An overview of the third, fourth and sixth cranial nerve palsies

Palsies of the third, fourth and sixth cranial nerves have ophthalmological consequences.

W Marais, MB ChB, MMed (Ophth); **S Barrett,** MB ChB, MMed (Ophth)
Consultants, Department of Ophthalmology, University of the Free State, Bloemfontein, South Africa

Correspondence to: W Marais (wjmicu@gmail.com)

Third nerve (oculomotor nerve)

Cranial nerve III (CN III) innervates the superior, inferior, medial recti and the inferior oblique muscles. It also innervates the levator palpebrae superioris and carries with it the parasympathetic innervations to the pupil. Involvement of CN III will produce a symptom complex that involves one or several of these muscles and usually results in double vision.[1]

Components of CN III

- nuclear complex
- fasciculus
- basilar
- intracavernous
- intraorbital
- pupillomotor fibres.

Nuclear complex[2]

- situated in the midbrain
- at the level of the superior colliculus
- ventral to the Sylvian aqueduct.

The nuclear complex is composed of the following paired and unpaired subnuclei:[2]

- Levator subnucleus
  - unpaired caudal midline structure
  - innervates both levator muscles
  - lesions confined in this area will therefore give rise to bilateral ptosis.
- Superior rectus subnuclei
  - paired
  - innervates the respective contralateral superior rectus
  - nuclear third nerve palsy will spare the ipsilateral, and affect the contralateral, superior rectus.
- Medial rectus, inferior rectus and inferior oblique subnuclei
  - paired
  - innervate their corresponding ipsilateral muscles
  - lesions confined to the nuclear complex are relatively uncommon
  - most frequent cause of palsy are vascular disease, primary tumours and metastases
  - involvement of the paired medial rectus subnuclei causes a *wall-eyed bilateral internuclear ophthalmoplegia* (WEBINO), characterised by exotropia, and defective convergence and adduction. Lesions involving the entire nucleus are often associated with involvement of the adjacent and caudal fourth nerve nucleus.
- Fasciculus[2]
  - consists of efferent fibres which pass from the third nerve nucleus through the red nucleus and the medial aspect of the cerebral peduncle
  - emerges from the midbrain and passes into the interpeduncular space
  - causes of nuclear and fascicular lesions are similar, except that demyelination may affect the fasciculus.[2]

Midbrain fascicular third cranial nerve palsies

Table 1 describes midbrain fascicular third cranial nerve palsies.[1,2]

Basilar part of CN III[2]

The basilar part of CN III

- starts as a series of 'rootlets'
- leaves the midbrain on the medial aspect of the cerebral peduncle, before coalescing to form the main trunk
- then passes between the posterior cerebral and superior cerebellar arteries
- runs lateral to and parallel with the posterior communicating artery
- is unaccompanied by other cranial nerves, therefore isolated CN III is commonly basilar (Fig. 1).

Important causes of basilar CN III palsy

Aneurysm

Aneurysm of the *posterior communicating artery* at its junction with the internal carotid artery typically presents as acute, painful third nerve palsy with pupil involvement.

Head trauma

Head trauma resulting in extradural/subdural haematoma (Fig. 2) causes a tentorial pressure cone with downward herniation of the temporal lobe and compresses the CN III as it passes over the tentorial edge, initially causing irritative miosis followed by mydriasis and total CN III palsy.

Intracavernous part of CN III[2]

The intracavernous part of CN III enters the cavernous sinus by piercing the dura

Table 1. Midbrain fascicular third cranial nerve palsies

Syndrome	Signs/characteristics	Location of lesion
Benedikt	Ipsilateral CN III palsy Contralateral extrapyramidal signs Hemitremor/involuntary movements	Red nucleus
Nothnagel	Ipsilateral CN III palsy Cerebellar ataxia	Fasciculus Superior cerebellar peduncle
Claude	Combination of Benedikt and Nothnagel syndromes	
Weber	Ipsilateral CN III palsy Contralateral hemiparesis	Cerebral peduncle

lateral to the posterior clinoid process (Fig. 3). Within the cavernous sinus the CN III runs in the lateral wall above CN IV. Anteriorly in the cavernous sinus it divides into superior and inferior branches, entering the orbit through the superior orbital fissure within the annulus of Zinn.

