INTRODUCTION

Diplopia may be the presenting symptom of disorders of cranial nerves III, IV or VI, and as such may alert the clinician to serious vascular, neoplastic, inflammatory or nutritional disease. Disorders associated with these cranial neuropathies include life-threatening conditions such as aneurysms of the circle of Willis and fungal infections of the orbital apex and cavernous sinus, and potentially blinding conditions such as giant cell arteritis. It is therefore imperative that the practitioner recognize the patterns of diplopia suggestive of cranial neuropathies so that the proper studies may be performed leading to a swift diagnosis. In this lecture, the clinical presentation, relevant anatomy, differential diagnosis and management of diplopia associated with individual and combined cranial neuropathies will be reviewed, using clinical cases as a starting point for each type.
Case 1: Diplopia from sinusitis?
A 52 year-old woman presented to the retinal clinic for follow up of vitreous floaters. She reported recent headaches and was felt to have sinusitis. She then developed oblique diplopia. She developed a droopy lid OS by day 4 and was sent to neuro-ophthalmology. On examination, there was complete ptosis of the left lid. The left pupil was larger than the right by 3 mm in the light but only 1 mm in the dark. There was near complete limitation of adduction, elevation and depression OS. A CT of the head with CT angiogram revealed a medium sized aneurysm of the left posterior communicating artery proximal to its take off from the internal carotid artery. She was urgently taken to interventional radiology suite where coiling of the aneurysm was performed.

Figure 1. A. CTA revealed a left sided aneurysm of the posterior communicating artery. B. Illustration showing medial location of pupillary fibers in the oculomotor nerve and proximity to the posterior communicating artery.

Figure 2. Functions of the third nerve. SR: superior rectus, IO: inferior oblique. MR: medial rectus. IR: Inferior rectus. LP: Levator palpebrae.

THIRD (OCULOMOTOR) NERVE PALSY
Background
Because of their association with aneurysms of the circle of Willis, third nerve palsies (TNP) always require an urgent assessment. The oculomotor nerve controls many functions:

Superior Division -
   a) Superior rectus – elevation, especially when the eye is abducted; incyclotorsion
   b) Levator palpebrae – lid elevation

Inferior Division -
   c) Inferior oblique – elevation when the eye is adducted; excyclotorsion
   d) Medial rectus – adduction

e) Inferior rectus – depression, especially when the eye is abducted; excyclotorsion
f) Parasympathetic fibers – pupillary constriction

However, third nerve palsies may be partial, with involvement of only a subset of these functions. Determination of which muscles are involved may help localize the site of injury and even predict the cause.

**Approach to Third Nerve Palsies**

Once it is determined that diplopia is resulting from a TNP, one must attempt to answer the following questions:

a) Is the pupil involved? As shall be discussed below, aneurysmal TNPs typically involve the pupillary fibers. A lack of pupillary involvement in the setting of an otherwise compete TNP is reassuring against that diagnosis, although in one large series, 2% of patients with aneurysm did spare the pupil.¹

b) Are there signs of uncal herniation such as lethargy?

c) Is the TNP complete or partial?

d) If it is partial, does it reflect selective involvement of the superior or inferior division?

e) Is it a nuclear third?

f) Is it a fascicular third (that is, involve the fibers coursing through the midbrain parenchyma from the nucleus?

g) Are there their neighborhood signs, i.e. other neurological signs and symptoms that can localize the injury to parts of the midbrain, to the cavernous sinus or to the orbital apex?

h) Are their signs, symptoms or risk factors of temporal arteritis?

**Nuclear Third Nerve Palsies**

**Causes**

Nuclear TNPs are rare, but may result from any focal injury to the midbrain, including tumor and stroke. Wernicke-Korsakoff syndrome from thiamine deficiency may cause hemorrhagic necrosis of the oculomotor nuclei causing diplopia alongside amnesia and ataxia. Leigh’s subacute necrotizing encephalomyopathy, a rare disease of mitochondrial metabolism affecting infants, may mimic thiamine deficiency in its predilection for ocular motor nuclei.

