**NEURO-OPTHALMIC UPDATE**

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**DISCLOSURE:**
Joseph Sowka, OD is/has been a Consultant/ Speaker Bureau/ Advisory Board member for Novartis, Allergan, Glaubos, and B&L. Dr. Sowka has no direct financial interest in any of the diseases, products or instrumentation mentioned in this presentation. He is a co-owner of Optometric Education Consultants.

Jessica Steen, OD: None

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**OCULAR MOTILITY PROBLEMS**
- Non-paralytic strabismus
- Paralytic strabismus (CN III, IV, VI palsy)
- Neuromuscular or muscular dysfunction

**THE 5 QUESTIONS OF DIPLOPIA**

1. Is it real?
2. Is the diplopia present monocularly?
3. Is the diplopia horizontal or vertical?
4. Does the diplopia increase in a particular direction of gaze?
5. Is the diplopia greater at distance or near?

Is the diplopia present monocularly?
NON-NEUROGENIC ETIOLOGIES

- Keratoconus
- Astigmatism
- Other uncorrected refractive error
- Iridectomy
- Cataract
- My own personal experience
- Macular edema
- Spectacle lens problems
- Ocular surface disease
- Pinhole cures monocular diplopia!

Is the diplopia horizontal or vertical?

PRESENTATION

- Real? Onset?
  - Acute onset likely vasculopathic – most common – 3 mos duration
- Course?
  - Getting better or worse
- Anything else new?
- Isolated - Fellow travelers?
  - Pupil
  - Lid
  - Numbness
WHICH IS BETTER? ONE OR TWO?

- Long standing glaucoma patient
- Sudden onset of orbital pain x 3 days
- + DM; +HTN
- On coumadin
- Pacemaker
- No vision change
- Presents as walk-in emergency glaucoma eval

63 YOIM

- Pupil involved CN III palsy
- 3 days duration at least
- Most likely cause: intracranial aneurysm
- Sent to ER with detailed notes and recommendations
- Endovascular therapy with coils
- Hospitalized 23 days
**CN III PALSY CLINICAL PICTURE**

- An eye that is down and out with a ptosis
- Adduction, elevation, depression deficits
- Isocoric or anisocoric

**CN III ANATOMY**

- Vulnerable to compression from aneurysm in subarachnoid space
  - Posterior communicating artery (PCOM)
  - Junction PCOM and ICA
  - Tip of basilar artery

**STILL MORE CLUES**

- A dilated, poorly reactive pupil means compression
- Pain can be anything
  - Aneurysms are always painful
  - Ischemic vasculopathies may be painful ... or not
  - Pain cannot be qualified - only helpful if not present
- A spared pupil does not always rule out aneurysm
  - Incomplete palsy
STILL MORE CLUES

- Pupil involved CN III palsy is PCOM aneurysm until proven otherwise
- Incomplete palsy is PCOM aneurysm until proven otherwise
  - Regardless of pupil
- 30% of CN III palsy are caused by aneurysm
- Vasculopathic CN III will resolve in time
- Life threatening posterior communicating aneurysm will rupture in time

RULES FOR CN III PALSY
IMAGING

- High suspicion of aneurysm: DSA (gold standard)
- CT/CTA is preferred non-invasive imaging for CN III palsy
  - CT for SAH
- CTA requires contrast- renal impairment prefers MRI/MRA
- CTA superior to MRI when patient can’t have MRI
  - Pacemaker, claustrophobia
- MRI superior for non-aneurysmal causes (tumor)
  - MRA adds very little time to scan

A DIFFERENT PATIENT AND PROGNOSIS

- 63 YOF
- Diabetes and HTN
- Sudden onset retro-orbital pain

CN III palsy caused by aneurysm

- 20% die within 48 hrs from rupture
- 50% overall die
- Average time from onset to rupture – 29 days
  - 80% rupture w/i 29 days
- Many never make it to hospital

Complete CN III palsy with pupil sparing and vasculogenic risk factors
WHICH IS BETTER? ONE OR TWO?

