Neuro-ophthalmic Update

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Diplopia: Non-Neurogenic causes

- Keratoconus
- Uncorrected astigmatism and refractive error
- Iridectomy
- Cataract
- Macular edema
- Eye wear (bifocal seg)

Diplopia: Motility Problems

- Non-paralytic strabismus
  - Tropias
  - Decompensating phoria
- Paralytic strabismus
  - CN palsy
- Muscle restriction
  - Trauma
  - Grave's disease
- Neuromuscular disease
  - Myasthenia gravis

The Four Questions

- Is the diplopia binocular or monocular?
  - Test both eyes
  - Monocular diplopia is NEVER neurogenic
    - Surface disorder
    - Refractive disorder
- Is the diplopia horizontal or vertical?
  - Horizontal diplopia is relegated to 2 medial recti or 2 lateral recti
  - Vertical diplopia is due to 2 superior obliques, 2 inferior recti, 2 superior recti, or 2 inferior obliques
- Does the diplopia increase in any direction of gaze?
  - Horizontal diplopia worse in right gaze is either the right lateral rectus or left medial rectus
- Is the diplopia greater at distance or near?
  - Horizontal diplopia worse at distance is one of the two lateral recti muscles
  - Horizontal diplopia worse at near is one of the two medial recti muscles
  - Horizontal diplopia worse at distance and in right gaze is the right lateral rectus

Cranial Nerve III Palsy:

- Is this CN III palsy?
- Is this an isolated CN III palsy?
- If this is an isolated CN III palsy, what is the work-up?

CN III Anatomy:

- CN III is the only CN with a sub-nuclear complex
  - Medial rectus (MR), inferior rectus (IR), superior rectus (SR-decussates with contralateral innervation), inferior oblique (IO), levator (bilateral upper lid)
- Paired sub-nuclei with decussation of one sub-nuclei
- One unpaired sub-nuclei controls both eyelids
- Arises in the midbrain (mesencephalon) at the level of the superior colliculus
- Breaks into a superior and inferior division
- Pupillomotor fibers travel with the inferior division and the inferior oblique

CN III Palsy: Clinical Picture

- Eye that is down and out with a ptosis
- Pupil features
  - Pupil may be dilated (involved) or normal (spared)
- Variations
  - Palsy is complete; paresis is incomplete
- Signature motility of CN III palsy:
  - A hyper deviation that increases in up gaze, reverses in down gaze
  - Exo deviation which increases in opposite gaze
- Other possibilities
  - Remember the possibility of a partial paresis or isolated muscle paresis. Isolated muscle paresis are in the orbit, nerve nucleus, or neuromuscular junction (myasthenia gravis)
  - Nuclear CN III palsy can not exist without contralateral involvement (contralateral ptosis and SR weakness)

CN III: Anatomic Course

- Fascicles pass through parenchyma of midbrain through Red Nucleus and Corticospinal Tract
  - A lesion, which involves the CN III fascicles as they pass through the Red Nucleus, will cause CN III palsy with a contralateral intention tremor and ataxic gate. This is termed Benedickt's syndrome.
  - A lesion which involves the CN III fascicles as they pass through the Corticospinal tract will result in a CN IIII palsy with a contralateral hemiplegia. This is termed Weber's syndrome.
- Exits midbrain into subarachnoid space between cerebral peduncles between superior cerebellar artery and posterior cerebral artery and follows posterior communicating artery

- Enters the lateral wall of cavernous sinus where it bifurcates into superior and inferior divisions just before exiting cavernous sinus
- Enters the superior orbital fissure where it further divides to innervate the individual muscles
- CN III is vulnerable to compression by aneurysm along course of posterior communicating artery or at tip of basilar artery
- Pupillomotor fibers are peripheral in nerve and prone to compression, but relatively immune to ischemia

CN III Palsy: Still More Clues

- A dilated pupil means compression by aneurysm (emergency!)
  - A sudden onset CN III palsy with a dilated, poorly responsive pupil is most likely to be caused by an aneurysm
- Pain can mean anything
- Aneurysms are always painful
  - Boring pain
- Ischemic vascular infarct is painful 90%
  - Retro-orbital pain
- A spared pupil does not always rule out aneurysm
  - There have been 7 cases reported where the pupil was initially uninvolved, but the etiology was an aneurysm. Most of these cases were partial CN III palsies that worsened and became pupil involving over 1 week. Watch these patients daily over one week. Never dilate CN III palsy
- An involved pupil does not rule out ischemia
  - In extreme infarcts, the pupil may be involved as well. These cases are in older patients with vascular disease and are complete CN III palsies
- In a patient with a paresis (incomplete palsy), you can not call the pupil
  - There is likely an incipient aneurysm growing. A spared pupil does not rule out a life-threatening emergency here.

