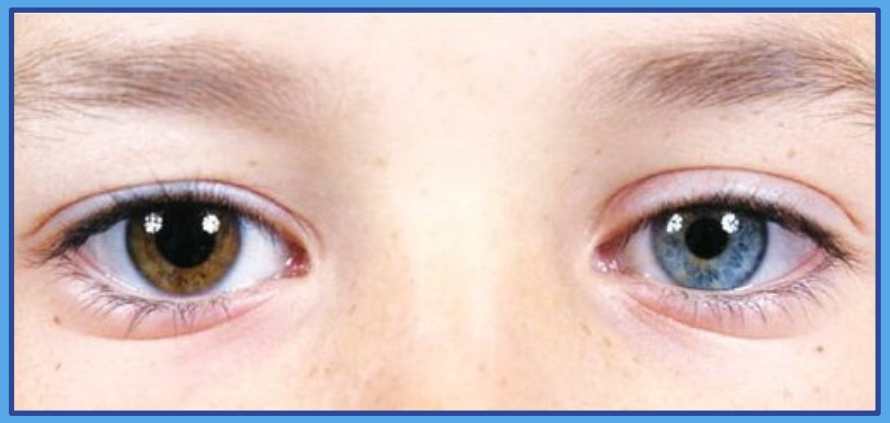
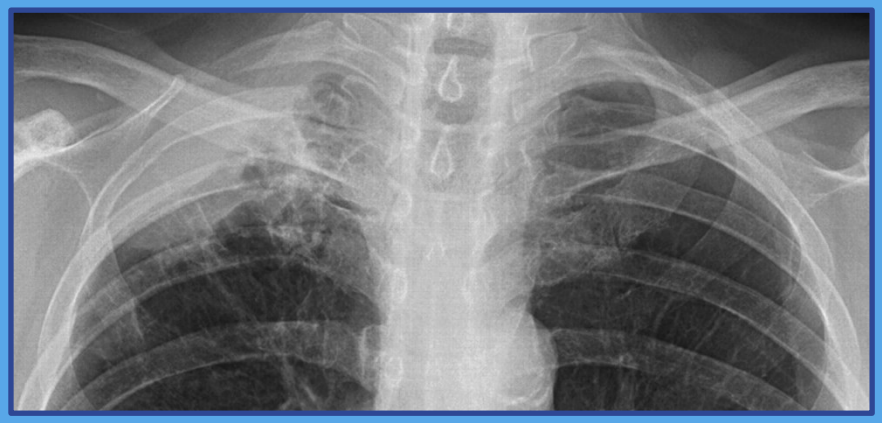




Horner Syndrome

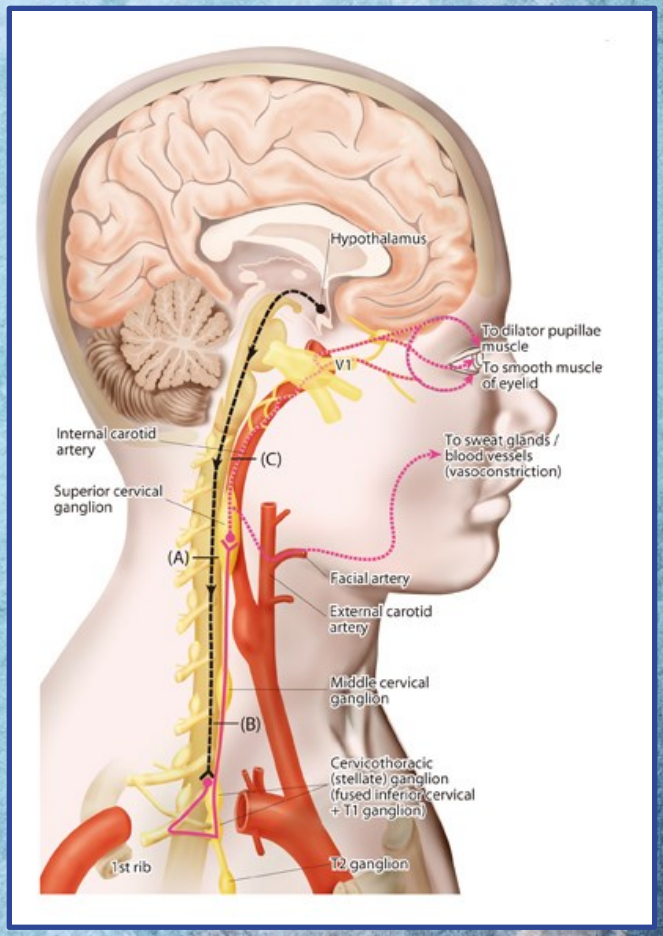
Ptosis, miosis, and a whole lot more!

Rick Trevino, OD, FAAO

Indiana University School of Optometry

Horner Syndrome

- Online notes
  - richardtrevino.net
- Email me
  - rctrevin@iu.edu
- Disclosures
  - None



Horner Syndrome

- Horner syndrome (HS) is oculosympathetic paresis
  - Loss of sympathetic innervation to the eye
- **No major loss of ocular function**
  - Vision and pupil reflexes remain intact
  - The disorder is largely asymptomatic and often clinically subtle
  - *Little need for therapeutic intervention*
- HS may be caused by lesions associated with significant **morbidity and mortality**