- Resolves over several weeks
- Hospitalized 23 days with 2 neurosurgical procedures

SUSPECT THE WORST

- Optometrist sees patient with CN III palsy
- Referred to ophthalmologist next day
- Pt dies from SAH before consult

DOES PRESENCE OF VASCULOPATHIC RISK FACTORS HELP?

- Arteriosclerotic risk factors in elderly favors microvascular etiology but does not rule out aneurysm
- HTN, DM, atherosclerosis, hypercholesterol all common and don’t protect against aneurysm
- Answer: no, but makes me very nervous when NOT present

DOES ACUTENESS OF PRESENTATION HELP?

- Ans: Yes and No
- Aneurysm expansion usually produces acute manifestations, but chronic and evolving cases well known
- Acute is more worrisome
- Chronic and improving less worrisome but does not rule out aneurysm
- Resolved without recurrence reassuring

ANEURYSM RISK ASSESSMENT: ISOLATED CN 3 PALSY

- Isolated dilated pupil none
- Complete CN3-normal pupil low
- Partial CN3 – normal pupil high
- Pupil involved CN3 emergency

RULE: ISOLATED DILATED PUPIL IS ALMOST NEVER AN ANEURYSM

Ambulatory patients with isolated fixed and dilated pupil unresponsive to light or near more likely to harbor iris or ganglion (Adie’s) lesion or medication misadventure than CN 3 palsy

Risk of angiography is much higher than risk of aneurysm in this setting

No imaging needed for isolated dilated pupil
NEVER OUT OF THE WOODS

- Pt develops CN III palsy from aneurysm
  - Treatment choices: aneurysm clip or endovascular coil packing
- Successfully treated with aneurysm clip
  - All coils are inert and MRI safe; not all clips are MRI safe
- Radiologic tech doesn't verify type of clip
- Pt undergoes F/U MRI with non-MRI safe clip in major medical center
- Clip displaces during MRI
- Patient has fatal hemorrhage during procedure
- Patient survived disease...killed by follow up

ODE TO A THIRD NERVE

When the eye is down and out with ptosis,
You better hope for miosis.
If the palsy is total with pupil sparing,
In an Oldie it's vascular and not too daring.
But if the pupil is dilated,
An aneurysm has violated.
No time for deferral and no time for referral.
Send to the ER without debate.
Remember, twenty percent will die within the first forty-eight

Joseph Sowka, OD

35 YEAR OLD MALE

- Patient referred by GP for emergency evaluation for vertical double vision for past 2 days
- BVA: 20/20 OD, OS
- Pupils: normal (-) RAPD
- Perimetry: normal OD, OS
- Motility: Right hyper deviation which worsens in left gaze and right head tilt.
- Medical Hx: Normal, but has worst case of sinusitis ever – began 1 week before double vision.
- DX: Right CN IV palsy

CN IV PALSY: THREE CARDINAL QUESTIONS:

- Which eye is higher in primary gaze?
- Does the hyper deviation worsen in right or left gaze?
- Does the hyper deviation worsen with right or left head tilt?
- CN IV Palsy: A hyper deviation in primary gaze which is greater in opposite gaze and ipsilateral head tilt
- Vertical diplopia is CN IV palsy until proven otherwise
  - And if it isn't CN IV palsy, then it is a skew deviation- supination testing

CN IV ANATOMY

- Exits the midbrain posteriorly and decussates
- Longest course
- Travels around tentorium, through cavernous sinus, through SOF
- Most prone to trauma
**CN IV PALSY**

- Longstanding CN IV palsy may present with diplopia from decompensation
  - Observe old photos for head tilt (*Facebook Tomography*)
- Rule of 40-30-20-10

**CN IV MANAGEMENT**

- Isolated, non-traumatic:
  - Evaluate for ischemic diseases
  - Non-ischemic causes of non-traumatic, isolated CN IV palsy rare
  - Look for longstanding decompensation
    - Increased vertical vergences
    - Old photos

**35 YEAR OLD BLACK MALE**

- What are the possible etiologies?
  - MG, MS, ischemia, syphilis, Lyme, Sarcoid
- What is the likely etiology?
  - Erosion of inflammation from adjacent sinus
- Outcome?
  - Resolution commensurate with sinus infection

**ODE TO VERTICAL DIPLOPIA**

When your patient sees double up and down,

Its rarely a cause to frown.

