Examination of a third nerve palsy

Of the cranial nerve palsies that affect the eye, the third (oculomotor) nerve palsy is the most important to swiftly recognize and diagnose. While the majority of cases have microvascular causes, third nerve palsy can be the first or last sign of a life-threatening posterior communicating artery aneurysm. The classic presentation of the third nerve palsy is a 'down and out eye' combined with ptosis with or without pupillary involvement. This article reviews the relevant neuroanatomy, classifies the causes of the third nerve palsy and provides clinical tips for diagnosis and appropriate management.

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The neuroanatomy of the oculomotor (III) nerve

Dissecting the clinical picture of a third nerve palsy relies on a detailed understanding of oculomotor nerve anatomy. The oculomotor nerve has two functional components: the motor supply to somatic striated muscles, and the parasympathetic (autonomic) supply to smooth muscles. The motor component of the oculomotor nerve supplies four out of the six extraocular muscles in the orbit (superior rectus, medial rectus, inferior rectus and inferior oblique) as well as the levator palpebrae superioris that elevates the upper eye lid. The trochlear (IV) and abducens (VI) nerves supply the superior oblique and lateral rectus muscles respectively. The parasympathetic component supplies intraocular muscles including the ciliary muscle and sphincter pupillae. *Table 1* summarizes the components and functions of each muscle supplied by the oculomotor nerve (Snell and Lemp, 2014).

Nerve nuclei

The oculomotor nerve has two motor nuclei:

1. The main motor nucleus (divided into subnuclei)
2. The accessory parasympathetic nucleus (Edinger–Westphal nucleus).

While the levator palpebrae superioris muscles of each eye are supplied by an unpaired midline levator subnucleus, the superior recti muscles are supplied by the contralateral superior rectus subnucleus. The medial and inferior recti and inferior oblique are supplied by the ipsilateral subnuclei.

Table 1. The actions of extraocular and intraocular muscles supplied by the oculomotor (III) nerve

Muscle	Nerve component	Nucleus for synapse	Nerve supply laterality	Action of muscle
Superior rectus	Motor	Oculomotor nucleus (superior rectus subnucleus)	Contralateral	■ Elevation in primary position ■ Intorsion in adduction ■ Elevation in abduction
Medial rectus	Motor	Oculomotor nucleus (medial rectus subnucleus)	Ipsilateral	■ Adduction in primary position
Inferior rectus	Motor	Oculomotor nucleus (inferior rectus subnucleus)	Ipsilateral	■ Depression in primary position ■ Extorsion in adduction ■ Depression in abduction
Inferior oblique	Motor	Oculomotor nucleus (inferior oblique subnucleus)	Ipsilateral	■ Extorsion in primary position ■ Elevation in adduction ■ Extorsion in abduction
Levator palpebrae superioris	Motor	Oculomotor nucleus (levator subnucleus)	Ipsilateral	■ Eyelid elevation and retraction
Sphincter pupillae	Parasympathetic	Edinger–Westphal nucleus→ ciliary ganglion	Ipsilateral	■ Pupil constriction (miosis)
Ciliary muscle	Parasympathetic	Edinge–Westphal nucleus→ ciliary ganglion	Ipsilateral	■ Ciliary muscle contraction → accommodation reflex (miosis, increased lens convexity)

The accessory parasympathetic nucleus lies posterior to the main oculomotor nucleus in the midbrain, and receives both corticonuclear and pretectal nucleus fibres for accommodation and direct and consensual light reflexes respectively (Snell and Lemp, 2014).

Midbrain

The aforementioned third nerve nuclei are located ventral to the cerebral aqueduct, on the pre-aqueductal grey matter. The oculomotor nerve fibres then pass through the red nucleus, the substantia nigra, and exit the midbrain through the interpeduncular fossa.

Subarachnoid space

The oculomotor nerve traverses between the posterior cerebral (above) and superior cerebellar (below) arteries, advancing lateral to the posterior communicating artery (*Figure 1*). The nerve perforates the dura mater on the lateral side of the posterior clinoid process, passing between the free and attached borders of the tentorium cerebelli.