Important causes of intracavernous CN III palsy

- Diabetes – causes a vascular palsy usually sparing the pupil.
- Pituitary apoplexy (haemorrhagic infarction) may cause a CN III palsy if the gland swells laterally and impinges on the cavernous sinus.
- Intracavernous pathology such as
  - aneurysm
  - meningioma
  - carotid-cavernous fistula
  - granulomatous inflammation (Tolosa-Hunt syndrome).

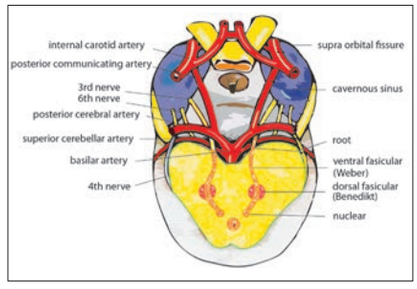

Fig. 1. Dorsal view of the course of the third nerve.

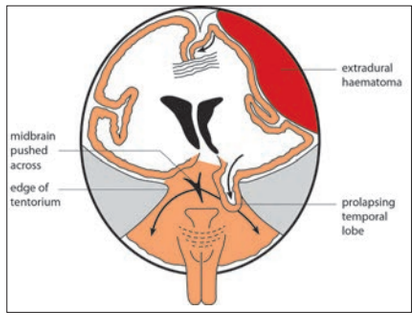

Fig. 2. Mechanism of third nerve palsy by extradural haematoma.

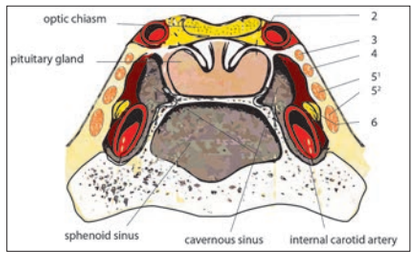

Fig. 3. Location of cranial nerves in the cavernous sinus viewed from behind.

Intracavernous CN III palsy is usually associated with

- CN IV
- CN VI
- first division of CN V.

The intra-orbital part of CN III[2]

The superior division innervates the

- levator
- superior rectus.

The inferior division innervates the

- medial rectus
- inferior rectus – the branch to the inferior oblique also contains *parasympathetic* preganglionic fibres from the Edinge-Westphal subnucleus
- sphincter pupillae.

Lesions to the inferior division are characterised by

- limited abduction
- limited infraduction
- dilated pupil.

Superior and inferior palsies are commonly traumatic or vascular.

Pupillomotor fibres[2]

These fibres are located superficially in the superomedial part of CN III. Their blood supply comes from the pial blood vessels. The main trunk of CN III is supplied by the vasa nervorum. Involvement of the pupil is of great importance because it differentiates a 'surgical' from a 'medical' lesion.

Surgical CN III lesions[2]

Causes include

- trauma
- aneurysms
- uncal herniation.

These lesions characteristically involve the pupil by compressing the pial blood vessels and the superficially located pupillary fibres.

Medical CN III lesions[2]

- causes include hypertension and diabetes
- characteristically spare the pupil
- the microangiopathy involves the vasa nervorum, causing ischaemia of the main trunk.

These principles are not infallible. Pupillary involvement may develop a few days after onset of diplopia as an aneurysm expands. Pupillary involvement may be the only sign of CN III palsy.

Signs of right CN III palsy[2]

- weakness of the levator with ptosis
- eye abducted in primary position due to unopposed action of the lateral rectus muscle
- normal abduction
- intorsion of the eye which increases on down gaze due to intact function of superior oblique muscle
- limited adduction due to weakness of medial rectus muscle
- limited supraduction due to weakness of superior rectus and inferior oblique muscles
- limited infraduction due to weakness of inferior rectus muscle
- dilated pupil with defective accommodation due to parasympathetic palsy.