Horner Syndrome

Suspect HS in any patient with

anisocoria

and

normal pupil reflexes

Need to differentiate HS from ***physiologic anisocoria***

Horner Syndrome

Stepwise approach to suspected HS

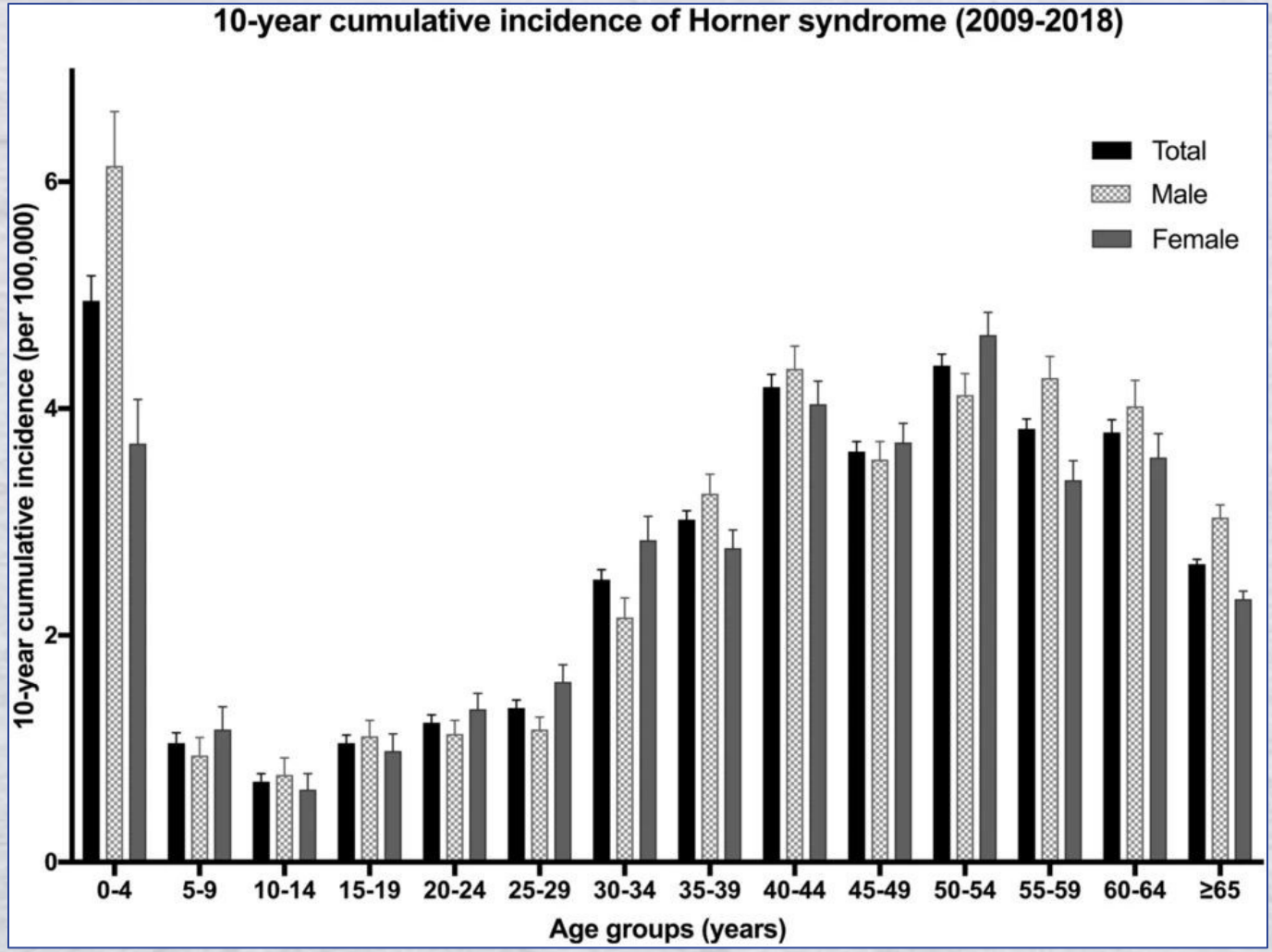
1. Aniso in light/dark 

2. Ask about high risk features
   (shoulder pain, neck pain, headache, TIA, smoker, etc)
3. Dilation lag 

4. Apraclonidine 

5. CT/MRI Angiography 

Horner Syndrome



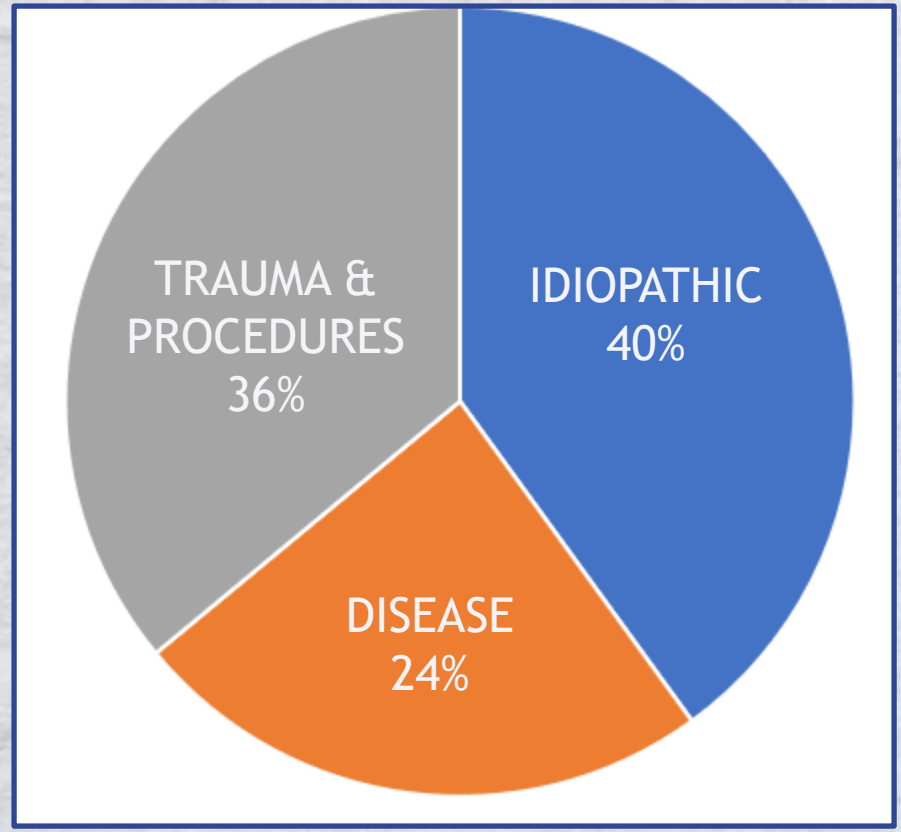
Incidence of HS in a population-based study