Isolated CN III: Work-up

- CN III palsy with an involved pupil: STAT arteriogram
- Adult CN III palsy with a spared pupil:
  - Under 50 yrs. - arteriogram and ischemic vascular evaluation
  - Over 50 yrs. - watch pupil daily, MRI, ESR, ischemic vascular work-up
- Every adult CN III palsy deserves an MRI
- If ischemic vascular etiology is diagnosed and palsy does not resolve after 90 days, you must re-evaluate
- Consider myasthenia gravis and Tensilon testing
- Look for aberrant regeneration

Causes of CN III Palsy:

ADULTS	CHILDREN

Undetermined (24%)	Congenital (44%)
Aneurysm (21%)	Trauma (16%)
Ischemia (18%)	Inflammation (11%)
Trauma (13%)	Miscellaneous (11%)
Neoplasm (12%)	Neoplasm (10%)
Miscellaneous (12%)	Aneurysm or ischemia (6%)

CN III Palsy: Aberrant Regeneration

- When damage to the CN III results in a resprouting and miscommunication of nerves to muscles
- Inferior rectus and medial rectus communicates with levator
- Medial rectus communicates with pupil
- Clinical picture:
  - Patient looks medial: lid elevates
  - Patient looks lateral: lid lowers
  - Patient looks down: lid elevates (Pseudo-Von Graefe's sign and the most identifiable sign)
  - Patient looks medial: pupil constricts

CN III Palsy: Two Types of Aberrant Regeneration:

- Primary: Occurs independent of antecedent CN III Palsy. Caused by aneurysm or meningioma within cavernous sinus
- Secondary: Occurs after an antecedent CN III palsy. Causes:
  - Aneurysm, trauma, tumor, inflammation
  - NEVER DIABETES! If cause of CN III palsy is determined to be ischemic vascular (diabetes, HTN, etc.) and then the eye undergoes aberrant regeneration, the initial diagnosis is wrong. You must re-examine for tumor or aneurysm within ipsilateral cavernous sinus.

CN IV Palsy:

- The 3 cardinal questions:
  1. Which eye is higher in primary gaze?
  2. Does the hyper deviation get worse in right or left gaze?
  3. Does the hyper deviation get worse on right or left head tilt?
- CN IV palsy is the most common cause of vertical diplopia. Vertical diplopia is CN IV Palsy until proven otherwise.

CN IV Palsy: Motility Pattern

- Presents with a hyper deviation that is greater on contralateral gaze and ipsilateral head tilt

CN IV Palsy: Anatomy Review

- CN IV exits the midbrain posteriorly and decussates within the anterior medullary vellum
- It has the longest course of any cranial nerve
- Is the most slender nerve
- Travels from subarachnoid space to enter the lateral wall of cavernous sinus inferior to CN III
- Travels from cavernous sinus through superior orbital fissure (within annulus of Zinn) to innervate superior oblique
- Due to course and length, CN IV is most prone to trauma

CN IV Palsy: Points to Remember

- Long-standing CN IV palsy can present with diplopia due to decompensation. Patient typically presents with head tilt opposite side of palsy
- RoboMuscle: muscle, tendon, fascia- many possibilities for things to go wrong
- Get FAT (Family Album Tomography) scan or FB (Facebook) scan
- 40-30-20-10 rule:
  - 40% traumatic- most common cause
  - 30% idiopathic
  - 20% ischemic vascular (diabetes and/or hypertension)
  - 10% tumor or aneurysm
- CN IV palsy in children: typically traumatic or congenital. Very safe
- May present bilaterally: on right head tilt the right eye moves up. On left head tilt, the left eye moves up. The patient presents with chin tucked down. Usually secondary to trauma or pinealoma in dorsal midbrain syndrome

CN IV Palsy: Management of Isolated, Non-traumatic Palsy

- Rule-out diabetes and hypertension
- Non-ischemic causes of non-traumatic isolated palsy is rare
- Under age 20: no work-up if present > 10 years
- Age 20-40: neuro-imaging (?) esp. if recent trauma
- Over 40 yrs: medical evaluation for ischemic vascular disease, neuro-imaging (?)

