It involves a bilateral upgaze paralysis, which can be overcome with a doll's head maneuver. Other characteristics include pseudo-Argyll Robertson pupils, convergence-retraction nystagmus during upgaze, eyelid retraction or the Collier sign, and setting-sun pupils in the primary position. Parinaud syndrome classically is due to direct compression to the dorsal midbrain and the signs are a result of damage to the

mesencephalic tectum at the superior colliculus. It involves several structures common to nuclear 3rd nerve lesions such as the origin of the oculomotor nucleus complex and the Edinger-Westphal nucleus. This can occur commonly with hydrocephalus.

Presentation of nuclear lesions. The levator subnucleus is an unpaired lower midline structure also known as the central caudal nucleus (CCN). It innervates the levator superioris muscles bilaterally and isolated lesions will cause bilateral ptosis. The Edinger-Westphal nucleus is a more rostral central midline structure that innervates the pupillary muscles through the parasympathetic pathway. More laterally, the medial rectus, inferior rectus, and inferior oblique subnuclei are paired structures (lateral ventral, lateral intermediate, and lateral dorsal subnuclei, respectively) that innervate their corresponding ipsilateral muscles.⁹ The superior rectus subnuclei or medial subnuclei are paired structures and innervate the respective contralateral superior rectus. Isolated lesions will spare the

Figure 2 (A) Examination of extraocular movements across cardinal directions shows unilateral upgaze restriction and (B) schematic shows how the various subnuclei innervate the eye muscles

ipsilateral, and affect the contralateral, superior rectus. The lesion in our patient was largely supranuclear in location and spared these subnuclei.

In a classic nuclear 3rd nerve lesion, the clinical picture is unilateral restricted ocular motility and contralateral superior rectus limitation. A more midline

lesion involving just the central caudal nucleus results in bilateral ptosis with no limitation in ocular movement. A slightly more rostral lesion would involve the Edinger-Westphal nucleus leading to pupillary involvement while sparing the ocular motility muscles⁹ (figures 1C and 2B, figure e-1, and table e-1). Another important localizing sign to observe is that unilaterally dilated pupil would indicate that the lesion is fascicular rather than nuclear. This is because the Edinger-Westphal nucleus is in the midline and causes bilateral mydriasis.

A more common scenario would be a larger lesion that would present with bilateral pupillary involvement with nuclear oculomotor palsy. A more ventral lesion will spare the central caudal nucleus and give 3rd-nerve palsies without any ptosis. Finally, involvement of the paired medial rectus subnuclei causes a wall-eyed bilateral internuclear ophthalmoplegia, characterized by exotropia, and defective convergence and adduction¹⁰ (figures 2B and e-1 and table e-1).

The most common etiology of the oculomotor nuclear lesions is ischemia from occlusions of the perforators from the basilar artery although hemorrhage and metastasis are other common causes.

Presentation of fascicular lesions. The oculomotor fascicles are located in the brainstem and pass through the red nucleus and medial cerebral peduncles as they exit from the front. They then run between the posterior cerebral artery and superior cerebellar artery and into the cavernous sinus.

Fascicular lesions can be due to ischemic, hemorrhagic, infiltrative, traumatic, compressive, or demyelinating causes. They present in several classic ways depending on the involvement of adjacent tissues:

1. Weber syndrome: 3rd-nerve palsy with contralateral hemiparesis, due to cerebral peduncle involvement.
2. Benedikt syndrome: 3rd-nerve palsy with contralateral tremor, due to red nucleus involvement.
3. Nothangel syndrome: 3rd-nerve palsy with ipsilateral ataxia, due to superior cerebellar peduncle involvement.
4. Claude syndrome: 3rd-nerve lesion with contralateral tremor and ipsilateral ataxia, due to involvement of the superior cerebellar peduncle directly below the red nucleus (figures 1C and e-1 and table e-1).

This case illustrates how detailed localization of lesions causing isolated nuclear III nerve palsies can be

identified via conscientious amalgamation of clinical presentation and radiologic findings.

AUTHOR CONTRIBUTIONS

Muhammad Bilal Abid: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, accepts responsibility for conduct of research and final approval, contribution of vital reagents/tools/patients, acquisition of data, study supervision, prepared the manuscript draft and subsequently contributed to revisions, drew figures. Derek T.L. Soon: drafting/revising the manuscript, accepts responsibility for conduct of research and final approval. Rahul Rathakrishnan: drafting/revising the manuscript, accepts responsibility for conduct of research and final approval, study supervision. Paul Zhao: drafting/revising the manuscript, accepts responsibility for conduct of research and final approval, study supervision. Clement Tan: drafting/revising the manuscript, accepts responsibility for conduct of research and final approval. Leonard L.L. Yeo: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, accepts responsibility for conduct of research and final approval, study supervision.

STUDY FUNDING

No targeted funding reported.

DISCLOSURE

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

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Neurology 2016;86:e195-e198
DOI 10.1212/WNL.0000000000002629

This information is current as of May 2, 2016

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