Cavernous sinus and superior orbital fissure

The oculomotor nerve subsequently traverses through the lateral walls of the cavernous sinus superior to the trochlear (IV) nerve, ophthalmic and maxillary divisions of the trigeminal (V) nerve, and the abducens (VI) nerve (*Figure 2*). Before entering the orbit, the nerve divides into small superior and large inferior divisions entering the orbit via the superior orbital fissure within the tendinous ring (*Figure 3*) (Snell and Lemp, 2014).

Orbit

The superior division of the oculomotor nerve traverses lateral to the optic nerve in each orbit, enters and supplies the superior rectus muscle, and then terminates by supplying the levator palpebrae superioris muscle. The inferior division splits into three branches, supplying the medial and inferior recti and the inferior oblique muscles. The thick nerve branch to the inferior oblique muscle contains parasympathetic nerve fibres that pass to and synapse in the ciliary ganglion. The postganglionic fibres then pass in the short ciliary nerves supplying the sphincter pupillae and ciliary muscles (*Figure 4*) (Snell and Lemp, 2014).

Figure 1. Diagram showing the cut midbrain and the origin of the oculomotor and trochlear nerves.

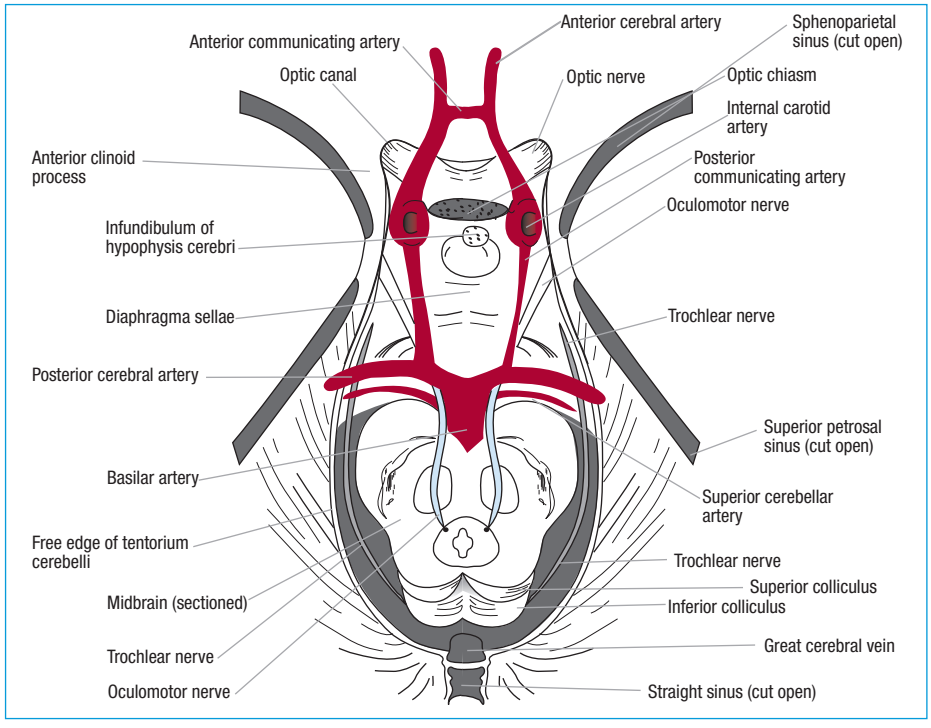
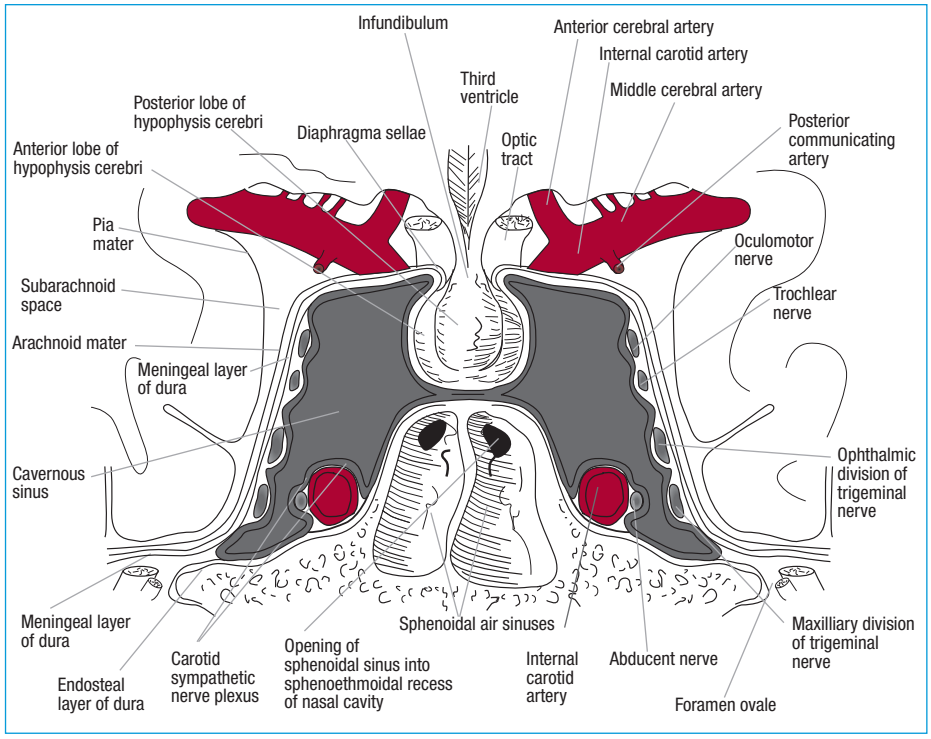