Adult HS most often appears between 40-60yo with no sex predilection

PMID: 33090271

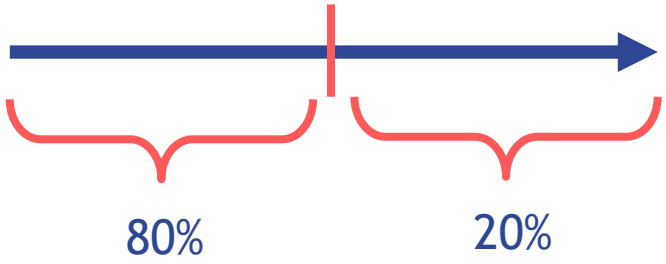
Horner Syndrome

Causes of HS in Korea



HS caused by Disease

80% of disease conditions producing HS were known prior to the diagnosis of HS

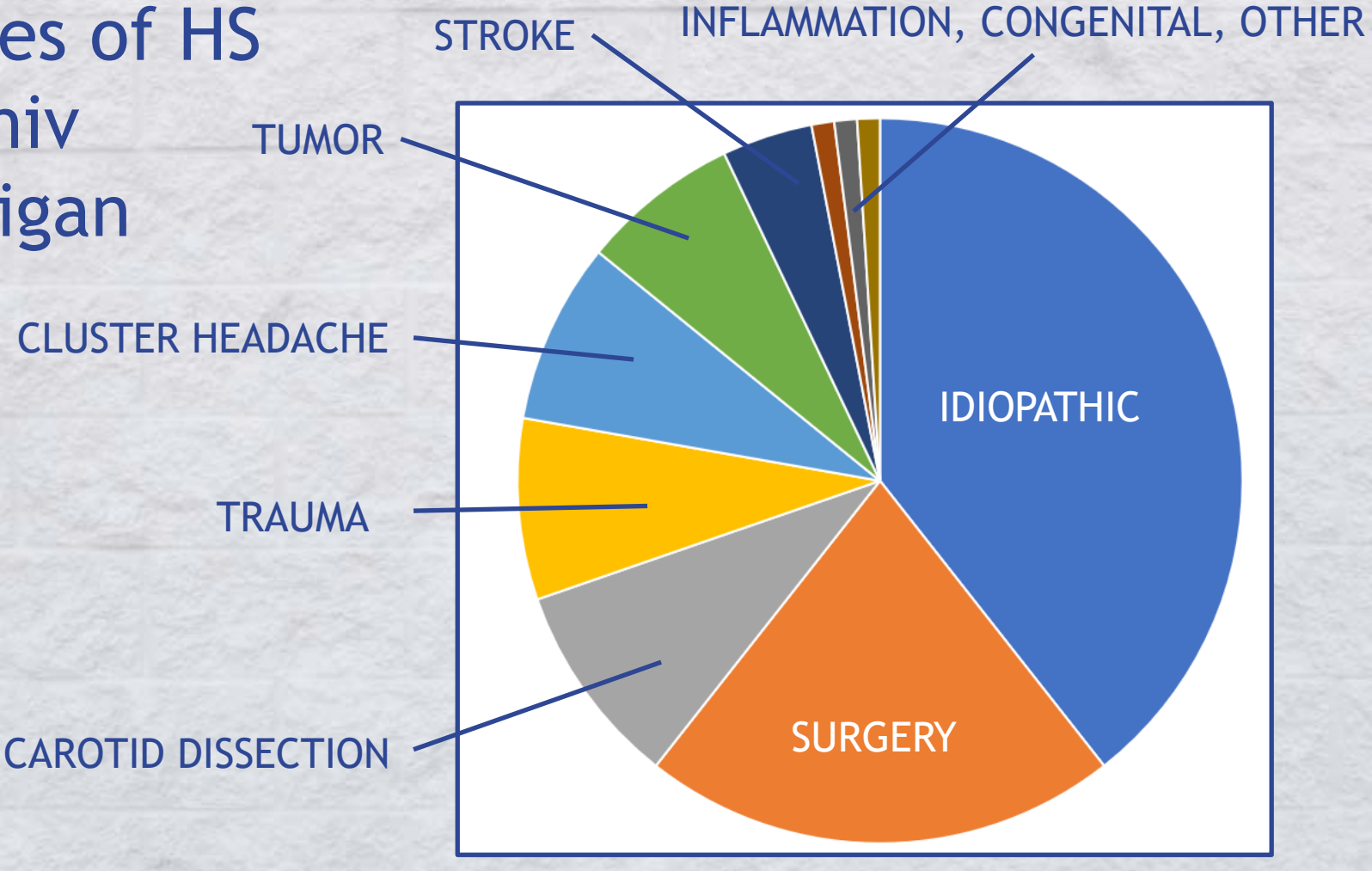


TIME

PMID: 33090271

Horner Syndrome

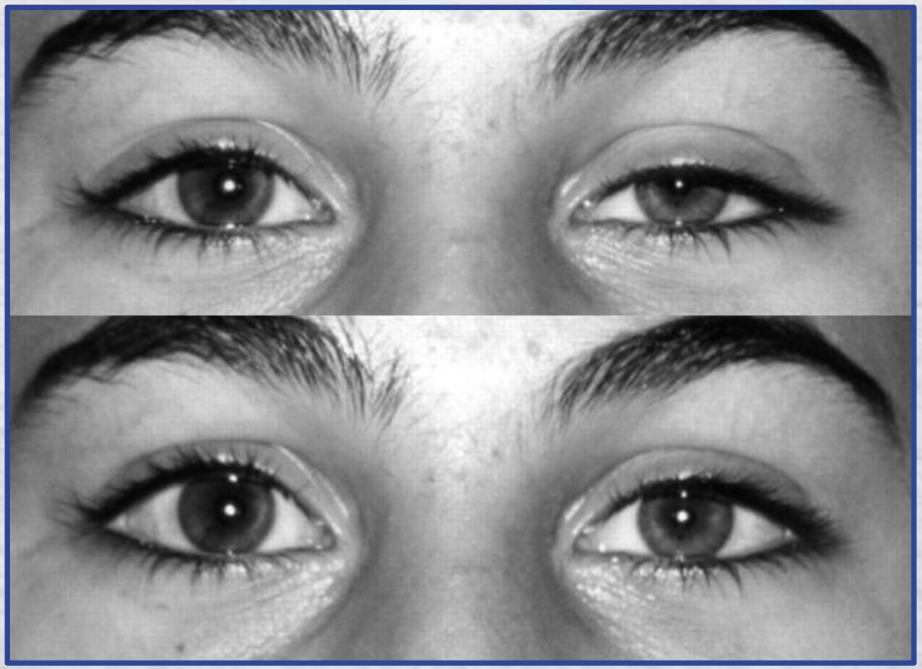
Causes of HS at Univ Michigan



PMID: 31609831

Horner Syndrome

- Therapy for HS
  - Treatment of the underlying cause
  - **Cosmetic concerns** secondary to ocular manifestations
  - Ptosis
    - Phenylephrine 2.5% eye drops OU
    - Blepharoplasty
  - Heterochromia
    - Colored contact lenses