CN VI Palsy:

- Hallmark sign is horizontal diplopia, greater at distance, with an Abduction deficit
- Underaction of the ipsilateral lateral rectus muscle.
- CN VI is the most common ischemic vascular palsy seen
- 25% of cases remain without etiology

CN VI Palsy: Four Questions for Diagnosis

1. Are you testing at distance?
2. Are ductions better than versions?

3. Is there asymmetric refixation of eye movements?
4. Is there a negative forced duction test?

CN VI Palsy: Anatomy Review

- CN VI arises at the pontomedulary junction close to CN VII, parapontine reticular formation (PPRF), and medial longitudinal fasciculus (MLF). It exits the pons and ascends over the clivus and courses over the petrous apex of the temporal bone to enter the cavernous sinus. It then travels through the superior orbital fissure to the orbit and the lateral rectus
- Because of the proximity of CN VII, MLF, and PPRF, isolated nuclear CN VI palsy is rare (unheard of). Usually will get brainstem syndromes

CN VI Palsy: Etiologies

- Petrous apex of temporal bone is prone to inflammation from otitis media: Gradenigo's syndrome- hearing loss, facial pain, CN VI palsy. Common in children
- In adults, same symptoms should lead you to consider nasopharyngeal carcinoma
- As a rule, if the onset is sudden, think ischemic vascular. If the onset is slow, think infiltration and compression.
- Ischemic vascular insult is a common cause of CN VI palsy
- Twenty-five percent remain without diagnosis
- Causes of painful CN VI palsy in older adults: Gradenigo's syndrome, giant cell arteritis, ischemic infarct
    - Never myasthenia gravis if pain is present

CN VI Palsy: More About Mass Lesion

- With space occupying lesions you can get rise in intracranial pressure (ICP)
- As ICP increases, the brainstem herniates down through the foramen magnum
- CN VI becomes stretched against the clivus. This is why CN VI palsy is common in mass lesions and pseudotumor cerebri syndrome (PTC)
- Bilateral CN VI palsy is indicative of increased intracranial pressure. Must do MRI. Papilledema also commonly seen

CN VI Palsy: Causes in Children and Adults

- There are three distinct demographic groups that develop CN VI palsy. Most patients developing acute CN VI palsy are older. This group often has a concurrent history of hypertension and/or diabetes
    - The peak incidence occurs in the seventh decade.
    - In adults over the age of 50 years with isolated sixth nerve palsy, a workup for ischemic vascular diseases such as diabetes and hypertension should be undertaken as this is the most likely cause.
    - If the patient is over the age of 60 years, then an erythrocyte sedimentation rate (ESR) should be ordered to rule out giant cell arteritis

- Children are also prone to develop CN VI palsy. The cause may range from benign, such as viral illness or trauma, to malignant.
    - Nearly half of all CN VI palsies in children are due to neoplastic disease, notably pontine glioma. Neurologic evaluation and consultation is urgent in this group and the cause of the palsy shouldn't be presumed to be benign
- The third group consists of young adults aged 20–50 years. This group is more likely to have neurologically complicated CN VI palsies involving other cranial nerves.
    - In contrast to older adults, vascular disease such as diabetes and hypertension are uncommon in this group with more serious conditions such as central nervous system (CNS) mass lesions and multiple sclerosis typically found
    - In this group, CNS mass lesions and multiple sclerosis account for 33% and 24% of CN VI palsies, respectively.
    - Idiopathic CN VI palsies account for 13% of cases and vascular disease only 4%. It should be noted that CN VI palsy caused by CNS mass lesions in young adults involve other cranial neuropathies and are not isolated. Thus, neuroimaging is highly recommended in this group.

Clinical Pearl: In any cases of diplopia in patients over 60 years, you must always consider giant cell arteritis.

Clinical Pearl: The cavernous sinus and clivus are two areas that can hide a cancerous neoplasm and cause an isolated CN VI palsy.

<u>Ocular Myasthenia Gravis</u>

- Autoimmune disease characterized by weakness of skeletal muscles
    - Ocular Myasthenia gravis: pupil sparing ophthalmoplegia
        - With or without variable ptosis
- Antibodies block or destroy acetylcholine receptors on the post synaptic neuron at the neuromuscular junction
    - Antibodies may also block muscle-specific receptor tyrosine kinase
- Bimodal age distribution
    - Early onset disease is 3x as likely in females as in males
    - Males slightly outnumber females in the late-onset disease
- Hallmark is weakness or fatigability of extraocular muscles resulting in diplopia
    - Variable angle incomitant deviation
    - Fluctuating lid position with varies with fatigue and temperature
    - Ocular symptoms are often the first presenting sign of disease
- Clinical Examination of ocular myasthenia
    - Ocular motility examination
    - Cover test
    - Fatigue testing
    - Cogan's lid twitch