Figure 2. Diagram showing a coronal section through the body of the sphenoid bone and the cavernous sinuses. Note the positions of the cranial nerves.



Causes of the third nerve palsy

There are numerous ways of classifying the third nerve palsy including congenital *vs* acquired, surgical (pupil-involving) *vs* medical (pupil-sparing) and complete *vs* partial. While pupil involvement suggests a compressive lesion such as an aneurysm, this rule is frequently over-relied upon and often the clinical picture can be more mixed. Compressive lesions may not affect the pupil, and microvascular causes may have some degree of pupillary involvement. It is

Figure 3. Diagram of the right orbital apex showing the right superior orbital fissure and optic canal.

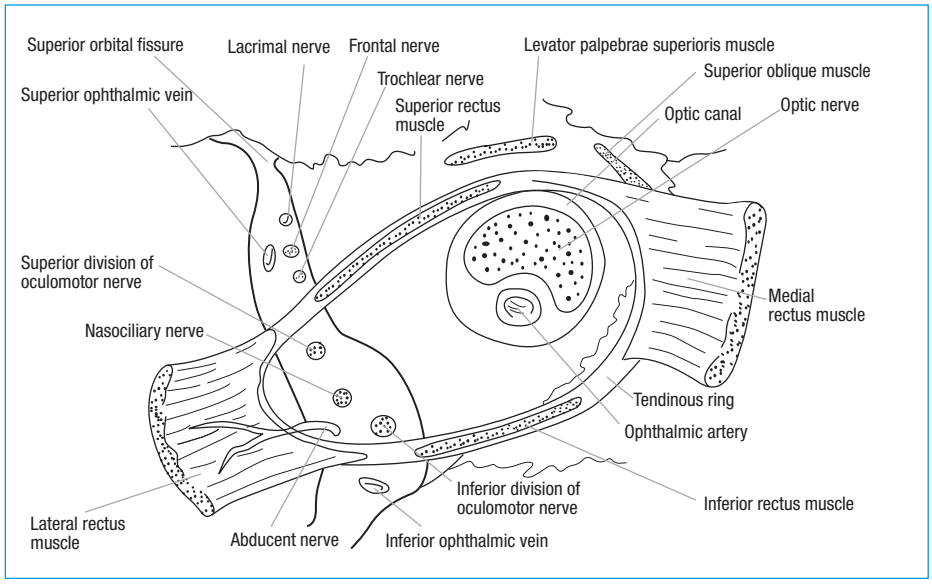
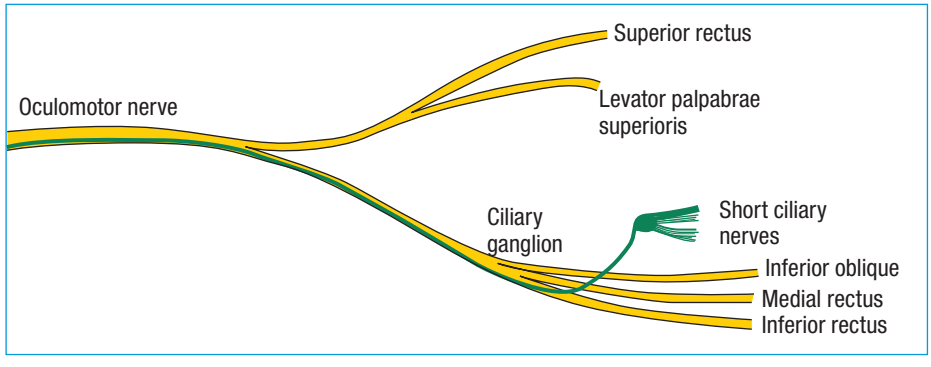