PMID: 9893610

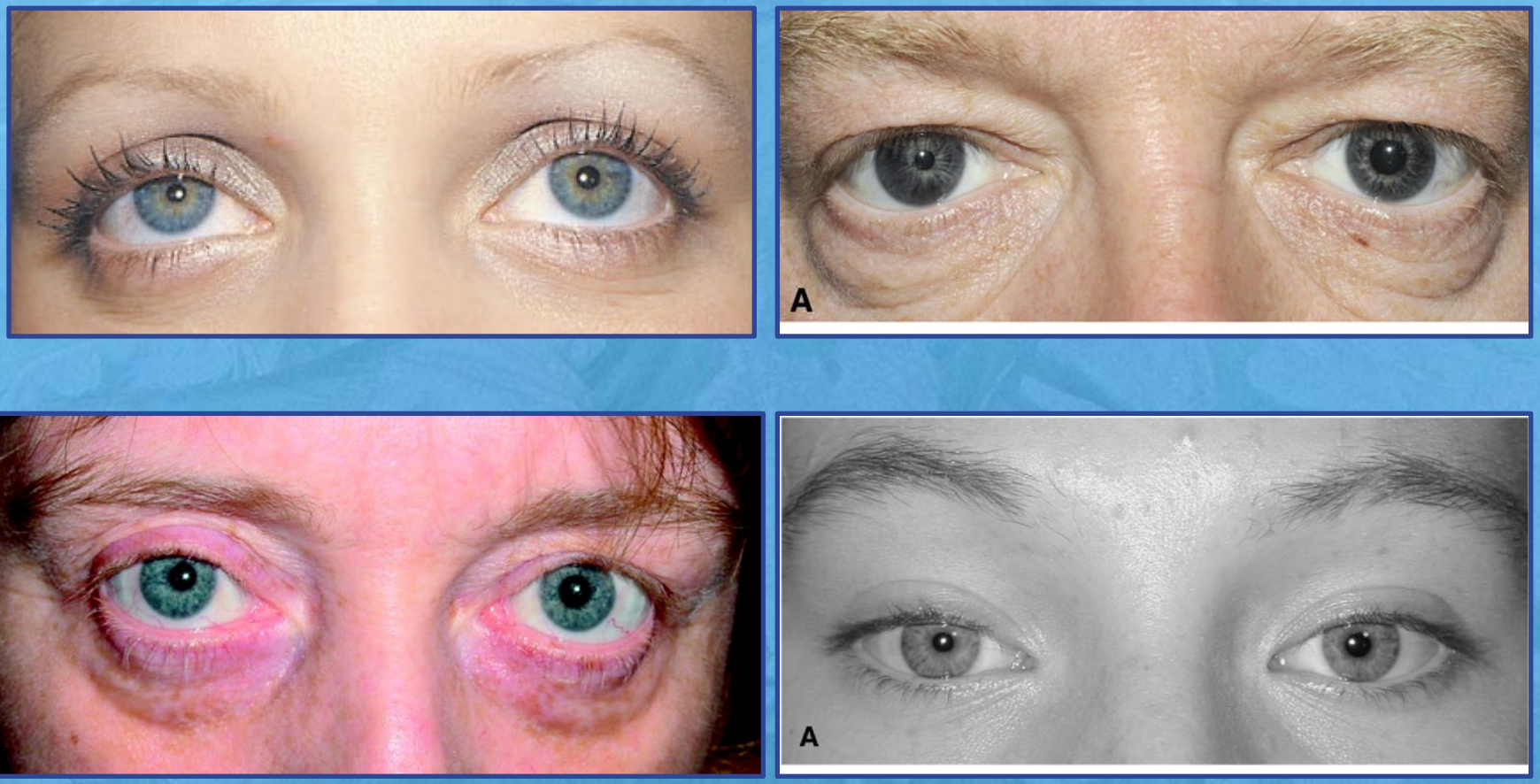
Features of HS

1. Ptosis
2. Miosis
3. Facial anhidrosis/hypohidrosis
4. Transient conjunctival hyperemia
5. Transient ocular hypotony
6. Increased amplitude of accommodation
7. Depigmentation
8. Slight elevation of lower lid
9. Apparent enophthalmos

Features of HS

- Ptosis
  - A mild drooping of the upper lid (~1-3 mm)
    - Subtle and easily missed
    - Can be mistaken for normal facial asymmetry
  - Due to loss of innervation of Muller's muscle
  - Ptosis is never more than a few millimeters
  - Ptosis may be variable depending upon degree of patient fatigue
  - **Ptosis may be absent in 10%-20% of cases***

* PMID: 20212203



Several examples of Horner syndrome. The right eye is affected in each case. Note a mild ptosis is more evident in some patients than in others

Features of HS

- Miosis
  - Small decrease (typically ≤1.0mm) of the diameter of the affected pupil
  - *Normal light reactivity*
  - Anisocoria variable and may be intermittent*
    - May vary with alertness of patient
  - The miotic pupil is still within the range of normal pupil sizes – **the affected pupil is <u>not</u> abnormally small**

* PMID: 17204927

Features of HS

- Miosis
  - Anisocoria is greatest under dim illumination
  - **Dilation lag:** Slow dilation in dark[1]
    - Normal: Takes 5-6s to fully dilate in darkness
    - HS: Takes 10-12s to fully dilate in darkness
  - Diagnostic for HS (avoids need for pharmacologic testing) **but it is not always present**[2]
    - Best assessed with photographs or video

1. PMID: 1218186
2. PMID: 17386292

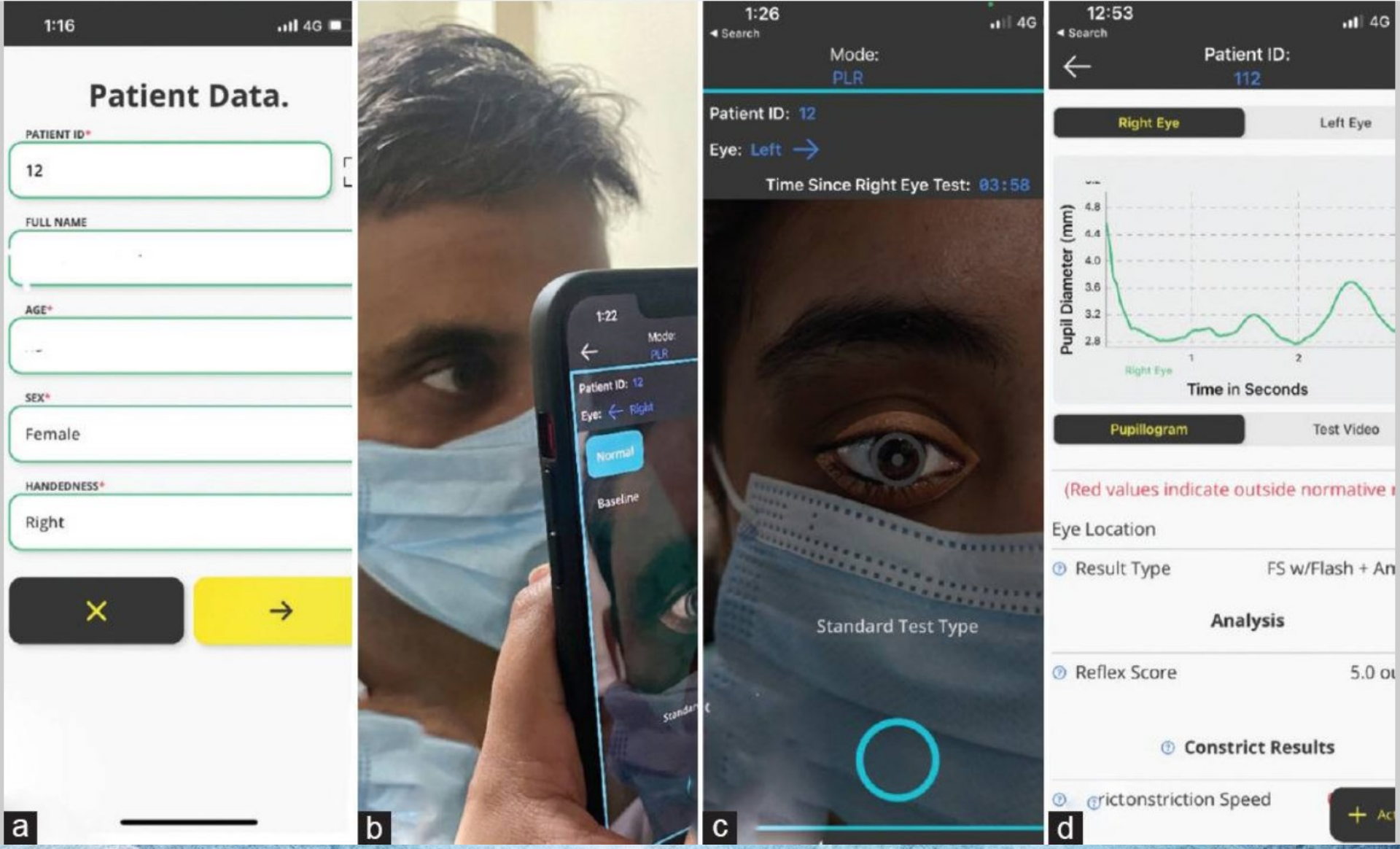
How to test for dilation lag

1. Room lights up bright
2. Patient fixates a distance target
3. Illuminate patient's eyes tangentially from below using penlight
4. Technician turns off room lights - *Noise optional but accentuates finding*
5. Observe both pupils simultaneously for 15-20 sec
6. Look for an initial increase in anisocoria followed by decreasing anisocoria
7. Repeat 2-3 times