**Presentation**

The oculomotor nucleus is comprised of several subnuclei containing the neurons targeting an individual muscle. For the most part, each subnucleus connects up with the ipsilateral muscle, with two exceptions.

A) Superior rectus – each superior rectus nucleus sends fibers which decussate and cross through the contralateral superior rectus nucleus before continuing towards the contralateral muscle.² A nuclear third therefore causes bilateral gaze limitation, typically worse in the contralateral eye.

B) Central caudal nucleus – neurons with axons destined for the left and right levator palpebrae muscles are intermingled on both the right and left side of this centrally located nucleus. A nuclear third therefore causes bilateral ptosis, even if the injury is only present on one side of the nucleus.
Fascicular Third Nerve Palsies

Causes
As the third nerve course through the midbrain parenchyma, it can be injured by any number of disease processes, including stroke, demyelination and neoplasm.

Presentation
Fascicular TNP is localized within the midbrain based on neighborhood signs, resulting in recognizable syndromes that were typically described in cases of small vessel infarct. Table 1 summarizes these subtypes, including their eponyms which are of mostly historical interest.

Table 1. Syndromes of Fascicular Third Nerve Palsies

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<th>Eponym</th>
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<td>Weber syndrome</td>
<td>Cerebral peduncle (corticospinal tract)</td>
<td>Contralateral weakness</td>
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<td>Benedikt syndrome</td>
<td>Red nucleus</td>
<td>Contralateral tremor</td>
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<tr>
<td>Claude syndrome</td>
<td>Superior cerebellar peduncle</td>
<td>Contralateral ataxia</td>
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Figure 3. Components of the third nucleus. Inferior oblique subnucleus has been left out for clarity.
Figure 4. Neuroanatomical correlates of Weber (W), Benedikt (B) and Claude (C) syndromes.

**Third nerve palsy in the subarachnoid space**
After leaving the midbrain, the third nerve courses through the subarachnoid space towards the cavernous sinus. There it can be affected by a myriad number of leptomeningeal processes.

**Figure 5. Diseases that may affect the oculomotor nerve in the subarachnoid space**
Aneurysm: PCOM, Basilar, PCA
Infection: Tuberculosis, Syphilis, Lyme disease.
Ischemic / vascular
Giant cell arteritis
Head trauma
Autoimmune: Miller Fisher Syndrome
Tumors: meningioma, schwannoma, neurofibroma
Malignant leptomeningeal disease

As mentioned above, aneurysms tend to cause pupillary dysfunction and mydriasis early because pupillary fibers are located dorsomedially in the nerve, close to the posterior communicating artery. Aneurysmal third nerve palsy tend to be painful, but other causes may also include pain, and lack of pain does not rule out an aneurysm. Whenever an aneurysm is suspected, a CT, MR or conventional angiogram must be obtained emergently as failure to diagnose may result in a subarachnoid hemorrhage with a high risk or mortality. Ischemic TNP, which are relatively common in the elderly, typically spare the pupil and typically recover spontaneously within three months. It is important to note that the pupil may be spared early in the course of aneurysmal TNP, especially when the remaining muscles are not all yet completely involved, and follow up examinations are warranted to monitor for change.

**Uncal Herniation**
Herniation of the uncus may pin the oculomotor nerve against the tentorial edge or clivus, typically resulting in mydriasis as an early sign. The patient may be lethargic or stuporous. Rapid identification using non contrast CT should be followed by definitive management of the herniation, which may include mannitol, hypertonic saline or surgical decompression.

