Neuroimaging of Ophthalmoplegia

Poster No.: C-2151
Congress: ECR 2015
Type: Educational Exhibit
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Keywords: Ischaemia / Infarction, Aneurysms, Education, Imaging sequences, Diagnostic procedure, MR, CT, Catheter arteriography, Neuroradiology brain, Head and neck, Anatomy, Neoplasia
DOI: 10.1594/ecr2015/C-2151

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Learning objectives

The purpose of our educational exhibit is to:

• outline the different categories of diseases encountered in patients with ophthalmoplegia (OP), based on their location along the oculomotor pathways and the most appropriate respective imaging strategies;
• cover basic anatomical and clinical concepts about OP, helping in understanding its pathophysiology;
• provide the neuroradiologist with the necessary knowledge to discuss clinical cases with the referring clinician.
Background

A variety of diseases can cause OP. They include benign, self-limiting conditions, but also serious diseases up to potentially lethal emergencies.

Diseases affecting ocular movement can be divided into categories including injuries or diseases of the cerebral hemispheres, midbrain, pons and cerebellum, ocular motor nerve palsies, intrinsic extra-ocular muscles (EOMs) diseases and orbital diseases secondarily affecting EOMs. The cranial nerves (CNs) responsible for ocular movements can be affected intrinsically or extrinsically along their nuclei, their course in the brainstem, in the cisterns, skull base, cavernous sinuses and orbits; EOMs can be affected primarily or secondarily, by adjacent pathological processes in the orbits. As a result, neuroimaging is mandatory to clarify the cause of OP and to guide treatment. Many different classes of diseases can involve the same anatomical structures:

- Ischemia
- Trauma
- Neoplasms
- Infections
- Inflammatory
- Auto-immune
- Demyelination
- Metabolic-toxic
- Congenital

Clinical presentation should suggest lesion localization and prompt the most appropriate neuroimaging techniques (1,2). In particular, potentially useful clinical information could be:

- Subjective diplopia or objective ocular palsy?
- Age? Risk factors? Trauma?
- Vertical? Horizontal? Isolated? Uni- or bilateral?
- Any other deficit, signs or symptoms?
- Miosis? Ptosis?
- Abrupt? Progressive? Chronic?
- Headache? Migraine? Retro-orbital pain?
- Proptosis? Ocular bruit?
Findings and procedure details

The neuroimaging of OP should include the whole efferent visual pathways, from the cortical impulses to the orbit (Fig. 1). We can schematically classify anatomical sites that could be involved in OP on the basis of the oculomotor cranial nerves' nuclei into:

- supranuclear
- nuclear and internuclear
- infranuclear (cisternal, skull base, cavernous sinus, orbit)

Generally speaking, neuroimaging of OP rests on the use of CT and MR imaging techniques. In selected cases conventional catheter digital subtraction angiography (DSA) is also necessary. MR is the single most accurate imaging modality in the setting of OP. Multiplanar images and different pulse sequences (T1-W, T2-W, FLAIR, DWI, 3D-steady state free precession, fat-saturated and post-contrast images) can demonstrate the underlying cause of OP. Non-enhanced CT is the most common initial imaging examination in the emergency setting and can be a complementary tool to MR for the study of the osseous structures of the skull base. Vascular imaging, with MR-angiography (MRA), CT-angiography (CTA), or DSA, is also used in selected cases.

Supranuclear OP: caused by lesions of different etiology involving cortical or subcortical frontal eye fields, the thalami or the dorsal midbrain (pretectal area and superior colliculi). While frontal eye fields, located in the pre-frontal cortex, initiate and control the contralateral gaze ocular movements, dorsal midbrain controls vertical gaze and pupillary light reflex. Moreover, the thalami are important relays stations.

- Vascular diseases: ischemic strokes in the middle cerebral artery territory involving the frontal cortex can present acutely with a gaze preference towards the side of lesion ("right-way eyes" sign), besides hemiparesis contralateral to the cortical lesions (Fig. 2) (3). Acute ischemic or hemorrhagic lesions involving the thalami, due to occlusion of the tip of the basilar artery (Fig. 3), proximal posterior cerebral arteries, or due to deep venous system thrombosis, present with a complex constellation of symptoms and neurological signs (4).
- Degenerative diseases: Progressive Supranuclear Palsy, characterized by midbrain tegmentum atrophy, downward gaze palsy ("surprised" look), dysarthria, parkinsonism and dementia. Characteristics imaging findings include flattening or concavity of the normally convex superior profile of the midbrain, dilation of the Sylvian aqueduct and relative increase in the length of interpeduncular fossa (Fig. 4) (5).
- Metabolic-toxic diseases: Wernicke encephalopathy, caused by thiamine deficiency and characterized by development of OP, ataxia and acute confusion. MR can demonstrate symmetrically increased T2 signal intensity
in the mammillary bodies, medial thalami, tectal plate, periaqueductal area (6).