    - Orbicularis strength
    - Icepack test
- Signs of generalized myasthenia
    - Difficulty swallowing
    - Difficulty chewing food
    - Change in voice
    - Limb weakness
    - Neck weakness
- Serological evaluation
    - Anti-ACh antibodies
    - Anti-muscle-specific kinase antibody (Anti MuSK)
        - May be positive in seronegative cases
    - Up to 50% of cases of OMG are seronegative
        - 10-20% of generalized MG are seronegative
- Other diagnostic modalities
    - Chest CT (With and without contrast)
        - Thymoma
    - Electromyography
        - Repetitive nerve stimulation
    - Tensilon testing
        - IV Tensilon (edrophonium) injected (acetylcholinesterase inhibitor)
            - Prolongs ACh in synaptic cleft
            - Potential for adverse cardiac effect
- Treatment is to improve signs and symptoms
    - Pyridostigmine (Mestinon)
        - Most frequent side effect is GI upset
        - Dose of pyridostigmine is based on basis of desired effect, dose-dependent side effects
    - Immunosuppression
        - Prednisone in combination with azathioprine
            - Azathioprine in addition provides a better result with fewer side effects than prednisone monotherapy
        - Rituximab
    - Intravenous immunoglobulin (gamma globulin)
    - Plasmapheresis
    - Prism correction is often of minimal help due to variability of angle of deviation
- Avoid
    - Muscle relaxants
    - Antibiotics
        - Fluoroquinolones
        - Macrolides
        - Aminoglycosides
    - Beta blockers

        - Includes timolol
    - Statins can unmask and aggravate MG-but not a contraindication
    - Quinidine and quinine
    - Anti-epileptic drugs
- Prognosis
    - 90% of patients with ocular myasthenia only after 2 years will never develop generalized MG
- Coexisting conditions are common
    - Thyroid disease
    - Immune disorders in early onset disease
        - Systemic lupus erythematosus and RA

OCT in Neuro-Ophthalmic Disease

Stroke

- Post-geniculate lesions result in homonymous visual field defect
- OCT findings
    - Retinal nerve fiber layer may be unaffected
    - Ganglion cell complex can show abnormality 'opposite' to that present in the visual field
- Retrograde trans-synaptic degeneration
    - Infarct in the cortex (post-geniculate) can lead to retinal ganglion cell loss
    - Death of lateral geniculate nucleus (LGN) neurons follow cortical injury resulting in decreased energy metabolite levels from synaptic targets
    - GCC thinning may occur as soon as 3 months following incident and continue for years
    - Does not occur in all cases of post-geniculate lesions
        - Larger lesions have a higher likelihood of retrograde trans-synaptic degeneration
        - Lesions close to LGN have a higher likelihood of damage

Idiopathic Intracranial Hypertension

- Obstruction of axoplasmic flow results in optic disc edema secondary to elevated intracranial pressure
- Optic neuropathy is a common cause of vision loss
- Vision loss may be reversible if intervention occurs in a timely manner
    - Ganglion cell analysis may be useful to determine potential for axonal damage prior to visual field defect
    - RNFL is not useful due to diffuse elevation

The Role of OCT in Neurodegenerative Disease

- Ultimate goal is to determine imaging biomarkers for disease diagnosis and to monitor progression

Multiple Sclerosis

- Inflammatory CNS disorder resulting in demyelination of CNS axons

- Nerve fiber layer and ganglion cell complex (GCC) thinning with and without history of optic neuritis
    - Greater loss with history of optic neuritis
- GCC thinning occurs due to axonal death and resulting loss of cell body support
    - Microinflammatory damage may also occur
- GCC correlates with brain-substructure volumes and grey and white matter volumes
- Peripapillary RNFL atrophy associated with worsening disability in disease course and lower quality of life
    - For patients with and without ON
- Ganglion Cell Complex Thickness
    - GCL/IPL seems to have better sensitivity to functional disability than temporal RNFL thickness
    - Potential predictor of axonal damage

Parkinson's Disease

- Second most common neurodegenerative disease
- Characterized by resting tremor, bradykinesia and rigidity
    - Cognitive dysfunction, autonomic failure and sleep disorders
- Dopamine in the retina is released by amacrine cells in the proximal inner nuclear layer of the retina
- OCT findings
    - RNFL
        - Decreased RNFL
        - Currently no correlation between disease severity or duration and pRNFL thickness
    - Macular thinning with disease progression
        - Especially temporal and inferior
    - Ganglion cell/inner plexiform layer
        - More affected with disease severity and duration as compared to other retinal layers
        - Seems to be able to predict axonal damage in Parkinson's disease

Alzheimer's Disease

- Progressive characterized by amyloid plaques and neurofibrillary tangles
- The most common cause of dementia
- RNFL thinning may be the earliest sign of damage
    - Even in the absence of hippocampus damage
- Ganglion cell complex may be reduced in Alzheimer's patients
    - Decreased grey matter volume in occipital and temporal lobes is associated with decreased GCC thickness
- Microvascular disease is a contributor to dementia