**Cavernous Sinus**
The third nerve courses along the superior lateral wall of the cavernous sinus and then divides into a superior division (with fibers for superior rectus and levator palpebrae) and inferior division (with all remaining fibers) in the anterior cavernous sinus. Concurrent fourth, fifth or sixth nerve palsies point toward the cavernous sinus. Simultaneous involvement of the sympathetic fibers causing a Horner’s syndrome may result in a syndrome quite unique to the cavernous sinus: alternating anisocoria. In the light, the TNP predominates and the ipsilateral pupil is larger. In the dark, the Horner syndrome is accentuated and the pupil is smaller.
Causes
Any cavernous sinus process may affect the third nerve, including tumors such as meningiomas, adenomas and rarely metastatic disease. Intracavernous carotid artery aneurysms may also compress the third nerve, but their rupture results not in a subarachnoid hemorrhage, but instead in a cavernous carotid fistula. The latter will be discussed further below. Cavernous sinus thrombosis, idiopathic inflammation (Tolosa-Hunt) and Zoster may also affect the intracavernous third nerve. Pituitary apoplexy may bleed into the surrounding cavernous sinus and cause acute ophthalmoplegia along with acute visual loss from chiasmal compression. MRI with thin cuts through the cavernous sinus is useful in confirming cavernous sinus disease, and may help elucidate the type of lesion. Tumors tend to enhance more than the surrounding venous lakes of the sinus, while thrombosis and aneurysms tend to cause a non-enhancing filling defect in the sinus.

Figure 6. Bilateral third nerve enhancement secondary to leptomeningeal spread of acute lymphocytic leukemia.

(ALL)

Management of third nerve palsies
Diagnostic work up has been described in detail above. Treatment is tailored to the underlying cause. Symptomatic treatment of diplopia from TNP may be treated with prisms, but can prove difficult as involvement of superior and inferior recti leads to a large variation in prismatic need in different fields of gaze.

Case 2: A lid with a mind of its own
A 65 year old woman presented with chronic oblique diplopia ever since resection of a meningioma 10 years prior. Additionally, she was now noticing that her left lid was lifting in attempted downgaze and she had developed secondary erosions in her cornea. Examination revealed elevation of the left lid with depression and adduction of the left eye.

Aberrant regeneration following third nerve palsies
Years after a TNP, injured fibers meant for the medial or inferior rectus may regrow ectopically and innervate the levator palpebrae. This aberrant regrowth results in lifting of the lid in attempted adduction and depression, the latter of which causes a lid lag similar to that seen in thyroid eye disease. (Pseudo Von Graefe’s sign) Keratopathy may sometimes ensue. Rarely, there may be pupillary constriction in attempted depression and adduction even when the light reflex is otherwise lost. Primary aberrant regeneration in which the presentation is not preceded by a simple third nerve palsy, has been described secondary to intracavernous meningioma and intracranial aneurysm.

Case 3: A Hidden Fourth
A 37 year old man with a history of optic neuritis OS in 2001 was subsequently diagnosed with multiple sclerosis based on MRI findings and presence of oligoclonal bands. He then developed horizontal diplopia, especially in left gaze and presented to neuro-ophthalmology clinic. On exam, there was a prominent left head tilt. There was 40% adduction and 20% abduction OU. Cross cover testing showed an esotropia of 8 prism diopters in primary gaze and an exotropia in right gaze, consistent with a combination of abducens palsies and an internuclear

ophthalmoplegia. Maddox rod testing revealed a left hypertropia that was worse in right and down gaze and worse in left head tilt. The patient found improvement in diplopia with a 4 prism diopters base down lens OS.

FOURTH (TROCHLEAR) NERVE PALSY

Background and Anatomy

The fourth nerve nucleus sits in the dorsal inferior midbrain at the floor of the cerebral aqueduct at the level of the inferior colliculus. Its neurons form the only cranial nerve that exits the dorsal surface of the brainstem and the only cranial nerve in which all the fibers decussate. After coursing lateral to the midbrain, the nerve travels between the posterior cerebral artery and superior cerebellar artery, through the lateral portion of the cavernous sinus after which it enters the orbit through the superior orbital fissure, to finally pierce the superior oblique muscle. The superior oblique muscle’s primary actions are to depress the globe, especially when it is adducted, and to intort the globe, especially in abduction. The latter function is made possible by a twist in the course of the muscle as it passes through the pulley-like trochlea which hangs from the superior medial orbit.

Figure 7. Course of the left trochlear nerve.