- Compressive causes: compression of dorsal midbrain and pretectal area typically presents with upward gaze palsy, convergence-retraction nystagmus and pupil light-near dissociation (pupils do not react to light, but react to accommodation), so called Parinaud’s syndrome. It has been associated with different types of tumors, such as pinealocytomas, pinealoblastomas, metastases, tectal gliomas and germ cells tumors (Fig. 5-6). Also hydrocephalus (7) can determine a mass effect upon the tectum of the midbrain causing Parinaud’s syndrome.

**Nuclear and Internuclear OP**: can be caused by lesions of the ventral midbrain and pons, involving the nuclei of the cranial nerves III, IV, VI, or the neuronal network connecting these nuclei, such as the medial longitudinal fascicle (MLF) and paramedian pontine reticular formation (PPRF). These structures are principally responsible for horizontal gaze and accommodation, except for the CN IV, whose dysfunction mainly causes vertical diplopia.

- Vascular diseases: ischemic infarcts in the territory of the basilar artery perforating branches, with associated variable involvement of adjacent nervous structures (including cortico-spinal tracts and red nuclei) and consequent different clinical presentations (Fig. 7-9) (8,9). Other causes consist of vasculitis and vascular malformations.
- Inflammatory causes: demyelinating lesions in multiple sclerosis (MS) can involve the brainstem causing OP (Fig. 10).
- Neoplastic diseases: including intra- and extra-axial tumors. Among intrinsic neoplasms, the most common in adults are metastasis, with brainstem gliomas and ependymomas more frequent in the pediatric population.
- Traumatic injuries: OP can be caused by shearing axonal injury in the brainstem (Fig. 11) and Duret's haemorrhage, as well as contusion to the dorso-lateral aspect of the midbrain against the tentorium following descending transtentorial herniation.
- Infectious diseases: rhomboencephalitis. The most common etiologic agents are Listeria and Herpes.
- Metabolic diseases: OP can be part of severe brainstem dysfunction in central pontine myelinolysis. The clinical presentation can be dramatic, with “locked-in syndrome” (Fig. 7) (10).

**Infranuclear OP**: the infranuclear compartment refers to the entire course of the nerves, distal to the nucleus and along their course to the EOMs in the orbits. It includes different anatomical spaces: the subarachnoid space ventral to the brainstem (cisternal portion of the CNs III, IV, VI), the skull base (for CN VI), the cavernous sinuses, and the orbits.

**Subarachnoid**: lesions in this compartment can result in OP with isolated or multiple CNs palsy.
• Vascular diseases: including micro-ischemia (with negative MR or nerve enhancement) (11), neurovascular conflict and compression from aneurysm (Fig. 12).

• Traumatic injuries: as a complication of surgery or caused by shearing injury or contusion against the edge of the tentorium after trauma (12).

• Neoplastic diseases: intrinsic diseases (schwannomas or leptomeningeal metastasis) or compression by extrinsic neoplastic masses, such as meningiomas, clival chordomas, dural or skull base metastasis, brainstem tumors, sellar tumors, epidermoids, or arachnoid cysts (Fig. 13).

• Infectious/inflammatory/degenerative/idiopathic diseases: infectious meningitis with leptomeningeal inflammation; viral neuritis; neurosarcoidosis; chronic idiopathic demyelinating polyneuropathy.

Skull base: the CN VI can be involved by pathological processes of the skull base due to its intraosseous course in Dorello's canal through the clivus and petrous apex, and then in the lateral basilar venous sinus.

• Traumatic injuries: skull base fractures can be the cause of traumatic Gradenigo's syndrome with ipsilateral CNs VI and VII palsy and trigeminal pain. Thin section CT with bone algorithm data reconstruction is the exam of choice (Fig. 14).

• Infectious diseases: inflammatory-infectious condition involving a pneumatized petrous apex with petrous apicitis and classical Gradenigo's syndrome (13).

• Vascular diseases: internal carotid artery dissections; lateral and inferior petrous venous sinus thrombosis or increased venous pressure in these structures, such as in dural fistulas, can cause CN VI palsy (14).

