Diagnosis and Management of Neuro-ophthalmic Disease: Rules, Exceptions to the Rules, and Exceptions to Exceptions to the Rules

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Dear Colleagues:
This course is designed to bring you the latest information regarding management of retinal and uveal conditions. I have included in this handout some key points regarding these clinical entities to satisfy the course requirements, however I vastly prefer to have an engaging dialogue with the audience – this cannot unfortunately be encapsulated in a handout. Please realize that these “notes” are neither exhaustive nor organized consistent with our presentation. They simply represent some facts about the entities which I may or may not cover.

I hope you understand my philosophy and enjoy the program!

Diagnoses – in Alphabetical Order:

| Diagnosis: Benign episodic pupillary mydriasis |

  **Signs and Symptoms:**
  - Episodic unilateral mydriasis
    - Lasts minutes to weeks
    - Accompanied by blurred vision and headache
    - Young healthy females predominate
    - Peculiar sensations about affected eye
      - Often progresses to headache
      - Not typical migraine
      - Defective accommodation
      - Lid and motility defects not present
      - Extensive medical testing unremarkable
Pathophysiology:
- Increased sympathetic activity?
  - Reverse Horner’s syndrome? Not likely
- Pupil paralysis following migraine?
  - Tends to last longer – not likely
  - No ophthalmoplegia
- Segmental spasm of iris dilator muscle?
  - Pupil round, so not likely
- Pharmacologically dilated?
  - Parasympatholytic – no reactivity whatsoever
  - Sympatholytic – can mimic and must be ruled out
- Anisocoria greater in bright light than dim
  - Parasympathetic dysfunction
    - Not an aneurysm
    - Edinger-Westphall lesion?
- Migraine variant – most likely etiology
- Treatment – none except to avoid unnecessary testing

Diagnosis: Carotid cavernous sinus fistula

Fistula:
- Rupture of intracavernous portion of internal carotid artery (ICA) or meningeal branch
  - Meningohypophyseal, McConnell’s Capsular, or Inferior Cavernous artery
- Mixing of high pressure oxygenated blood into low pressure deoxygenated venous system

Fistulas: Classification
- Hemodynamically
  - High flow (ICA rupture) or low flow (meningeal branch)
- Angiographically
  - ICA or meningeal branches ruptured
- Etiology
  - Traumatic (ICA rupture) or spontaneous (meningeal branch)
    - Theorized that there are small aneurysms on meningeal branches in hypertensive, middle age females which rupture and lead to low flow fistula

Carotid Cavernous Sinus Fistula: Signs and Symptoms
- Increased venous pressure
- Orbital congestion
- Proptosis (pulsatile)
- Corneal exposure
• Arteriolization of conjunctival and episcleral vessels
  • “Caput Medusa”
    • Medusa’s head of snakes
• Orbital bruit
• Myopathies and cranial neuropathies with diplopia and ophthalmoplegia
• Secondary glaucoma from increased episcleral venous pressure
  • High-pressure arterial blood increases pressure in venous system.
  • Blood backs up and moves toward eye through superior ophthalmic vein
  • Episcleral veins increase pressure
    • IOP always exceed episcleral venous pressure

Carotid Cavernous Sinus Fistula: Management
• Vision threatening – not life threatening
• Spontaneous etiology – spontaneous resolution
  • Wait it out for a few months – monitoring is most prudent
• Traumatic
  • Clipping and ligation
  • Balloon or particulate embolization
• Glaucoma difficult to manage
  • Prostaglandin analogs most suited because they decrease IOP independent of episcleral venous pressure

Diagnosis: Ischemic vascular CN VI palsy

CN VI Palsy:
• Hallmark sign is horizontal diplopia, greater at distance, with an Abduction deficit
• CN VI is the most common ischemic vascular palsy seen
• 25% of cases remain without diagnosis

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

**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 almost always indicative of increased intracranial pressure (ICP). Must do MRI. Papilledema also commonly seen in association

**CN VI Palsy: Causes in Children**
- Trauma (40%)
- Neoplastic disease (33%)
- Vascular disease (<5%)
- Idiopathic/presumed viral (12%)

**CN VI Palsy: Management in Children**
- Examine at 2 week intervals
- Pediatric neurologist referral

**CN VI Palsy: Causes in Adults**
- Vascular disease
- Neoplasm
- Trauma
- Demyelinating disease (MS)
- Giant cell arteritis
- Spread if inflammation from adjacent sinuses

**CN VI Palsy: Management in Adults**
- Young adults: rule-out HTN, DM, collagen vascular disease, syphilis, Lyme, MS
- Older adults: consider inflammatory and infectious etiologies as well
- Order: CBC, FBS, ANA, FTA-ABS, Lyme titre, ESR
- Neuro-radiological studies (CT, MRI)
  - 15-40yrs: always indicated, esp. if palsy is complicated, progressive, or unresolved
  - Over 40 years: if suspect vasculogenic cause, it will resolve within 90 days. If unresolved at day 91 - SCAN!