Figure 4. Branches of the oculomotor nerve that supply extraocular and intraocular muscles.



of greater value to determine whether or not the palsy is isolated or complex, and the time course (acute *vs* chronic *vs* relapsing or cyclical). *Table 2* summarizes the main causes of a third nerve palsy (Bowling, 2016).

The third nerve palsy becomes more common as age increases. In people over 60 years of age, it has an annual incidence of 12.5 per 100 000 compared to 1.7 per 100 000 in those under 60 years of age. In those older than 50 years of age, microvascular ischaemic causes tend to be more common (Fang et al, 2017). In childhood and young adulthood, the most common cause is trauma (Wyatt, 2014).

Clinical tips for examination

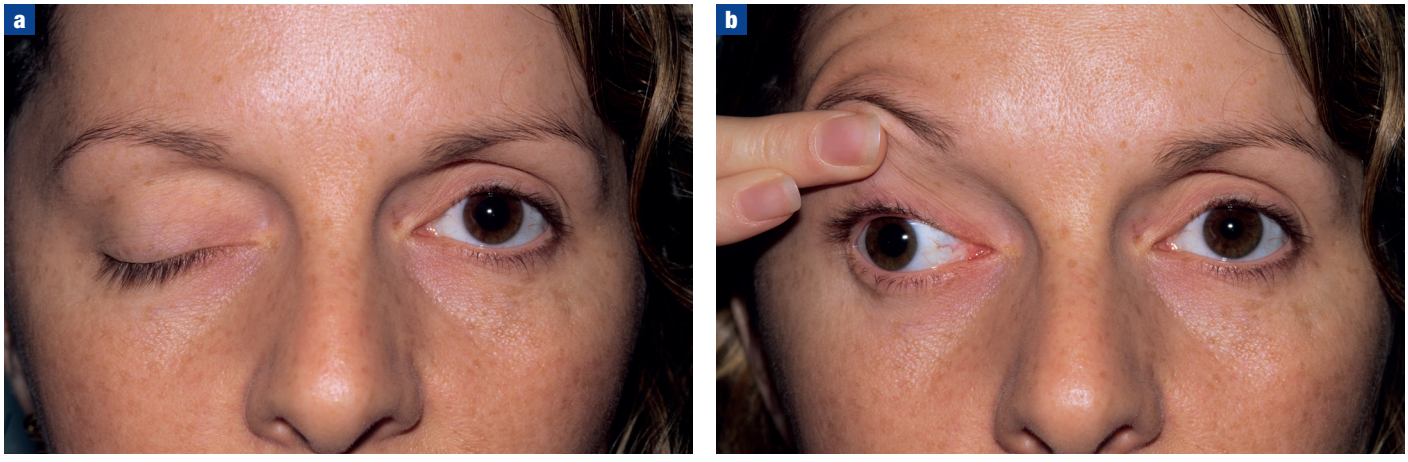
Remember in the clinical setting, subtle signs are often missed. It is therefore important to take a systematic approach and remember diagnostic sieves. The clinical presentation of a third nerve palsy (*Figure 5*) varies depending on many factors including anatomical location and aetiology. It is also important to carry out a full examination of the cranial nerve and peripheral nervous system. The following signs should not be missed (Bowling, 2016):