• Neoplastic causes: several neoplastic processes can involve the skull base and present with OP, including chordoma, nasopharyngeal carcinoma and chondrosarcoma of the skull base, metastasis, plasmocytomas and also benign expansile processes of the petrous apex (epidermoids, cholesterol granulomas and mucoceles) (Fig. 15-16). Neuroimaging differential diagnosis basis on the supposed site of origin, osseous changes (well depicted on unenhanced CT), and on MR signal characteristics.

Cavernous sinus: pathological processes involving the cavernous sinus can cause cavernous sinus syndrome, with paresis of some combination of the CNs III, IV, VI, V1 and V2, peri or retro-orbital pain, and conjunctival chemosis.

• Vascular causes: carotid-cavernous fistula (Fig. 17), post-traumatic or consequent to intracavernous aneurysmal rupture; sinus thrombosis (15); cavernous internal carotid artery aneurysms.

• Neoplastic diseases: including extrinsic masses invasion, for instance due to intrasellar tumors and skull base cancers, or intrinsic cavernous sinus tumors such as meningioma, schwannoma and hemangioma.
• Inflammatory and pseudo-tumoral causes: Tolosa-Hunt syndrome (Fig. 18) (16) and sarcoidosis.

**Orbit**

Pathological processes in the orbit can cause OP affecting the distal portion of the nerves or the EOMs. There is frequent overlap of pathology and clinical picture between cavernous sinus and orbital apex (Fig. 19).

- Trauma: fracture of the orbital apex, muscle entrapment (Fig. 20), intra/extra-conal hematoma.
- Tumors: such as lymphoma, meningioma, schwannoma.
- EOMs myopathy (Fig. 21).
- Infections.
**Fig. 1:** The efferent visual pathways reside in different anatomical compartments, encompassing supra- and infra-tentorial, intra- and extra-axial, intra- and extra-dural structures, skull base, cavernous sinuses, and orbits (A-C). For many of these structures tailored imaging protocols are required (Red colour: frontal eye fields; orange: thalami, pretectal area and superior colliculi; yellow: cisternal space; green: midbrain and pons; blue: skull base; light orange: cavernous sinus; coral: orbit).

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**Fig. 2:** Acute stroke in left hemisphere. A 71 year-old male presenting with right hemiparesis and conjugate left gaze deviation. The initial CT scan without contrast do not shows early signs of brain ischemia (A). CT- perfusion (B) demonstrates a prolonged
mean transit time (MTT) in the left middle cerebral artery territory. In this acute stroke patient looks at his lesion: "right-way eyes" sign (arrows in A).

Fig. 3: Tip of the basilar syndrome. Male patient presenting with vertical gaze palsy, skew deviation, convergence defect, somnolence. Diffusion-weighted image (A) e CT without contrast (B) show bilateral paramedian thalamic ischemia. Coronal maximum intensity projection (MIP) and Volume Rendering (VR) CTA images reveal a basilar tip occlusion.

Fig. 4: Progressive Supranuclear Palsy. Sagittal T1-w image (A) shows concave superior profile of the midbrain tegmentum and tectum due to midbrain atrophy. This appearance is called "humming bird sign". Note the convex superior profile of the midbrain in a normal patient (B).
**Fig. 5:** Tectal glioma. Sagittal T1-w (A) and axial FLAIR (B) images show altered signal intensity of the quadrigeminal plate with involvement of the posterior commissure and left thalamus. This lesion shows no enhancement on post-contrast T1-w image (C).

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**Fig. 6:** Germinoma. A 20 year-old male presenting with Parinaud's syndrome. Sagittal pre (A) and post-contrast (B) T1-w, axial FLAIR (C) and axial contrast-enhanced T1-w (D) images demonstrate two masses with enhancement after gadolinium, respectively in the suprasellar region and in the epiphyseal area.

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**Nuclear and internuclear OP: some clinical classical presentations**

<table>
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<tr>
<th>SYNDROME</th>
<th>characteristics</th>
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<tr>
<td>INOP</td>
<td>adduction palsy, preserved convergence (MLF)</td>
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<tr>
<td>1 1/2 syndrome</td>
<td>INOP + contralateral gaze palsy</td>
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<tr>
<td>Divergence gaze palsy</td>
<td>bilateral VI palsy; increased ICP</td>
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<tr>
<td>Total pontine gaze palsy</td>
<td>conjugate gaze palsy on lesion side</td>
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<tr>
<td>Locked-in syndrome</td>
<td>Quadriplegia, anarthria and partial spare of upward gaze and blinking (rostral portion of III CN)</td>
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<tr>
<td>Weber syndrome</td>
<td>III palsy + contralateral hemiparesis</td>
</tr>
<tr>
<td>Benedikt syndrome</td>
<td>III palsy + contralateral ataxia and rubral tremor</td>
</tr>
<tr>
<td>Millard-Gubler syndrome</td>
<td>VI palsy + ipsi-facial + contralateral hemiparesis</td>
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**Fig. 7:** Some of the classical presentations of lesions of the ventral midbrain and pons, due to close contiguity of different nervous structures in this area.

