PICTORIAL REVIEW

Neuroimaging of isolated and non-isolated third nerve palsies

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ABSTRACT. A variety of aetiologies may cause third nerve palsy (TNP), and some manifestations may herald neurological emergencies. This article describes and illustrates various diseases that lead to TNP.

Received 29 March 2011

Revised 7 July 2011

Accepted 20 July 2011

DOI: 10.1259/bjr/38090653

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The two major functions of the third nerve are oculomotor and pupillomotor. The evaluation of patients with third nerve palsy (TNP) requires an understanding of the normal anatomy of the third nerve. The primary imaging modality used for patients with TNP is MRI because of its high soft-tissue contrast and ability to show the entire course of the third nerve. The MRI sequences used, besides T_1 weighted and T_2 weighted images, should include diffusion-weighted images, MR angiography, thin-slice (<1mm) steady-state free precession (SSFP) and contrast-enhanced spoiled gradient-recalled echo (SGRE) sequences. The current SSFP [e.g. fast imaging employing steady-state acquisition (FIESTA) for a GE scanner; constructive interference steady state (CISS) for a Siemens scanner] and SGRE

sequences [e.g. spoiled gradient recalled (SPGR) for a GE scanner; fast low-angle shot (FLASH) for a Siemens scanner] provide submillimetric spatial resolution and are capable of depicting the cisternal segments of all 12 cranial nerves and the relationship of the nerves to pathological processes. They also allow reconstruction in multiplanar images that highlight the course of each cranial nerve (Figure 1). CT scanning is limited in patients with spontaneous subarachnoid haemorrhage (SAH) to exclude cerebral aneurysm and in patients head trauma with suspected skull fracture. Digital subtraction angiography is reserved for cases in which cerebral aneurysm or carotid-cavernous sinus fistula (CCF) is suspected and there is no clue on CT angiography or MR angiography. In this article, we discuss the anatomy and lesions in the

Figure 1. MRI of a normal 30-year-old male subject. (a) Reconstructed oblique axial image (fast imaging employing steady-state acquisition; 1 mm slice thickness) depicts the entire cisternal segment of the bilateral third nerves (arrows). (b) On the oblique sagittal plane, the right third nerve (black arrow) that runs parallel and inferior to the right posterior communicating artery (white arrow-head) is well delineated.

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Figure 2. A 53-year-old female presented with right incomplete third nerve palsy and contralateral ataxia. Diffusion-weighted MRI shows acute ischaemic infarction in the right-sided mid-brain, presumably involving the right oculomotor nucleus and fascicles as well as the red nucleus and part of the cerebral peduncle.

Figure 3. A 57-year-old male presented with left third nerve palsy, weakness of the bilateral superior rectus muscles (more on the right side), and bilateral incomplete ptosis. An axial contrast-enhanced T_1 weighted image shows a rim-enhancing lesion with perifocal oedema involving the left-sided mid-brain, which was proved to be adenocarcinoma of the lung with mid-brain metastasis.

Figure 4. A 51-year-old female with multiple sclerosis presented with bilateral third nerve palsy (more on the right side) and ptosis. Axial T_2 fluid-attenuated inversion-recovery MRI shows a hyperintense demyelinating plaque (arrow) involving the periaqueductal midbrain.

oculomotor nucleus, fascicles, subarachnoid space, cavernous sinus, superior orbital fissure and orbital apex.

Nucleus and fascicles

The oculomotor nuclear complex consists of multiple subnuclei in the ventral periaqueductal mid-brain at the level of the superior colliculus. The most rostral and dorsal Edinger–Westphal nuclei supply the parasympathetic fibres to ipsilateral pupillary sphincters and ciliary muscles via the ciliary ganglion. The caudal central nucleus is a single midline nucleus that innervates the bilateral levator palpebrae superioris muscles. The superior rectus nuclei supply the contralateral superior rectus muscles. The medial rectus, inferior rectus and inferior oblique nuclei supply the ipsilateral corresponding muscles. The oculomotor fascicles are the portions of the nerves that travel through the brain stem parenchyma to exit ventrally. The fascicles pass through red nuclei, cerebellar projections and cerebral peduncles.

Common pathologies involving the oculomotor nucleus and fascicles include ischaemic infarction (Figure 2), haemorrhage, primary or metastatic neoplasms (Figure 3), cavernous malformation, abscess and demyelinating diseases (Figure 4) [1]. A complete oculomotor nucleus dysfunction manifests as ipsilateral mydriasis, bilateral ptosis, contralateral elevation deficit, and ipsilateral adduction and depression deficits. Fascicular lesions often accompany nuclear lesions, and pure fascicular lesions cause a

Figure 5. A 68-year-old female presented with right complete third nerve palsy (including ptosis and pupillary paralysis). (a) Time-of-flight MR angiography shows a right posterior communicating artery aneurysm (arrow). (b) T_2 weighted image (fast imaging employing steady-state acquisition; 1 mm slice thickness) shows compression of the right third nerve by the aneurysm (arrow) compared with the normal left third nerve (arrowhead).