- Abduction and depression in the primary position. Typically, a third nerve palsy presents with ophthalmoplegia as a 'down and out' eye as a result of the unopposed action of the lateral rectus and superior oblique muscles
- Limited adduction as a result of medial rectus weakness
- Limited elevation as a result of weakness of the superior rectus and inferior oblique muscles
- Limited depression as a result of weakness of the inferior rectus
- Normal abduction as the lateral rectus is intact
- Ptosis as a result of weakness of the levator palpebrae superioris muscle
- Mydriasis (dilated pupil that is unreactive to light) and defective accommodation as a result of parasympathetic palsy

Table 2. Common causes of a third nerve palsy

Cause	Notes
Microvascular	Systemic vascular disease of which the commonest causes are hypertension and diabetes mellitus. In diabetes-related third nerve palsy, there is usually (75%) relative or total pupil sparing whereas motility problems are more marked
Aneurysm	Posterior communicating artery aneurysms at the junction with the internal carotid artery are very important causes of pupil-involving third nerve palsies. Internal carotid artery aneurysms within the cavernous sinus usually involve other cranial nerves
Trauma	Both direct trauma or secondary to a subdural haematoma with uncal herniation
Tumour	Metastases, meningioma, parasellar tumours, cavernous sinus thrombosis
Miscellaneous	Inflammatory or infectious conditions such as demyelination, syphilis, sarcoidosis, Lyme disease, herpes zoster virus, tuberculosis, giant cell arteritis and other vasculitides Cerebrovascular accident or stroke of posterior circulation: Benedikt syndrome and Weber syndrome Congenital
Episodic	Based on careful patient history; ophthalmic migraine. Myasthenia gravis can mimic a pupil-sparing third nerve palsy

Figure 5. Oculomotor nerve palsy. **a**. Patient with right-sided third nerve palsy – note marked ptosis indicating involvement of the superior division of the oculomotor nerve. **b**. Once lid is manually lifted, one can note the pupil is dilated and the eye position is down and out, indicating complete third nerve palsy.



- Pain from compressive lesions or headache.

Asking oneself the following questions can aid in the diagnoses of a third nerve palsy:

Is it isolated or complex?

There may be other cranial nerves involved. Check for involvement of the optic nerve (II) by checking visual fields, Ishihara and optic discs, and the abducens (VI) nerve by checking for an abduction deficit. It is particularly important to exclude trochlear nerve involvement, where there will be an intorsion and depression deficit in the affected eye. The close proximity of the course of the fourth nerve to the third, especially in the cavernous sinus (where it lies inferior), makes it clinically important to exclude fourth nerve involvement, which can be the case in vascular or compressive lesions such as cavernous sinus thrombosis. Never forget other neurological signs from the cerebellum and peripheral nervous system, and disseminated signs as in demyelination.

If one suspects myasthenia gravis, assess for muscular fatigability in the levator palpebrae superioris, orbicularis oculi and extraocular muscles (often the medial rectus muscle). One may note ptosis that may be unilateral, bilateral or variable. Additionally, a patient may have diplopia from an incomitant strabismus that worsens on fatigue, and facial, bulbar and respiratory muscle fatigability. If there is a ptosis, assess for Cogan's lid twitch that is elicited by asking the patient to re-fixate from downgaze to primary position. A positive test will show an overshooting of the upper lid before returning to the ptotic position.

Is it pupil-involving or pupil-sparing?