**CN VI Palsy: Pain**
- Ischemic vascular infarct
- Gradenigo’s syndrome
- Nasopharyngeal carcinoma
- Rise in intracranial pressure (ICP)
- GCA (over 65 yrs)
Diagnosis: CN IV palsy secondary to sinus infection

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?
- 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: 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 scan
- 40-30-20-10 rule:
  - 40% traumatic
  - 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 (?)

Diagnosis: Craniopharyngioma
- Craniopharyngiomas are benign tumors
- Arise from vestigial remnants of Rathke’s pouch
- Peak incidence
  - 1st two decades
  - 50’2-70’s
- Children are likely to experience endocrine dysfunction
- Adults have visual abnormalities
• Craniopharyngioma compresses optic chiasm from above
  • Inferior bitemporal quadrantanopsia
• MRI superior to CT in diagnosis
  • Delineates extent of adjacent involvement of cavernous sinus and other structures
  • CT important in determining calcification of tumor and cyst formation
• Treatment is craniotomy and surgical resection

**Diagnosis: Cryptogenic optic neuropathy – likely infiltration from lymphoma**

• **Infectious/infiltrative optic neuropathy**
  • **Infectious**
    • Syphilis
      • Retrobulbar, papillopathy, neuroretinitis, perineuritis
      • Retrobular, bulbar: severe vision reduction
      • Perineuritis has normal vision, normal CSF pressure, normal MRI
    • Lyme
      • Mimic syphilitic optic neuropathy
  • Toxoplasmosis, HIV/AIDS, CMV
    • Destructive to vision
  • Neuroretinitis
    • Good visual function
    • Typically benign lymphoreticulosis (cat scratch disease)
    • Gram-negative bacillus
  • **Infiltrative**
    • Sarcoidosis
    • Systemic lupus erythematosus
    • Leukemia
    • Lymphoma
    • Carcinoma

**Diagnosis: CVA – infarct of right occipital lobe**

**Homonymous Field Defect:**
• Represents post-chiasmal pathway lesion
• Congruity often dictates lesion
  • Greater congruity = more posterior lesion
  • Complete homonymous defects have no localizing value
• Possible etiologies include;
  • Cerebral infarct (CVA)
  • Traumatic brain injury
  • Compressive space occupying lesion
    • Neoplasm, cerebral hemorrhage, vascular malformation
  • Demyelinating plaque
  • Abscess or toxic disorder (rare)
Homonymous Field Defect: Management

Acute Intervention:
- Full cardiac/cerebral vascular evaluation if CVA
- Neurologic screening

Visual Management:
- Visual rehabilitation if patient has difficulty adapting
- Low vision devices?

Medical management:
- Control underlying condition
- Patient education – curtail contributory factors
  - Tobacco, obesity

Diagnosis: Optic neuritis from multiple sclerosis

- **Inflammatory / Demyelinating Optic Neuropathy**
  - Referred to clinically as “optic neuritis” or “papillitis”
  - Demyelinating optic neuropathy is a unique subset of this category, since it is not truly an inflammatory condition
  - Unilateral
  - Presents with sudden onset vision loss, pain on palpation and eye movements
  - Optic nerve is hyperemic; juxtapapillary retina is mildly edematous and may show exudate; vessels are engorged and distended; posterior vitritis likely
  - Visual fields may demonstrate arcuate, altitudinal, or cecocentral scotomas
  - Numerous systemic etiologies (e.g., multiple sclerosis)
  - Management involves targeted systemic workup (hematology/serology and radiology) with MRI (most crucial) to r/o multiple sclerosis

Diagnosis: Orbital infiltration by metastatic breast disease masquerading as CN III primary aberrant regeneration

Cavernous sinus anatomy
- CN III, IV, V1, VI, oculosympathetics, internal carotid artery
- Superior and inferior ophthalmic vein drains eye and adnexa to sinus and out via inferior and superior petrosal sinus to jugular vein

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 Benedikt’s syndrome.
  • A lesion which involves the CN III fascicles as they pass through the Corticospinal tract will result in a CN III 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:

<table>
<thead>
<tr>
<th>ADULTS</th>
<th>CHILDREN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Undetermined (24%)</td>
<td>Congenital (44%)</td>
</tr>
<tr>
<td>Aneurysm (21%)</td>
<td>Trauma (16%)</td>
</tr>
<tr>
<td>Ischemia (18%)</td>
<td>Inflammation (11%)</td>
</tr>
<tr>
<td>Trauma (13%)</td>
<td>Miscellaneous (11%)</td>
</tr>
<tr>
<td>Neoplasm (12%)</td>
<td>Neoplasm (10%)</td>
</tr>
<tr>
<td>Miscellaneous (12%)</td>
<td>Aneurysm or ischemia (6%)</td>
</tr>
</tbody>
</table>

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). This typically is the most identifiable sign in primary or secondary aberrant regeneration
- 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 within subarachnoid space, 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.