Aberrant regeneration[1,2]

- may follow acute traumatic and compressive (but not vascular) third nerve palsies
- the endoneural nerve sheaths remain intact in vascular pathology, may be breached in traumatic and compressive lesions
- bizarre defects in ocular motility
- elevation of the upper eyelid on attempted abduction or infraduction
- caused by misdirection of regenerating axons which reinervate the wrong extraocular muscle
- pupil may also be involved.

Causes of isolated CN III palsy[2,3]

1. Idiopathic – 25 %
2. Vascular disease
   - diabetes
   - hypertension
   - most common cause of pupil-sparing CN III
   - spontaneous recovery in 3 months
   - diabetic CN III palsy may be associated with periorbital pain
   - occasionally the presenting feature of diabetes
   - pain is therefore not helpful in differentiating aneurismal and diabetic CN III nerve palsy
3. Aneurysm
   - the posterior communicating artery at its junction with the internal carotid artery
   - pupil involvement

4. Trauma
- direct and secondary to subdural haematoma with uncal herniation
- trivial head trauma not associated with loss of consciousness should alert one of a basal intracranial tumour causing the nerve trunk to be stretched and tethered

5. Miscellaneous (uncommon)
- tumours
- syphillis
- meningeal inflammation
- giant cell arteritis
- vasculitis associated with collagen vascular disorders
- ophthalmoplegic migraine
- internal carotid artery dissection
- myasthenia may also mimic intermittent pupil-sparing CN III palsy
- chemotherapeutic toxicity.

Investigation of the third cranial nerve palsies[1]

Table 2 describes the investigation of third cranial nerve palsies.

Treatment of CN III lesions[2,4]

Non-surgical

Non-surgical management is indicated during the acute phase, which lasts as long as 6 months, and also when definitive surgical management is contraindicated (e.g. by neurological disease or central fusion disruption). This includes:
- Fresnel prisms if angle of deviation is small
- uniocular occlusion to avoid diplopia (if ptosis is partial)
- botulinum toxin injection of the uninvolved lateral rectus preventing contraction.

Surgical

Surgical management is to be considered only after all spontaneous improvement has ceased and not earlier than 6 months from the date of onset.

Fourth nerve (trochlear nerve)

Anatomy of CN IV[2,3]

Important features of CN IV
- only cranial nerve to emerge from the dorsal aspect of the brain (Fig. 4)
- crossed cranial nerve – it means that nerve nucleus innervates the contralateral superior oblique muscles
- very long and slender nerve.

Components of CN IV
- nucleus
- fasciculus
- trunk
- intracavernous
- intraorbital.

Nucleus
- located at level of the inferior colliculus ventral to the Sylvian aqueduct
- caudal and continuous with CN III nuclear complex.

Fasciculus
- consists of axons which curve around the aqueduct
- decussate completely in the anterior medullary velum.

Trunk
- leaves the brainstem on the dorsal surface
- caudal to the inferior colliculus and then curves laterally around the brainstem
- runs forward beneath the free edge of the tentorium
- like CN III, it passes between the posterior cerebral artery and superior cerebellar artery
- then pierces the dura and enters the cavernous sinus.

Intracavernous part of CN IV
- runs in the lateral wall of the sinus
- inferior to CN III and above the first division of CN V
- in the anterior part of the cavernous sinus it rises and passes through the superior orbital fissure above and lateral to the annulus of Zinn.

Intraorbital part of CN IV
- innervates the superior oblique.

Symptoms and signs of CN IV palsy[5]

A fourth nerve palsy typically causes diplopia that is worse in down gaze. Hence, patients almost always report diplopia (or tendency to close one eye) while reading.

Signs of CN IV palsy[2]
- acute onset of vertical diplopia in the absence of ptosis
- characterised by a head posture
- features of nuclear, fascicular and peripheral CN IV are clinically identical
- all except the nuclear palsies produce a contralateral superior oblique weakness.