While pupil involvement suggests a compressive cause (aneurysm or tumour), it is overall an unreliable sign. It is more important to determine if the onset is acute or chronic and isolated or complex. To determine pupillary involvement, first ask the patient to focus on a distant target, then measure each pupil diameter (millimetres) in both ambient bright then dim lighting. Pupil diameters and presence of anisocoria should be noted. One should also check for direct and consensual pupillary responses. A useful way of discerning if there is true pupil mydriasis secondary to a third nerve lesion is to instill a drop of pilocarpine 1% eye drops (made up by combining one drop each of 2% pilocarpine and normal saline 0.9% eye drops) into each eye. The dilated pupil should constrict after waiting for 45 minutes, as the muscarinic receptors of the pupil sphincter muscle are still intact.

What is the severity of the pain?

A severe headache ('worst headache of my life') should be assumed to be a subarachnoid haemorrhage until proven otherwise. Marked periorbital pain also presents in microvascular ischaemic events or with compressive lesions.

Is it nuclear or fascicular?

Nuclear

Certain signs are quintessentially localizing and help determine whether there is a nuclear or fascicular lesion. A levator subnucleus lesion would manifest as a bilateral ptosis, whereas a superior rectus subnucleus lesion would cause contralateral superior rectus paresis.

Fascicular

The efferent fibres that pass from the third nerve nucleus through the red nucleus and the medial aspect of the cerebral peduncle form the fasciculus. Demyelination is more likely to affect the fasciculus (Denniston and Murray, 2009). Benedikt syndrome involves the fasciculus as it passes through the red nucleus and is characterized by an ipsilateral third nerve palsy, with contralateral hemiataxia. Weber syndrome is secondary to vascular infarction and involves the fasciculus as it passes through the cerebral peduncle. It is characterized by ipsilateral third nerve palsy with contralateral hemiplegia (Bowling, 2016).

Management of a third nerve palsy

All acute third nerve palsies should have an urgent same-day computed tomography angiogram to rule out a life-threatening aneurysm, regardless of pupil signs.

If one suspects a brainstem stroke or tumour, cavernous sinus or orbital apex lesion, magnetic resonance imaging of the brain and orbits with contrast will exclude these causes. If normal, consider demyelination or infectious causes and carry out a lumbar puncture to look for oligoclonal bands, glucose, protein, xanthochromia, microscopy and culture, and cytology in CSF (Denniston and Murray, 2009).

The likelihood of an ischaemic cause is increased in an older patient if the onset is acute with no other neurological abnormality or progression of signs. It is therefore important to assess the patient's cardiovascular risk factors including blood

KEY POINTS

- Life-threatening conditions can manifest as third nerve palsies so candidates must be vigilant for specific signs that are not to be missed.
- The oculomotor nerve contains both motor and parasympathetic fibres, with the parasympathetic fibres supplying the pupil constrictor muscle.
- All acute third nerve palsies should have a same-day scan to rule out aneurysms, regardless of pupil signs.
- General neurological conditions such as strokes, demyelination and subarachnoid haemorrhages can present with localized symptoms such as a third nerve palsy.
- Always remember to gain a thorough history, examine the patient's central and peripheral nervous system, and piece the signs together to enhance the bigger diagnostic picture.

pressure, blood glucose, lipids, full blood count, C-reactive protein and erythrocyte sedimentation rate. If the clinical picture is atypical, supplementary investigations including syphilis, Lyme disease or vasculitis screening should be checked.

Treatment of a third nerve palsy inevitably depends on the underlying cause. In the case of a posterior communicating artery aneurysm, trauma, tumour or subarachnoid haemorrhage, immediate neuroradiological imaging and transfer to a neurosurgical unit for surgical management may be indicated. Presumed microvascular cases would be best managed medically with control of cardiovascular risk factors. Although diplopia is usually self-resolving with recovery over 4 months, it is often upsetting and disruptive to the patient. Orthoptist referral is important to manage symptoms, as diplopia can be relieved by occlusion or use of Fresnel prisms.

Conclusions

Neurological signs of a third nerve palsy can be frustratingly subtle to appreciate, but a tailored and thoughtful approach with consideration of the anatomy and varied pathology will help the candidate to skilfully discern emergencies from non-urgent cases. **BJHM**

Conflict of interest: none.

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