Figure 6. A 67-year-old male presented with fever, headache and left incomplete third nerve palsy. (a) Sagittal contrast-enhanced T_1 weighted image shows abnormal leptomeningeal enhancement along the brain stem surface (arrow). (b) Diffusion-weighted MRI shows abnormal high signal intensity in the interpeduncular cistern and left ambient cistern, consistent with meningitis with cerebrospinal fluid (CSF) empyema. CSF culture revealed *Streptococcus constellatus*.

peripheral type of oculomotor palsy with sparing of the contralateral eye. Symptoms of TNP and contralateral tremor reflect lesions involving the red nucleus (Benedikt syndrome). TNP with contralateral hemiparesis reflects lesions involving the cerebral peduncle (Weber syndrome). TNP with ipsilateral ataxia (Nothnagel syndrome) and contralateral ataxia (Claude syndrome) reflects lesions involving the cerebellar projections.

Subarachnoid space

The third nerves exit the brain stem medial to the cerebral peduncles, and course forward and laterally in the interpeduncular cistern between the posterior cerebral arteries–posterior communicating arteries (PcomA) above and superior cerebellar arteries below. The pupillary fibres are located dorsomedially and peripherally at this segment.

Common pathologies involving this segment include aneurysm at PcomA (Figure 5; rarely at the basilar tip), dolichoectatic vessels, microvascular ischaemia, SAH, meningitis (Figure 6), neoplasms (leukaemia, lymphoma, neurogenic tumours and leptomeningeal carcinomatosis; Figures 7–9), inflammatory disease (neurosarcoidosis, Wegener's granulomatosis), demyelinating disease, transtentorial herniation (from supratentorial tumour, haemorrhage or brain swelling; Figure 10), and head trauma with nerve avulsion (usually at the posterior petroclinoid ligament where the third nerve is stretched because of

Figure 7. A 45-year-old female presented with bilateral incomplete third nerve palsies (pupil spared). Axial contrast-enhanced T_1 weighted image (fast low-angle shot; 1 mm slice thickness) shows abnormal enhancing lesions distributed along the bilateral third nerves (arrows). The final diagnosis was B-cell lymphoma, diffuse large cell type.

Figure 8. A 20-year-old female with type II neurofibromatosis presented with bilateral asymmetrical ophthalmoplegia and facial pain, progressive ataxia and bilateral deafness. (a–c) Axial contrast-enhanced T_1 weighted image (fast low-angle shot; 1mm slice thickness) shows multiple nodular enhancing lesions (schwannomas) distributed along the bilateral third (arrows), fifth (arrowheads) and eighth (curved arrows) cranial nerves.

Figure 9. A 52-year-old male with lung cancer presented with right incomplete third nerve palsy. Axial contrast-enhanced T_1 weighted image shows abnormal leptomeningeal enhancement along the ventral surface of the mid-brain and cerebellar fissures (arrows) as well as the root entry zones of the bilateral third nerves (arrowheads) due to leptomeningeal carcinomatosis.

Figure 10. A 62-year-old female with presumed gliomatosis cerebri presented with right ptosis, pupil dilatation and poor light reflex. Axial T_2 weighted image shows transtentorial herniation of the uncus of the right temporal lobe and the right third nerve (arrow) being compressed by the herniated brain tissue.

Figure 11. An 80-year-old female with type D carotid-cavernous sinus fistula presented with right incomplete ptosis and spontaneous symptom relief without any treatment. (a, b) Digital subtraction angiograms show small fistulae (arrows) from the meningeal branches of the right internal and external carotid arteries to the right cavernous sinus and drainage to the inferior petrosal sinus. (c) Source image of time-of-flight MR angiography shows abnormal high signal intensity of arterialed flow in the right cavernous sinus (arrow).

Figure 12. A 50-year-old male with a presumed cavernous sinus meningioma presented with right ophthalmoparesis (pupil involved) and blindness. (a) Axial T_2 weighted image shows a hypointense infiltrating lesion (arrows) involving the right cavernous sinus with extension to the orbital apex through the superior orbital fissure. (b) Coronal contrast-enhanced T_1 weighted image shows an enhancing tumour with encasement of the right cavernous sinus and extension to the sellar fossa (arrows). Note the loss of flow void in the right internal carotid artery due to tumoral compression.

Figure 13. A 47-year-old male with pituitary adenoma presented with progressive bilateral painful ophthalmoplegia, amaurosis, acute onset of explosive headache, blindness and drowsiness. (a, b) Coronal non-enhanced T_1 weighted image and axial T_2 weighted image show a bulky sellar tumour (arrows) with suprasellar extension, leading to compression of the brain and encasement of the bilateral cavernous sinuses. The heterogeneously high-signal areas within the tumoral stroma suggest spontaneous haemorrhage (apoplexy).