Document dilation lag

A. Take baseline photos/video with lights on
B. Options for documenting pupils in the dark
    1. Infrared camera – Affordable “night vision goggles” marketed to hunters
    2. Use video camera with “night mode”
    3. Flash photo with “red eye” feature turned off
C. Repeat 2-3 times
D. Playback video or compare photos searching for slow dilation of affected eye compared to fellow eye

Dilation Lag

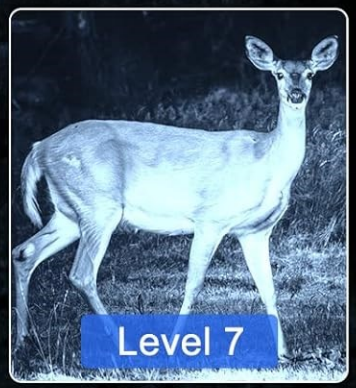


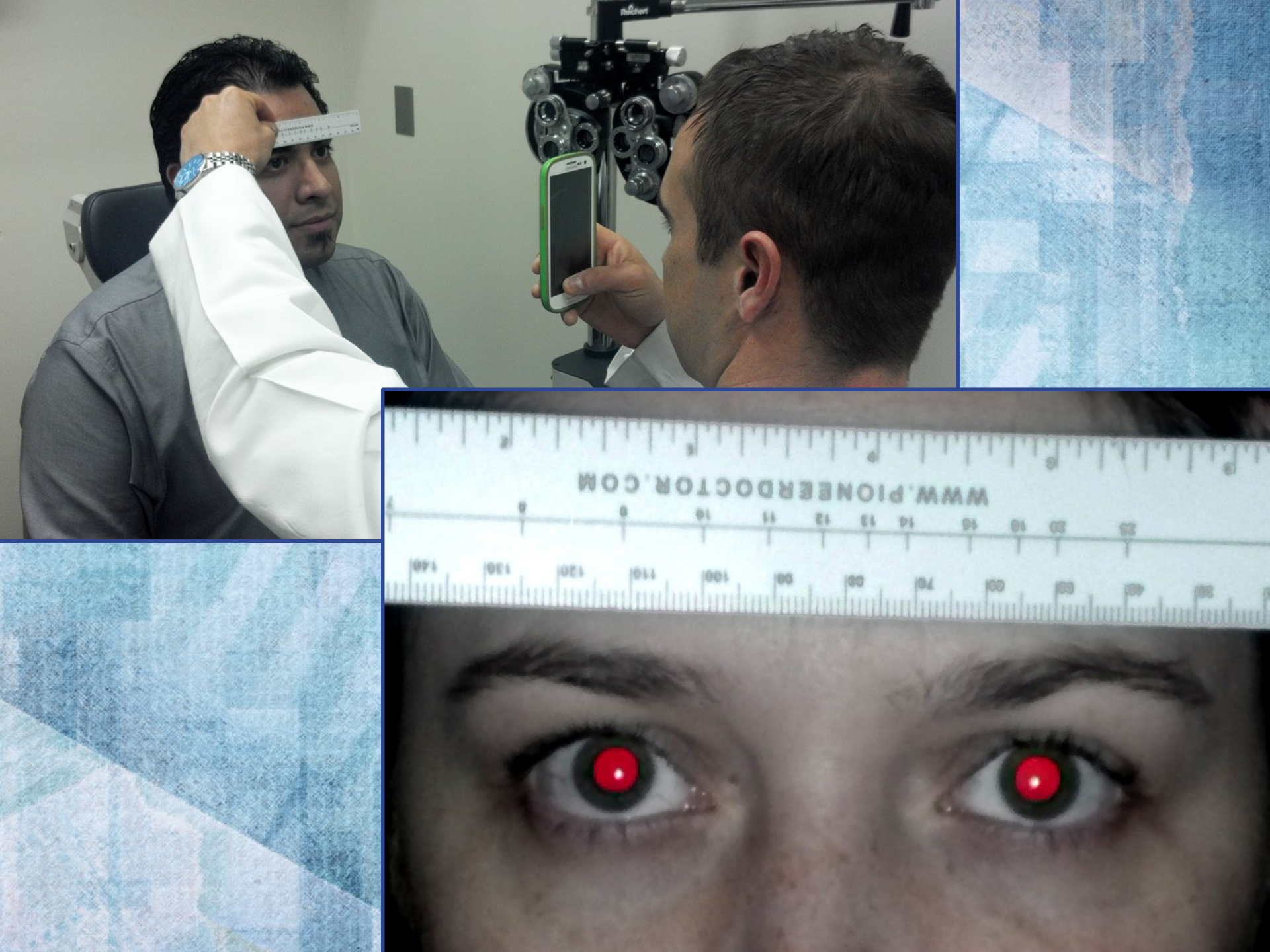
Smartphone pupillometry

No reliable apps available at present time

PMID: 38504836

7 Levels Adjustable IR

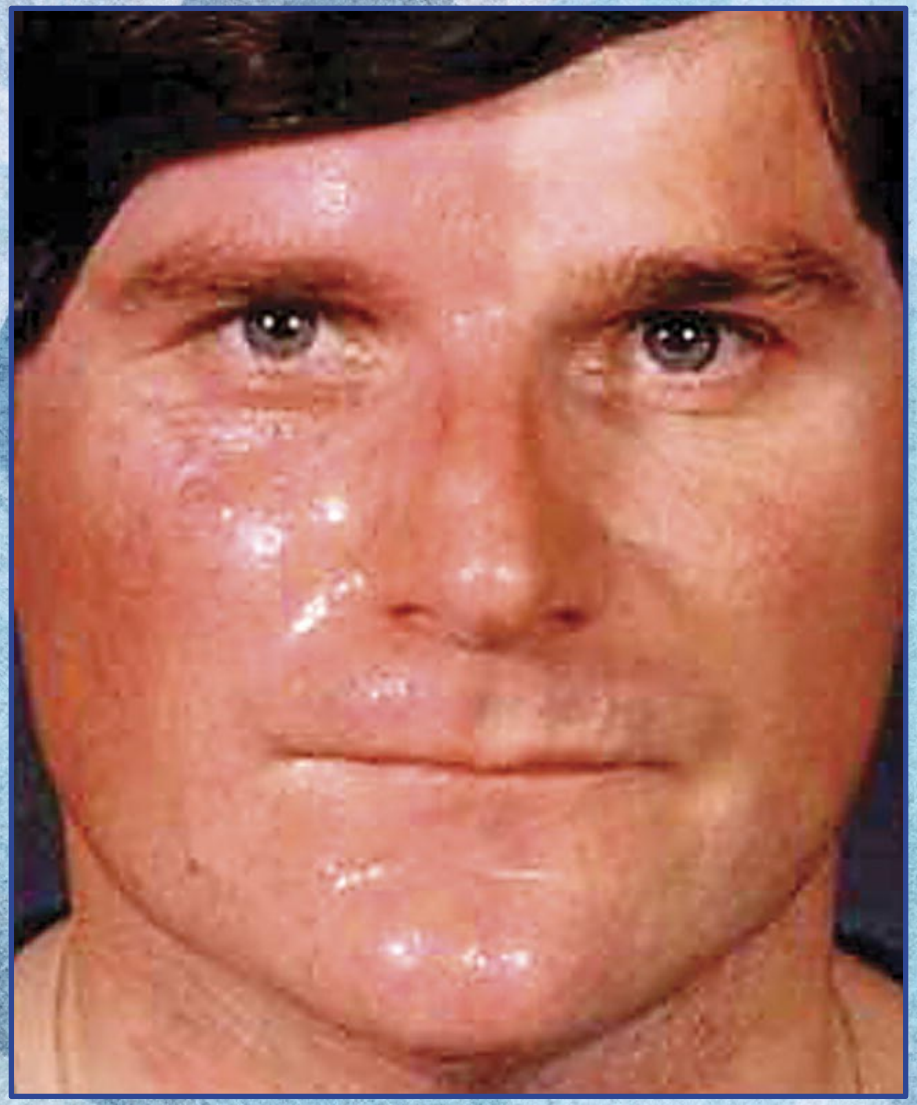


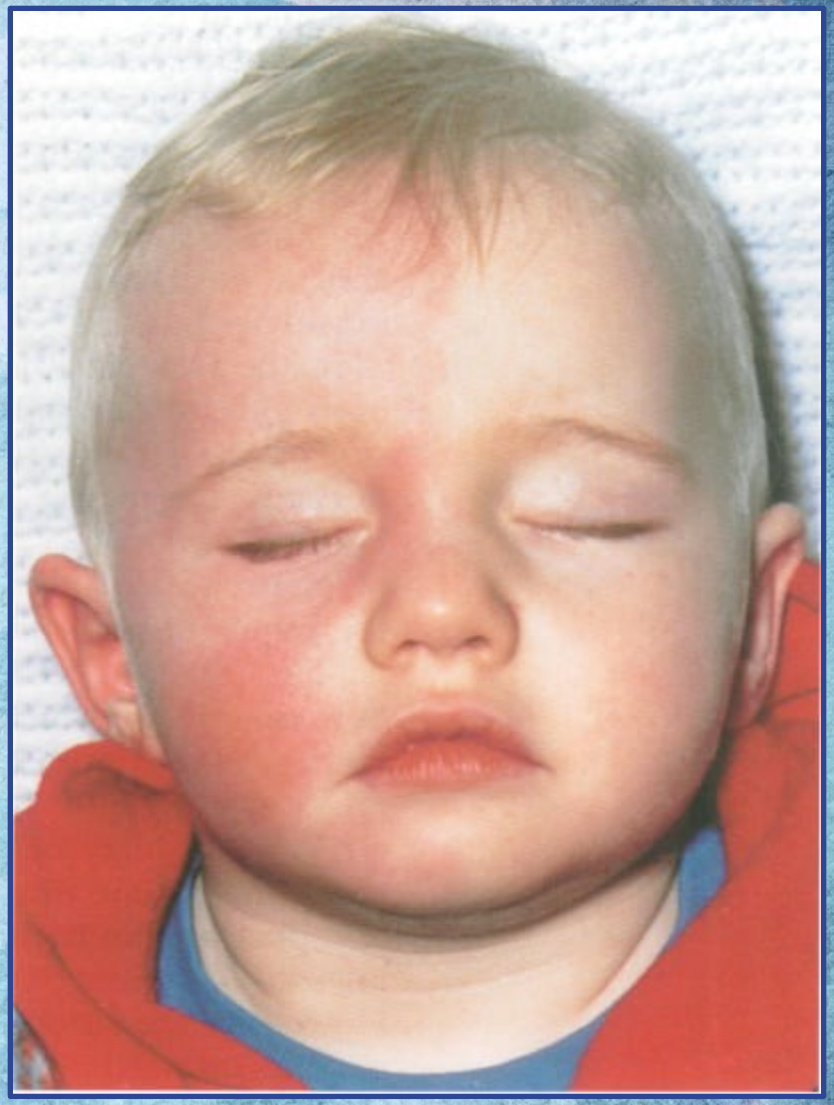

Reichert
WWW.PIONEERDOCTOR.COM

Features of HS

- Facial anhidrosis
  - Decreased or absent sweating of the face.
    - May affect half the face or only a small patch on forehead (*Localizing value*)
  - **Difficult and impractical to assess clinically**
    - Use of starch iodine or a friction test
  - Harlequin sign: Absence of facial flushing on the affected side*
    - Supersensitivity of denervated blood vessels with resultant vasoconstriction

*PMID: 18769278





Harlequin sign: Absence of flushing on affected side of the face

Features of HS

- Transient conjunctival hyperemia
  - Acute loss of vasomotor control may produce a transient dilation of conjunctival blood vessels
- Transient ocular hypotony
  - 2-4 mmHg decrease in IOP lasting about 6 weeks
  - Mechanism may be loss of sympathetic innervation of the ciliary body

PMID: 929803

Features of HS

- Increased amplitude of accommodation
  - 0.5 to 1.5 D greater accommodation
  - Mechanism may be loss of sympathetic inhibitory accommodative inputs
- Iris Depigmentation
  - **Heterochromia** is typically seen if the onset is congenital or prior to the age of 2 years.
  - Rare reports of heterochromia developing in adults with long-standing acquired HS*
  - Sympathetic innervation required for normal melanin production in the iris melanocytes

*PMID: 1602322

Congenital HS of the left eye. Note heterochromia secondary to hypochromia of the affected iris