Clinical Presentation

Fourth nerve palsies produce vertical and torsional diplopia, although many patients only recognize the vertical component. The pattern observed on examination is one of an ipsilateral hypertropia that is worse in contralateral gaze (when the eye is adducted) and worse in downgaze, in the direction of its action. The vertical diplopia also worsens in ipsilateral head tilt because the compensatory intorsion of the superior oblique is weakened and the superior rectus, which is also an intorter, is recruited. This superior rectus activation elevates the eye further. Since fourth nerve palsies are not always easily observed with testing of versions, Maddox rod and cross cover testing can prove very useful in confirming the pattern of strabismus. When a fourth nerve palsy is suspected, the side of the palsy can be quickly checked by showing the patient a horizontal stimulus such as a pencil. They should see a second image which is tilted to one side. The side in which the horizontal and tilted images would meet if they were long enough is the side of the fourth nerve palsy. Excycloversion also may be confirmed by inspection of the fundus or of fundus photographs. An imaginary horizontal line through the center of the fovea should cross the optic disc about two thirds towards the bottom edge. Using a horizontal beam on the slit lamp, one can tilt the slit lamp until the light crosses properly and measure the required degrees of tilt.
Bilateral fourth nerve palsies
The trochlear nerves decussate at the anterior medullary vellum where they may both be injured by head trauma, producing bilateral fourth nerve palsies. In such cases, there is typically a right hypertropia in right head tilt and a left hypertropia in left head tilt. There may also be an esotropia that is worse in downgaze since the tertiary function of each trochlear nerve is abduction. This results in a characteristic chin-down position. Bilateral trochlear nerve palsies may be detected with use of double Maddox rod, whereby a red Maddox rod is placed over one lens and a white over the other. The patient turns one of the lenses until the two vertical lines match up and the numbers of degrees of combined torsion is measured. Readings of greater than 10 degrees are suggestive of bilateral fourth nerve palsies.

Causes
The majority of acquired trochlear nerve palsy cases result from head trauma or are idiopathic. Because it travels along the free edge of the tentorium within the prepontine cistern, it is particularly susceptible to crush injury in the setting of head trauma. Ischemic palsies may occur as with third nerve palsies, are typically painful and also recover within a few months.

Nuclear and fascicular fourth nerve palsies
Injury to a trochlear nucleus causes a contralateral fourth nerve palsy since the nerve decussates. It may be associated with a Horner’s syndrome ipsilateral to the nucleus due to involvement of sympathetic fibers in the dorsolateral tegmentum. These tend to be associated with neighborhood signs that aid in localization. These may include an ipsilateral tinnitus (inferior colliculus), or a contralateral relative afferent pupillary defect without vision loss (pretectal pathways). Injury to either the nucleus or fascicle may occur due to midbrain hemorrhage, infarction, tumor or demyelination.

Subarachnoid fourth nerve palsies
These causes are similar to those of the third nerve, and include aneurysm, giant cell arteritis, ischemia, infectious and neoplastic leptomeningeal disease and hydrocephalus. Trochlear nerve dysfunction following temporal lobectomy may occur, likely due to intraoperative traction of the nerve.

Congenital fourth nerve palsies
Congenital fourth nerve palsies are common and often unrecognized by the patient until either a head tilt is recognized or decompensation occurs later in life. Several characteristics suggestive of a congenital fourth nerve palsy are worth mentioning. Hypertropia may be worse in upgaze rather than downgaze if inferior oblique overaction has developed (theoretically due to lack of antagonist resistance). Furthermore, these patients are typically able to fuse their vision with a large spectrum of vertical prisms in place due to a long history of cortical compensation. This is known as having a large fusional amplitude. Finally, review of old photographs may reveal a longstanding head tilt.
Figure 9. Characteristics suggestive of congenital fourth palsies
- Hypertropia worse in upgaze
- Inferior oblique overaction
- Large fusional amplitudes
- Contralateral head tilt in old photographs

Differential Diagnosis
Fourth nerve palsies may be mimicked by ocular myasthenia, thyroid eye disease and skew deviation, all of which are discussed in detail in other lectures. Skew deviation results from an imbalance in utricular-vestibular output which normally controls the vertical and torsional position of each eye in response to body tilt. A new test comparing the vertical deviation in upright vs. supine positioning can help differentiate the two entities since by lying the patient down, one reduces gravitational effects on the utricles thereby reducing the relative contribution of this system to vertical alignment of the eyes and reducing the vertical deviation in skew but not trochlear nerve palsies.