Characteristics of a left CN IV palsy[2]
- left hypertropia (left over right) in primary position
- increase in left hypertropia on right gaze due to the left inferior oblique overaction
- limitation of left infraduction on adduction
- normal left abduction
- normal left infraduction
- normal left elevation
- abnormal head posture.

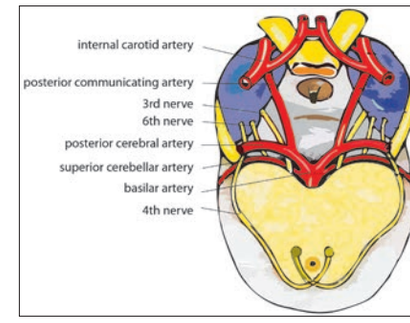

Fig. 4. Dorsal view of the course of the fourth cranial nerve.

Table 2. Investigation of third cranial nerve palsies

	Under 10 years	11 - 50 years	>50 years
Anisocoria less than 2 mm	MRI, MRA	MRI, MRA. If negative, perform medical work-up	Observe without imaging*
Anisocoria greater than 2 mm	MRI, MRA‡	MRI, MRA. If negative, catheter angiography	MRI, MRA. If negative, catheter angiography

*Determine the status of the blood pressure, glucose metabolism, and the presence of other medical risk factors.
‡ Catheter angiography may be justified if these tests are negative.

Abnormal head posture[2]
- the abnormal head posture avoids diplopia which is vertical, tortional and worse on looking down
- to intort the eye there is contralateral head tilt to the right
- to alleviate the inability to depress the eye in adduction, the face is turned to the right and the chin is slightly depressed
- the left eye cannot look down and to the right or intort.

Bilateral involvement[2]
- always suspect bilateral involvement until proven otherwise
- right hypertropia in left gaze and left hypertropia in right gaze
- greater than 10 degrees of cyclodeviation on the double Maddox rod test
- V pattern esotropia
- bilaterally positive Bielschowsky test.

Special tests[2,3,5]
Parks-Bielschowsky 3-step test is useful in the diagnosis.

Step 1
- Assess which eye is hypertropic in primary position when the patient is looking in the distance.
- Left hypertropia may be caused by weakness of the following 4 muscles
  - One of the depressors of the left eye: superior oblique and inferior rectus
  - One of the elevators of the right eye: superior rectus or inferior oblique.
- In a CN IV palsy, the involved eye is higher.

Step 2
- Determine whether the left hypertropia is greater in right gaze or left gaze.
- Increase on right gaze implicates either the right superior rectus or left superior oblique.
- Increase on left gaze indicates either a right inferior oblique or left inferior rectus.
- In CN IV palsy the deviation is worse on opposite gaze (WOOG).

Step 3
- The Bielschowsky head tilt test is performed with a patient fixating straight ahead.
- The head is tilted to the right and then to the left.
- Increase of the left hypertropia on left head tilt implicates the left superior oblique.
- Increase of right hypertropia on left head tilt implicates the right inferior rectus.
- In the CN IV palsy a deviation is better on opposite tilt (BOOT).

Double Maddox rod test[2,6]
- Red and green Maddox rods, with the cylinders vertical, are placed in front of either eye.
- Each eye will therefore perceive a horizontal line.
- In the presence of a cyclodeviation the line perceived will be tilted and therefore distinct from that of the other eye.
- One Maddox rod is then rotated until fusion of the lines is achieved.
- The amount of rotation can be measured in degrees, indication of the extent of the cyclodeviation.
- Unilateral CN IV palsy is characterised by less than 10 degrees.
- Bilateral cases may have greater than 20 degrees of cyclodeviation.

Causes of isolated CN IV palsy[2,3]
Congenital
- common
- presents in adulthood when it de-compensates
- unlike acquired lesions patients are not usually aware of the torsional aspect
- examination of old photos is helpful to make the diagnosis.