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**Fig. 8:** Internuclear OP (INOP). Axial DWI (A), FLAIR (B) and coronal T2-w (C) images demonstrate an ischemic stroke involving left MLF (arrows). Patient presenting with ipsilateral adduction palsy and preserved convergence.
Fig. 9: Weber/Benedikt syndrome. DWI image (A) shows an ischemic stroke of the midbrain with involvement of the right cerebral peduncle and periaqueductal area. Coronal MIP CTA image (B) demonstrates ipsilateral P1 segment occlusion.

Fig. 10: Multiple Sclerosis. Axial (A), coronal T2-w (B) and sagittal FLAIR (C) images show multiple periventricular (C) and pontine (A, B) demyelinating lesions, with bilateral involvement of MLFs.
Fig. 11: Post-traumatic INOP. T2* image shows hypointense lesions in the temporal grey-white matter interface and pons with involvement of MLFs (arrows), consistent with diffuse axonal injury (DAI).

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**Fig. 12:** Posterior communicating artery (PCoA) aneurysm. Patient with acute onset of right CN III palsy and thunderclap headache. Non-enhanced CT (A) and axial FLAIR (B) images show massive subarachnoid hemorrhage. MR-angiography with 3D-TOF sequence (C) and DSA (D, E) demonstrate a right PCoA aneurysm.

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**Fig. 13:** Congenital OP. Sagittal T1-w (A) and axial high-resolution 3D-steady state free precession (B, C) images show an interpeduncular arachnoid cyst with extrinsic compression of the right oculomotor nerve (arrow).

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**Fig. 14:** Traumatic skull base injury. Patient with right sensorineural hearing loss and left VI CN palsy. Axial non-enhanced CT scan with bone window shows fracture of the right bony labyrinth and of the left petrous apex (Dorello's canal for CN VI).

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**Fig. 15:** Cholesterol granuloma. Non-enhanced CT scan with bone window (A), axial T2-w (B) and fat-saturated T1-w (C) images demonstrate expansive bone remodeling of the right petrous apex due to a mass with sharp margins. The lesion is very bright on T1-w and bright on T2-w images.

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Fig. 16: Chondrosarcoma of the skull base. Non-enhanced CT scan with bone window (A) and pre- (B) and post-contrast (C) axial T1-w images show a destructive infiltrative solid tissue with enhancement after gadolinium that involves the right petrous apex, the clivus and the right long muscle of neck.

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Fig. 17: Carotid-Cavernous Fistula. Axial unenhanced CT (A) and CTA (B) show dilated left superior ophthalmic vein. DSA (C) reveals opacification of the cavernous sinus during arterial phase (arrow).

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**Fig. 18:** Painful inflammatory OP: Tolosa-Hunt syndrome. Axial pre (A) and post-contrast (B) T1-w and axial T2-w (C) images show solid enhancing and T2-hypointense tissue that fills and expands the right cavernous sinus. The tissue usually regresses under steroidal treatment.

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**Fig. 19:** Meningioma. Patient presenting with orbital apex syndrome (cavernous sinus syndrome, optic neuropathy and proptosis). Axial T2-w (A-B) and post-contrast T1-w (C-D) images demonstrate a meningioma of the left cavernous sinus and orbital apex.

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**Fig. 20:** Traumatic orbital injury. Unenhanced coronal CT image shows left medial orbital wall fracture with medial rectus entrapment (arrow).

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**Fig. 21:** Thyroid Ophthalmopathy. Unenhanced coronal CT images (A, B) of two patients with proptosis reveal bilateral EOMs enlargement, with sparing of the lateral rectus muscles in B.
Conclusion

OP can have numerous etiologies and varying clinical presentations. Most causes of this condition can be narrowed to specific anatomical locations based on clinical data.

By understanding the pathophysiology of OP, the radiologist can discuss clinical cases with the referring clinician and determine a timely, accurate method of imaging, achieving the most precise differential diagnosis.
References