Look for a tilt and prove its old,

And remember vertical vergences will be bold.

It’s a fourth until proven otherwise.

Trauma, congenital, and idiopathic you should surmise.

But if its not a fourth and its new,

Lay them back because its probably a skew.

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**37 YEAR OLD WHITE MALE**

- CC: Sudden onset painful horizontal diplopia x 6 days- Worse at distance and right gaze
- Medical Hx: reportedly normal
  - Evaluated at ER: CBC and CT scan (non-contrast) - normal
- Social Hx : Smoker (1 PPD); recovering alcoholic
- BVA: 20/20 OD, OS
- Motility: Right ABduction deficit
- Pupils: normal (+) RAPD
- Forced duction test: Negative
- BP: 144/102

**37 YEAR OLD WHITE MALE**

- Diagnosis: Right vasculogenic CN VI palsy secondary to undiagnosed hypertension.
- Further imaging: not ordered at this time
- OD patched during diplopic period; ophthalmoplegia disappeared within 12 weeks.
CN VI PALSY

- Hallmark sign is horizontal diplopia, greater at distance, with an abduction deficit.

MORE ABOUT MASS LESIONS

- CN VI is stretched against the clivus.
- CN VI palsy common in ICP rises/mass lesions/PTC.
- Bilateral CN VI palsy and disc edema is indicative of mass lesions and increased intracranial pressure.

CN VI MANAGEMENT

- Each case of CN VI palsy should be classified as traumatic or non-traumatic.
- Non-traumatic cases should be subdivided as neurologically isolated (just CN VI palsy) or non-neurologically isolated (something else).
- Additionally, patients should be ascribed to one of 3 groups: children, young adults, and older adults.

CN VI DEMOGRAPHIC GROUPS

- Older adults (usually not bad)
  - Vascular disease common- resolves-3mos
  - Consider GCA over 60 yrs
- Children (may be bad)
  - Presumed viral illness, trauma, malignancy (50%)
- Young adults (usually bad)
  - Vascular disease (4%) and idiopathic (13%) uncommon
  - Usually complicated CN VI palsy (hemiparesis, Horner syndrome, facial paresis)
  - Cerebrovascular accidents involving the pons, aneurysm (typically within the cavernous sinus) or neoplasm (33%-cavernous sinus, pons). MS (6%).
CN VI PALSY IN OLDER ADULTS

- In cases of isolated CN VI palsy in older adults with a history of diabetes or hypertension, neuroimaging and other extensive evaluation can be deferred, unless the palsy progresses, fails to improve over 3 months, or other neurologic complications develop.
- Ischemic vascular palsies typically progress over several days, but progression over two weeks warrants neuroimaging.

ODE TO A SIXTH

When the double is side by side,  
And abduction does not abide.  
Prove it’s a sixth with a forced duction test, 
Eliminate muscle, thyroid and all the rest. 
In kids and young adults it’s a worry. 
Get a scan and you better hurry. 
But in an Oldie you’re practically free. 
Prescribe a patch and check to see its better in three.

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CRANIAL NERVE PALSY CHEAT SHEET

- Horizontal diplopia = CN VI  
  - MR palsy?  
    - No: INO; entrapment, MG  
- Nearly all CN III will get some form of imaging  
- Vertical diplopia = CN IV (or SKEW)  
  - Nobody does forced duction for vertical diplopia  
  - CN III palsy doesn’t cause just vertical diplopia

CRANIAL NERVE PALSY CHEAT SHEET

- Vasculopathic risk factors (diabetes, hypertension, hypercholesterolemia, coronary artery disease, myocardial infarction, stroke, and smoking) significantly associated with presumed microvascular cause