Trauma
- Frequently causes bilateral CN IV palsy.
- Bilateral lesions are often thought to be unilateral until squint surgery is performed, following which the contralateral CN IV palsy is often revealed.

Vascular
- common, but aneurysms and tumours are extremely rare
- routine neuroimaging for isolated CN IV palsy is not required.

Treatment of CN IV palsy[1]
Non-surgical
Prisms may be tried, but because of the incomitant and torsional nature of this ocular misalignment, they are often not successful.

Surgical
This is often the final solution for these patients.

Sixth nerve (abducent nerve)
The sixth cranial nerve
- entirely motor in function
- supplies the lateral rectus muscle
- abduction of the eye
- a*bd*ucent nerve – a*bd*uction.

Components of CN VI[2]
- nucleus
- fasciculus
- basilar part
- intracavernous and intraorbital.

Nucleus
- lies at the level of the pons
- ventral to the floor of the fourth ventricle
- closely related to the horizontal gaze centre
- an elevation in the floor of the fourth ventricle (facial colliculus) is produced by the fasciculus of the seventh nerve as it curves around the sixth nucleus.

Lesions
- Lesions in and around the sixth nerve nucleus cause the following signs
  - ipsilateral weakness of abduction as a result of involvement of the sixth nerve

- failure of horizontal gaze towards the side of the lesion due to involvement of the horizontal gaze centre in the PPRF (pontine paramedian reticular formation).

Fasciculus

Passes ventrally to leave the brainstem at the pontomedullary junction, just lateral to the pyramidal prominence.

Syndromes related to fasciculus involvement:[2]

1. Foville syndrome
- involves the fasciculus as it passes through the PPRF
- caused by vascular disease/tumours involving the dorsal pons
- characterised by ipsilateral involvement of CN V – CN VIII
- central sympathetic fibres
- CN V – facial analgesia
- CN VI palsy combined with gaze palsy
- CN VIII nuclear/fascicular damage – facial weakness
- CN VIII – deafness
- central Horner syndrome.

2. Millard-Gubler syndrome

It involves the fasciculus as it passes through the pyramidal tract and is most frequently caused by vascular diseases, tumours or demyelination.

Characterised by
- ipsilateral CN VI palsy
- contralateral hemiplegia (because the pyramidal tracts decussate further inferiorly)
- variable number of signs of a dorsal pontine lesion.

Basilar part of CN VI
- leaves the brainstem at the ponto-medullary junction and enters the prepontine basilar cistern
- passes upwards close to the base of the skull and is crossed by the anterior inferior cerebellar artery
- pierces the dura below the posterior clinoids and angles forward over the tip of the petrous bone, passing through or around the inferior petrosal sinus, through the Dorello canal (under the petroclinoid ligament) to enter the cavernous sinus (Fig. 5).

Important causes of damage to the basilar part of CN VI

1. Acoustic neuroma (Fig. 6)

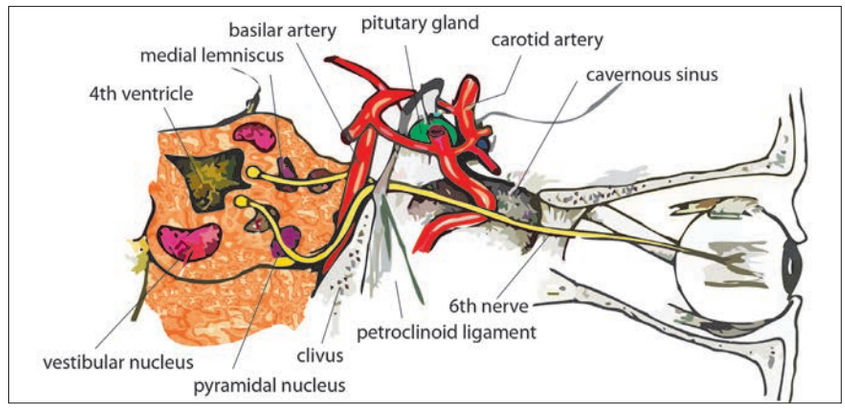

Fig. 5. Lateral view of the course of the sixth cranial nerve.