Management
Some patients may realize that tilting the head to the contralateral side ameliorates diplopia. Since the degree of hypertropia is typically worse in downgaze activities such as reading, separate glasses with different prism strengths may be needed for primary gaze and reading. Torsional diplopia is resistant to prismatic therapy and may require surgical correction. A common surgical solution is weakening of the antagonist inferior oblique.

Case 3: A stethoscope is a neuro-ophthalmologist’s best friend
A 41 year old woman who recently arrived from China presented with intermittent binocular horizontal diplopia at distance that occurred 10 times per day for the last 4 days. She was treated for conjunctivitis in the right eye 1 week ago with antibiotic drops and the eye was still a little red. Three months ago she had noticed some pulsatile tinnitus and a right sided occipital headache. The latter resolved after a week. MRI, MRA and CTA were all normal two months ago in China. Examination revealed a subtle limitation of abduction of the right eye without pain. There was an esophoria of 8 prism diopters in primary gaze and 30 prism diopters in right gaze. A corkscrew vessel was present on the inferior lateral conjunctiva OD. There was no proptosis and intraocular pressures were equal at 18 mm Hg OU. Auscultation of the orbits with a stethoscope revealed a loud pulsatile bruit over the right globe. MRI with thin cuts through the cavernous sinus with MRA revealed a right sided cavernous carotid fistula as the cause of the abducens palsy. An enlarged superior ophthalmic vein was also supportive of the diagnosis. A few days later, intraocular pressure climbed to 24 mm Hg in the right eye and she developed some proptosis. She went for intravascular repair in China a few weeks later.

Figure 10. MRA shows a right sided cavernous-carotid fistula with associated enlargement of the superior ophthalmic vein.
SIXTH (ABDUCENS) NERVE PALSIES

Background and anatomy
The sixth nerve nucleus may be found in the in the medial pons, anterior to the fourth ventricle. Seventh nerve fibers from the adjacent facial nucleus course medial and dorsal to the abducens nucleus before exiting the lateral pons, so that combined sixth and seventh nerve palsies may occur from pontine disease. The abducens nucleus is actually a gaze nucleus because it also contains interneurons which send axons that decussate and climb to the contralateral medial rectus subnucleus in the medial longitudinal fasciculus (MLF), causing concomitant adduction of the contralateral eye with abduction of the ipsilateral eye. Diplopia resulting from MLF injury will be discussed in the lecture on supranuclear causes of diplopia. Abducens fascicular fibers course anteriorly through the pons to form the abducens nerve which exits anteriorly and enters the subarachnoid space. It then climbs up the clivus and makes a sharp turn at the petrous part of the temporal bone where it pierces the dura and travels through Dorello’s canal to then enter the cavernous sinus. There it travels next to the carotid artery and sympathetic fibers before coursing anteriorly to the superior orbital fissure and into the orbit where it innervates the lateral rectus.

Presentation
Abducens palsies result in limitation of abduction to varying degrees. Occasionally, mild vertical deviations may be observed, ostensibly because of unmasking of baseline vertical phorias.

Causes
Its long intracranial course and relatively fixed attachment to the petrous apex make the abducens nerve particularly susceptible to stretch injury in the setting of raised intracranial pressure and associated downward displacement of the brainstem. It is a common finding in idiopathic intracranial pressure. Decreased intracranial pressure from a spontaneous cerebrospinal fluid leak or after lumbar puncture can also cause an abducens palsy. Rarely, an abducens palsy may be the lone presenting sign of a pontine glioma. It is particularly susceptible to carotid artery pathology (aneurysms and fistulae) in the cavernous sinus because of its proximity. Assorted causes are listed in figure 5.