PMID: 16319395

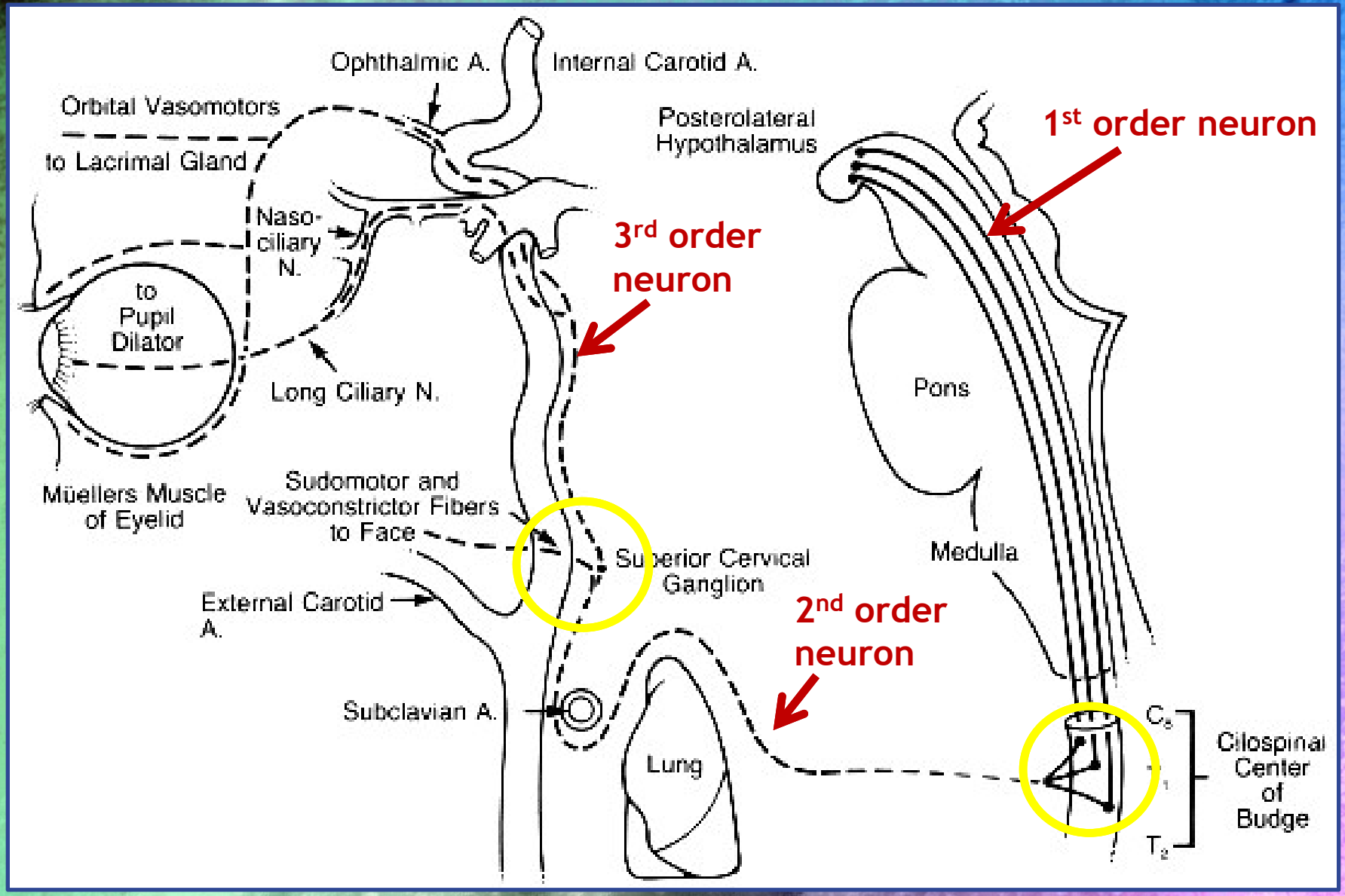
Features of HS

- Slight elevation of lower lid
  - "Upside-down ptosis"
  - Loss of sympathetic innervation to the smooth muscle of the lower lid
- Apparent enophthalmos
  - Narrowing of the palpebral fissure may give the impression of enophthalmos
  - No true enophthalmos occurs secondary to HS

PMID: 929803

Features of HS

1. Ptosis
2. Miosis
3. Facial anhidrosis/hypohidrosis
4. Transient conjunctival hyperemia
5. Transient ocular hypotony
6. Increased amplitude of accommodation
7. Depigmentation
8. Slight elevation of lower lid
9. Apparent enophthalmos



Adapted from: 7387512

Sympathetic Pathway

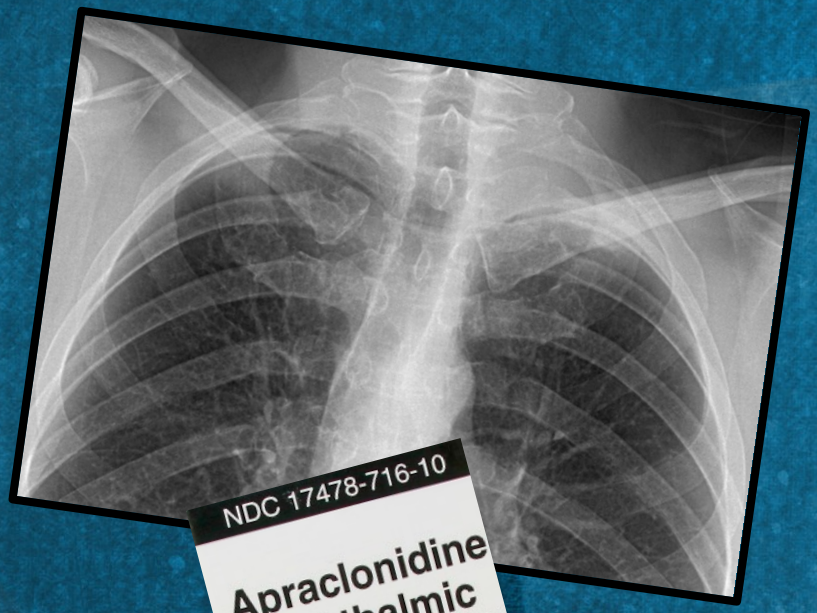
Most common

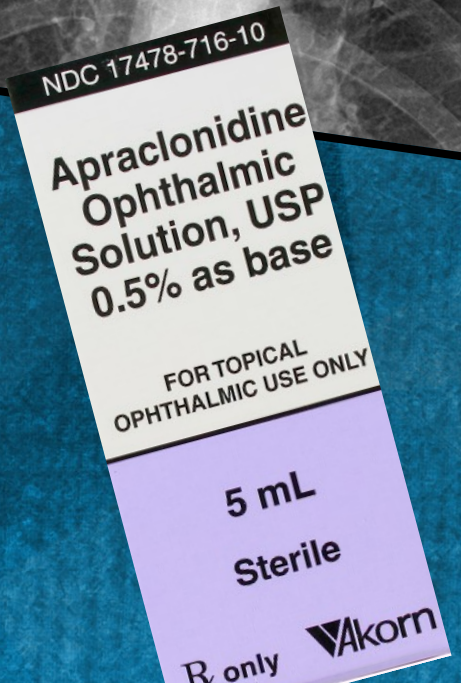
Study	#	1st (%)	2nd (%)	3rd (%)
Karti (2022)	40	45	45	10
Almog (2010)	36	28	44	28
Maloney (1980)	450	13	43	44
Grimson (1979)	120	6	57	37
Keane (1979)	100	65	25	12
Giles (1958)	216	11	88	1