CRANIAL NERVE PALSY CHEAT SHEET

- Vasculopathic risk factors were also present in 61% of patients with other causes  
  - Just because pt is older and has risk factors doesn’t mean they can’t have something else  
- In patients with vasculopathic risk factors only, with no other significant medical condition, 10% were found to have other causes, including midbrain infarction, neoplasms, inflammation, pituitary apoplexy, and GCA

CRANIAL NERVE PALSY CHEAT SHEET

- By excluding patients with third cranial nerve palsies and those with GCA, the incidence of other causes for isolated fourth and sixth cranial nerve palsies was 4.7%

**CRANIAL NERVE PALSY CHEAT SHEET**

- Patients with acute isolated ocular motor nerve palsies can have other causes, including neoplasm, GCA, and brain stem infarction.
- Brain MRI and laboratory workup have a role in the initial evaluation of older patients with isolated acute ocular motor nerve palsies regardless of whether vascular risk factors are present.


**FINAL PALSY RULES**

- Sudden onset palsies are typically vasculopathic… but could be something else
  - Check lipids, FBS, BP – internist
  - F/u 2-6 weeks looking for improvement
- Imaging isolated complete palsies?
  - Yes- definitely under age 50
- Not isolated – scan
- Ischemic microvascular palsies are allowed to get worse over 1 week and be no better at 2 weeks, but are not allowed to get worse over 2 weeks.

**FINAL RULE**

- Whenever dealing with suspected cranial neuropathies, always remember that it could be myasthenia gravis

**Ocular myasthenia gravis**

- Autoimmune disease characterized by weakness of skeletal muscles
  - Ocular MG: “pupil-sparing ophthalmoplegia”
    - With or without variable ptosis
- Bimodal age distribution
  - Early onset-females
  - Late onset-males

**Ocular myasthenia gravis**

- Antibodies block or destroy ACh receptors on post-synaptic neuron
  - Antibodies may also block muscle-specific receptor tyrosine kinase
Ocular myasthenia gravis
- Fatigability of EOMs resulting in diplopia
  - Incomitant deviation, variable angle
  - Fluctuating lid position
    - Effect of fatigue and temperature
- Clinical examination
  - Ocular motility examination
  - Cover test
  - Fatigue testing
  - Cogan’s lid twitch
  - Orbicularis strength
  - Icepack test
    - Levator function (2-5 minutes)

How does cooling improve muscle function?
- May decrease cholinesterase activity
- May improve efficacy of ACh at eliciting depolarization at the muscle end plate

Generalized myasthenia gravis
- Difficulty swallowing, chewing food, breathing
- Change in voice
- Limb weakness
- Neck weakness

Serological evaluation for MG
- Anti-ACh antibodies
  - Up to 50% of cases of OMG are sero-negative
  - Vs. 10-20% of generalized MG
- Anti-muscle-specific kinase antibody (Anti-MuSK)
  - May be positive in sero-negative cases

Other diagnostic modalities
- Chest CT (with and without contrast)
  - Thymoma
- Electromyography
  - Repetitive nerve stimulation-often normal in patients with OMG
- Tensilon testing
  - Acetylcholinesterase inhibitor (edrophonium chloride)
    - Prolongs ACh in synaptic cleft
    - Potential for cardiac arrest and cardiac arrhythmia
    - Negative result does not exclude diagnosis
Treatment strategy in MG

- Goal is to improve signs and symptoms
- Pyridostigmine (Mestinon)
  - GI upset
  - Dose is based on desired effect
    - Dose-dependent side effects
- Immunosuppression
  - Prednisone (+/- azathioprine)
  - Rituximab
- Prism?

AVOID

- Muscle relaxants
- Antibiotics (be FAMiliar)
  - Fluoroquinolones
  - Macrolides
  - Aminoglycosides
- Beta-blockers
- Statins?