Figure 14. A 60-year-old male with right-sided nasopharyngeal carcinoma presented with right ophthalmoparesis (pupil spared) and upper trigeminal sensory loss. (a) Axial contrast-enhanced and fat-suppressed T₁ weighted image shows an infiltrating tumour (arrows) involving the right lateral recess of the nasopharyngeal mucosal space with extension to the parapharyngeal space. (b, c) Coronal and sagittal images show extension of the tumour from the right parapharyngeal and masticator spaces to the right cavernous sinus (arrows) through the foramen ovale (perineural spreading along the mandibular nerve). (d) Sagittal image also shows extension of tumour from the right cavernous sinus (white arrow) through the foramen rotundum (arrowhead) to the pterygopalatine fossa and inferior orbital fissure region (black arrow).

Figure 15. A 78-year-old female presented with left incomplete third nerve palsy, headache and proptosis due to sinusitis (mixed *Pseudomonas* and *Aspergillus* infections). (a) Axial contrast-enhanced T₁ weighted image (spoiled gradient recalled; 1 mm slice thickness) shows left maxillary (M) and sphenoid (S) sinusitis with extension of the infectious process through the sphenopalatine foramen (black arrow) and pterygopalatine fossa to the medial margin of the masticator space (white arrow). (b) The infectious process also extends to the inferior orbital fissure (black arrow) and through the foramen rotundum (arrowhead) to the left cavernous sinus (white arrow).

Figure 16. A 36-year-old male with Tolosa–Hunt syndrome presented with left painful ophthalmoplegia (pupil spared), facial pain and mild facial weakness. (a, b) Axial contrast-enhanced T_1 weighted image (fast low-angle shot; 1 mm slice thickness) shows thickening and enhancement of the left cavernous sinus and adjacent dura from the sphenoid ridge to the tentorium cerebelli (arrows).

downward displacement of the brain stem at the time of impact) [1–3].

Acute isolated TNP with a normal internal (pupil) function and complete external (extraocular muscles) dysfunction in a patient older than 50 years with underlying vascular risk factors such as diabetes or hypertension—and with spontaneous recovery within 4 weeks without other neurological symptoms—is generally considered to be due to microvascular ischaemia of the nerve (usually painful), and neuroimaging studies may not be needed (rule of pupil) [1, 4, 5]. This is because the parasympathetic pupillomotor fibres are superficial and receive a greater blood supply from the vasa nervorum than from the central trunk. As a result, they are usually spared from ischaemic injury, whereas a compressive lesion such as a PcomA aneurysm usually affects the superficial fibres. Patients with both complete internal and external dysfunctions are at highest risk of PcomA aneurysm [4–6]. Patients under 40 years of age, patients without vascular risk factors and vasculopathic patients who do not improve within 12 weeks (or progress) should undergo neuroimaging study (usually MR with MR angiography for screening of the entire course of the third nerves) [4]. TNP may improve after treatment of the PcomA aneurysm, by either endovascular coiling or surgical clipping, but the predictive factors are still under debate [2, 3].

Cavernous sinus, superior orbital fissure and orbital apex

The third nerves pierce the dura to enter cavernous sinuses and are embedded within the dural folds directly lateral to the pituitary fossa, and then enter the orbits through superior orbital fissures and split into a superior division (innervates levator palpebrae superioris and superior rectus muscles) and an inferior division (innervates the pupil, medial rectus, inferior rectus and inferior oblique muscles). Lesions in the cavernous sinus can co-involve cranial nerves III, IV, V (the first and second divisions) and VI, and the sympathetic pathways (may also involve the optic nerve at the orbital apex).

Common pathologies involving those regions include CCF (Figure 11), internal carotid artery (ICA) aneurysm, ICA dissection (may affect blood supply to the third nerve or the sympathetic pathways to produce Horner syndrome), neoplasms (cavernous sinus meningioma, haemangioma, neurogenic tumours, pituitary adenoma, pituitary apoplexy, lymphoma, metastasis and perineural spreading from head and neck cancer; Figures 12–14), infectious process (usually from adjacent sinusitis; Figure 15) and inflammatory diseases [neurosarcoidosis and Tolosa–Hunt syndrome (THS); Figure 16] [1, 7–9].

Diseases at those regions may be unilateral or bilateral and involve one or several nerves. For example, the intercavernous sinuses connect both sides of the cavernous sinuses, and the pressure of CCF can be transmitted to the contralateral side to involve multiple cranial nerves, with the third nerve being the most frequently affected [7]. A pituitary macroadenoma or pituitary apoplexy due to infarction/haemorrhage may also cause compression of the cavernous sinus, and the third nerve is still the most frequently involved one, followed by the sixth and fourth nerves [8]. THS is characterised by painful ophthalmoplegia due to idiopathic granulomatous inflammation involving the cavernous sinus, superior orbital fissure or orbital apex. The International Headache Society proposed the following criteria for the diagnosis of THS: episode(s) of unilateral orbital pain associated with paresis of one or more of the third, fourth and sixth cranial nerves (within 2 weeks following orbital pain) and/or demonstration of a granuloma by MRI or biopsy; pain resolution within 72 h with corticosteroid therapy; and exclusion of other causative lesions by appropriate investigations [9]. The differential diagnosis of TNP requires physical examination by experienced clinicians and proper neuroimaging.

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