Figure 11. Causes of abducens palsies
- Raised or lowered intracranial hypertension
- Head trauma
- Ischemic
- Idiopathic
- Demyelination
- Brainstem tumors including brainstem glioma
- Clivus tumors
- Cavernous sinus disease
  - Cavernous carotid fistula
  - Cavernous sinus thrombosis
  - Cavernous aneurysm
- Infectious (Lyme or syphilis), inflammatory (Sarcoidosis, Behcet’s) leptomeningeal disease
- Giant cell arteritis
- Neoplastic leptomeningeal disease
- Wernicke-Korsakoff (thiamine deficiency)
- Congenital: Duane’s syndrome

Management
Management begins with diagnosis and treatment of the underlying cause when possible, such as tumor resection or correction of raised ICP. Base-out prisms can be used to treat esotropia. Finally, if spontaneous improvement has not occurred over a period of at least 6 months, surgical correction may ultimately be used to restore single vision. This may include recession and weakening of the medial rectus. Paresis with botulin toxin may also be used for temporary treatment of diplopia from third, fourths or sixth nerve palsies but show varied results.
SYNDROMES AFFECTING MULTIPLE CRANIAL NERVES

Cavernous sinus syndrome
As a rule, combined deficits in III, IV, V₁, V₂, sympathetic fibers and VI reflect cavernous sinus disease. Since the abducens nerve and sympathetic fibers both travel adjacent to the carotid artery, they are often affected together; a combined abducens palsy / Horner’s syndrome is a cavernous sinus lesion until proven otherwise. Involvement of the Oculomotor nerve and sympathetics may produce an alternating anisocoria as mentioned previously. When V₃ is affected, it is suggestive of spread to Meckel’s cave, which is located inferior to the cavernous sinus.


Figure 13. A large meningioma is seen within the right cavernous sinus expanding and compressing the right temporal lobe and touching the left optic chiasm. The patient’s exam revealed a right fourth, fifth, sixth nerve palsies and a right Horner’s syndrome which is evident in the picture.

Orbital Apex
Lesions at the orbital apex may cause a syndrome similar to that of the cavernous sinus except that V₂ is spared and the optic nerve may be involved. This is a common site of compression by thyroid eye disease, but in diabetic or immunocompromised patients, infiltration by fungal infections, specifically *mucor*, should be suspected.

Gradenigo’s Syndrome
Lesions near the petrous apex of the temporal bone may affect both the abducens and trigeminal nerve producing esotropia with ipsilateral numbness, referred to as Gradenigo’s syndrome. In children this may result from otitis media and mastoiditis, but in adults it may be the presenting sign of nasopharyngeal carcinoma.

TABLE 2. Syndromes of multiple cranial neuropathies

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SYNDROMES OF CONGENITAL ABSENCE OF OCULAR MOTOR CRANIAL NERVES

Duane’s Retraction Syndrome
Duane’s syndrome is characterized by absence of the abducens nucleus and innervations of the lateral rectus muscle by the inferior division of the oculomotor nerve. Patients consequently demonstrate limited abduction of the affected eye as well as retraction of the eye in attempted adduction due to co-contraction of both the medial rectus and ectopically innervated lateral rectus muscle. This same co-contraction may also result in an upshoot of the eye in attempted abduction. Various types of Duane’s syndrome refer to varying amounts of abduction and adduction weakness. About 20% are bilateral. Patients typically present with a compensatory head turn. Diplopia is mild or even absent. Some cases may be associated with a mutation in the CHN1 gene which codes for a signaling protein involved in axon guidance, α2-chimaerin.

Congenital Fibrosis of the Extraocular Muscles, Type I (CFEMI)
Patients born with CFEMI have bilateral ptosis and limited eye movements, particularly vertical. Eyes typically are depressed at rest. Post-mortem autopsies have shown absence of the nuclei providing the superior branch of the oculomotor nerve, which carries the nerve to the levator palpebrae and superior rectus. Other subnuclei may be diminutive as well. Heterozygote mutations in KIF21A which encodes for a kinesin motor cause the disease and are inherited in an autosomal dominant fashion.

SUMMARY
Diplopia localizing to cranial nerves III, IV and VI may be the gateway to diagnosis of serious neurological and medical disease. Rapid diagnosis and treatment can be life-saving and prevent future morbidity. Management of diplopia can have a profound effect on patients’ daily quality of life.

SUGGESTED REFERENCES