Prognosis

- 90% of patients with OMG after 2 years will never develop generalized MG
- Coexisting conditions are common
  - Thyroid disease
  - Immune disorders
    - SLE & RA

Cerebral vascular accident

- 58 yo white female
- CC: “Blurred vision for almost a year, floaters”
- PMHx:
  - TIA 2014, Stroke 2010
  - MRI Brain: Acute non-hemorrhagic infarct in the left thalamus extending into the left temporal lobe
  - DM II x 22 years (controlled)
  - HTN x 22 years (controlled)
- BCVA: 20/25 OD and OS
- Pupils: PERRL (-) APD

24-2 SITA STD
**RNFL vs GCC**

- **Nerve fiber layer**
  - Non-neuronal elements
    - RNFL thickness impacted by blood vessels, glial elements
  - Swollen optic nerve = greatly elevated RNFL = no assessment of neuronal loss
    - Prolonged in AION, pseudotumor cerebri, optic nerve sheath meningioma

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**RNFL vs. GCC**

- **Macular GCC**
  - Retinal ganglion cells most dense at the macula
  - Lack of retinal blood vessels

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**Ganglion cell analysis**

- OD: VF defect superotemporal in relation to macula
- GCC defect opposite to VF defect
Retrograde trans-synaptic degeneration

- Infarction in the cortex (post-geniculate) → retinal ganglion cell loss and RNFL loss

How quickly does it happen?

- Most GCC thinning occurs within the first few years following infarction
- As soon as 3 months following incident
  - Jindahra (2011): >10 years following event, GCC thinning was approximately the same as aging alone

Why doesn't TSRD occur in all cases of stroke?

- Size of the lesion is sometimes correlated with amount of GCC thinning
  - Large lesions = higher likelihood
- Lesion location has significant impact on GCC damage
  - i.e. small lesion in close proximity to LGN has significant damage to retinal ganglion cells

THE ROLE OF OCT IN NEURODEGENERATIVE DISEASE

Oct in neurodegenerative disease

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

Multiple sclerosis

- Inflammatory CNS disorder with underlying neurodegeneration
  - Results in demyelination of CNS axons
  - But ganglion cells aren't myelinated-how does GCC loss occur?
    - Local pathogenesis
    - Subclinical optic neuritis
    - Retrograde trans-synaptic degeneration
      - Demyelination → loss of axonal support → axonal death → loss of ell body support → cell body death
Multiple Sclerosis and Optic Neuritis

- Hx of Optic Neuritis OD >25 years ago
- Hx of Optic Neuritis OD only

Multiple Sclerosis

- GCC thinning occurs due to axonal death and loss of cell body support
  - Microinflammatory damage may also occur
- GCC correlated with grey and white matter volumes
- Ganglion cell complex thickness seems to correlate better with functional disability in MS than RNFL thickness

PARKINSON’S DISEASE

Parkinson’s disease

- Second most common neurodegenerative disorder
- Characterized by
  - Resting tremor, bradykinesia and rigidity
- In the retina:
  - Dopamine is released by amacrine cells in the INL
    - Project into IPL

OCT findings

- RNFL
  - Decreased without evidence of correlation between disease severity or duration
- Diffuse macular thinning
  - Increased with disease progression
- Ganglion cell/inner plexiform layer
  - Increased thinning with disease duration
  - May be able to better predict damage in Parkinson’s disease
  - Potential issues with imaging in Parkinson’s disease?
Alzheimer's disease

- Progressive degenerative disease
  - Amyloid plaques & neurofibrillary tangles
- The most common cause of dementia
  - Affected population doubles every 20 years
- RNFL thinning may be the earliest sign of damage
  - Even in the absence of hippocampal damage
OCT findings

- Diffuse RNFL thinning which increases in moderate-advanced disease
- GCC may be reduced
  - Decreased grey matter volume in occipital and temporal lobes associated with decreased GCC thickness

Microvascular role

- MV disease contributes to dementia
- Clinical examination:
  - Theoretically may be able to appreciate venous branching asymmetry
    - Amyloid deposition from CNS to retina results in BV wall destruction
- Role of OCTA?

Looking ahead

- No longitudinal studies of disease process using OCT
  - Need for further validation and comparison with other biomarkers
- Caution is recommended in interpretation of OCT in patients with diagnosed or suspected neurodegenerative disease
- GCC could potentially be a biomarker of choice for disease diagnosis, severity and progression in neurodegenerative disease

May all your palsies be isolated

LIVE LONG AND PROSPER