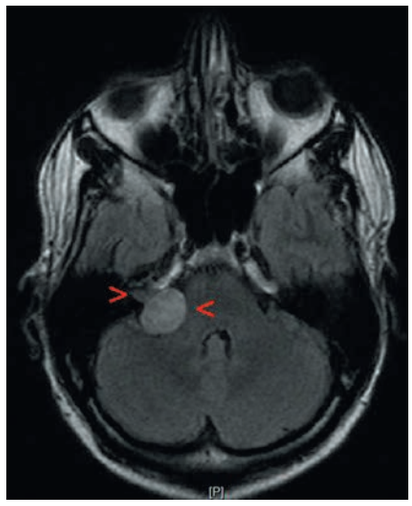

Fig. 6. MR enhancement of acoustic neuroma.

Damages CN VI at the pontomedullary junction
- The first symptom is hearing loss.
- The first sign is diminished corneal sensitivity.
- Always test for hearing and corneal sensation in all patients with CN VI palsy.

2. Nasopharyngeal tumours – invade the skull and its foramina and damage the nerve during its basal course.

3. Raised intracranial pressure – caused by posterior fossa tumours/idiopathic intracranial hypertension causing a downward displacement of the brainstem stretching CN VI over the petrous lip.

4. Basal skull fracture – causes both uni/bilateral palsies.

5. Gradenigo syndrome – caused by acute petrositis. Petrositis is accompanied by facial weakness, pain and hearing difficulties.

Intracavernous part of CN VI
- runs forward below CN III, CN IV and first division of CN V
- the other nerves are protected within the wall of the sinus. CN VI is medially situated and runs through the middle of the sinus in close relationship to the internal carotid artery and is therefore more prone to damage
- intracavernous CN VI palsy is accompanied by a post-ganglion Horner syndrome (Parkinson sign)
- CN VI palsy is joined by sympathetic branches from the paracarotid plexus.

Intraorbital part of CN VI

Enters the orbit through the superior orbital fissure within the annulus of Zinn to innervate the lateral rectus muscles.

Diagnosis

1. Signs of left CN VI palsy
- left esotropia in the primary position due to unopposed action of the left medial rectus
- esotropia worse for distance target and less/absent for near fixation
- mark limitation of left abduction
- normal left adduction.

Patients also show compensatory face turn into the field of action of the paralysed muscle to minimise diplopia, so that the eye does not need to look towards the field of action of the paralysed muscle.

Causes

In contrast to CN III palsy, aneurysms rarely affect CN VI, but vascular causes are common.

Management of CN VI palsy

Non-surgical

Children
- In children up to 4 years of age, treatment of acute CN VI palsy is aimed

at preventing amblyopia and preserving binocular fusion.
- Parents should permit a head tilt.
- If head posture disappears with persistence of the esodeviation – high suspicion of amblyopia.
- Alternate occlusion prevents secondary contracture of muscles and also amblyopia.

Adults
- Intervention is aimed at preventing secondary contracture of medial rectus.
- Botulinum toxin
- Timing is variable:
  - depends on degree of incapacitation
  - with total paralysis, botulinum toxin is indicated 2 weeks after onset.

Surgical
- to be contemplated only after all spontaneous improvement has ceased
- not earlier than 6 months from date of onset.

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In a nutshell

- Cranial nerve III (CN III) innervates the superior, inferior, medial recti and the inferior oblique muscles. It also innervates the levator palpebrae superioris and carries with it the parasympathetic innervations to the pupil. Involvement of CN III will produce a symptom complex that involves one or several of these muscles and usually results in double vision.
- Cranial nerve IV is the only cranial nerve to emerge from the dorsal aspect of the brain. A fourth nerve palsy typically causes diplopia that is worse in down gaze. Hence, patients almost always report diplopia (or tendency to close one eye) while reading.
- Cranial nerve VI is entirely motor in function. It supplies the lateral rectus muscle and is responsible for abduction of the eye.