Preganglionic (2nd neuron) lesions tend to be the most common. Central lesions tend to be the least common, except in hospitalized settings. **Up to 80% of HS cases have no identifiable cause**

Diagnostic Evaluation

- History
- Physical exam
  - Pupils
  - Lids
- Pharmacologic studies
  - Diagnostic
  - Localization
- Radiographic evaluation
  - MRI or CT





History

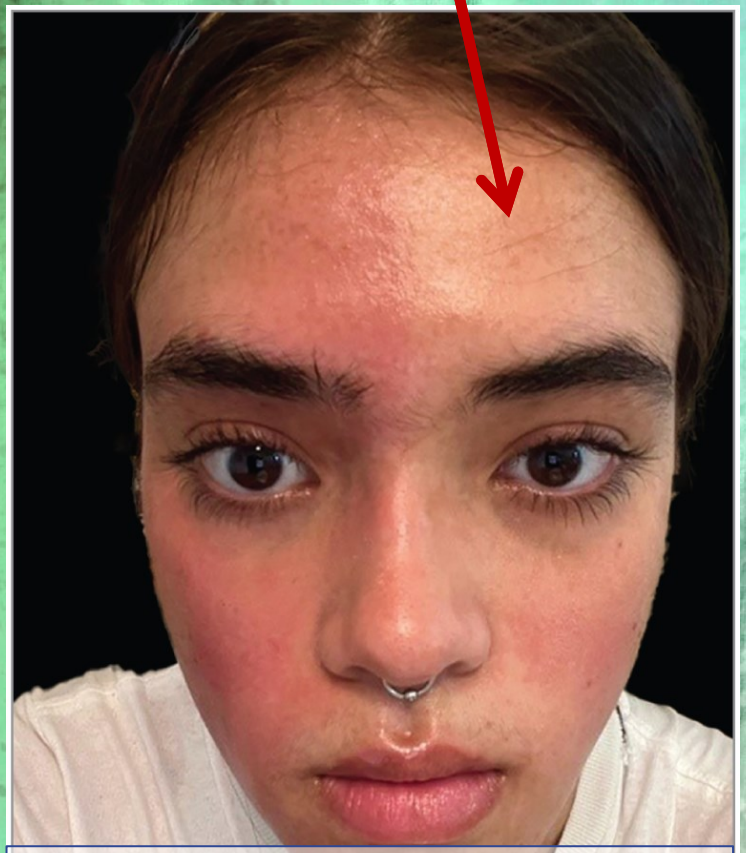
- *HS is usually asymptomatic*
  - Anisocoria or ptosis may be noticed by a friend or family member.
  - Incidental finding on routine examination
- If it can be established that isolated HS is long-standing (≥1yo) no further work-up may be warranted*
  - History, heterochromia, and photographs can help establish duration of condition
- **Acute onset necessitates search for underlying cause**

*PMID: 21918445

History

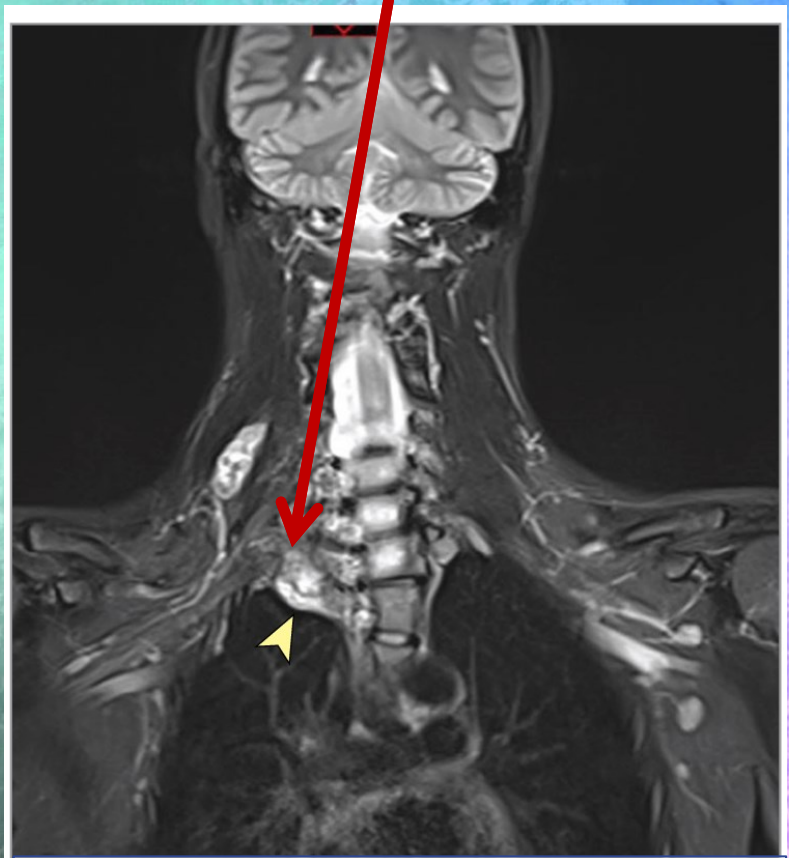
- ***Beware selfie-photo diagnostic confusion***
  - Android devices: Selfie images are saved in a mirrored format (left side of image is patient's left).
  - Apple devices: Selfie images are shown in mirrored format but saved in the traditional format (left is right).
- When reviewing patient's selfie photos, need to establish what is L/R in the images are being saved

Patient reports intermittent hemifacial pallor, and her selfie shows pallor on the right side of photo



Left Horners?

MRI reveals a tumor in the region of the right thoractic outlet producing a right-sided Horner syndrome with Harlequin sign



No! Right Horners

PMID: 37902734

History

- High risk features in patients with HS
  - *Pain in arm, shoulder, neck or face*
  - Acute onset
  - TIA
  - H/O malignancy
  - H/O neck trauma

These findings are suggestive of Pancoast tumor or carotid dissection

PMID: 23370415

Physical Exam

- Some patients with HS may <u>not</u> present with simultaneously occurring ptosis and miosis
- *It is important to **<u>not</u>** eliminate the possibility of HS when only miosis or only mild ptosis is seen*

PMID: 22784676, 20625060

Ptosis

- Ptosis is subtle and variable: ≤2mm
- Margin-reflex distance of 1.5 mm indicates 2–3 mm of ptosis (normal >2.5 mm)
- Normal levator function
- Dermatochalasis and orbital fat prolapse may masquerade as mild ptosis
- ***Congenital ptosis***: Fissure width increases on down gaze
- ***Pseudo-enophthalmos***: Elevation of the lower eyelid

PMID: 7425056

Anisocoria Evaluation

- Which is the abnormal pupil?
  - Identify signs of local disease
    - Synechias, sphincter tears, etc
  - Abnormal response to light
    - Suggests local defect or parasympathetic lesion
    - **Light response is normal in HS**
  - Degree of anisocoria in darkness and light

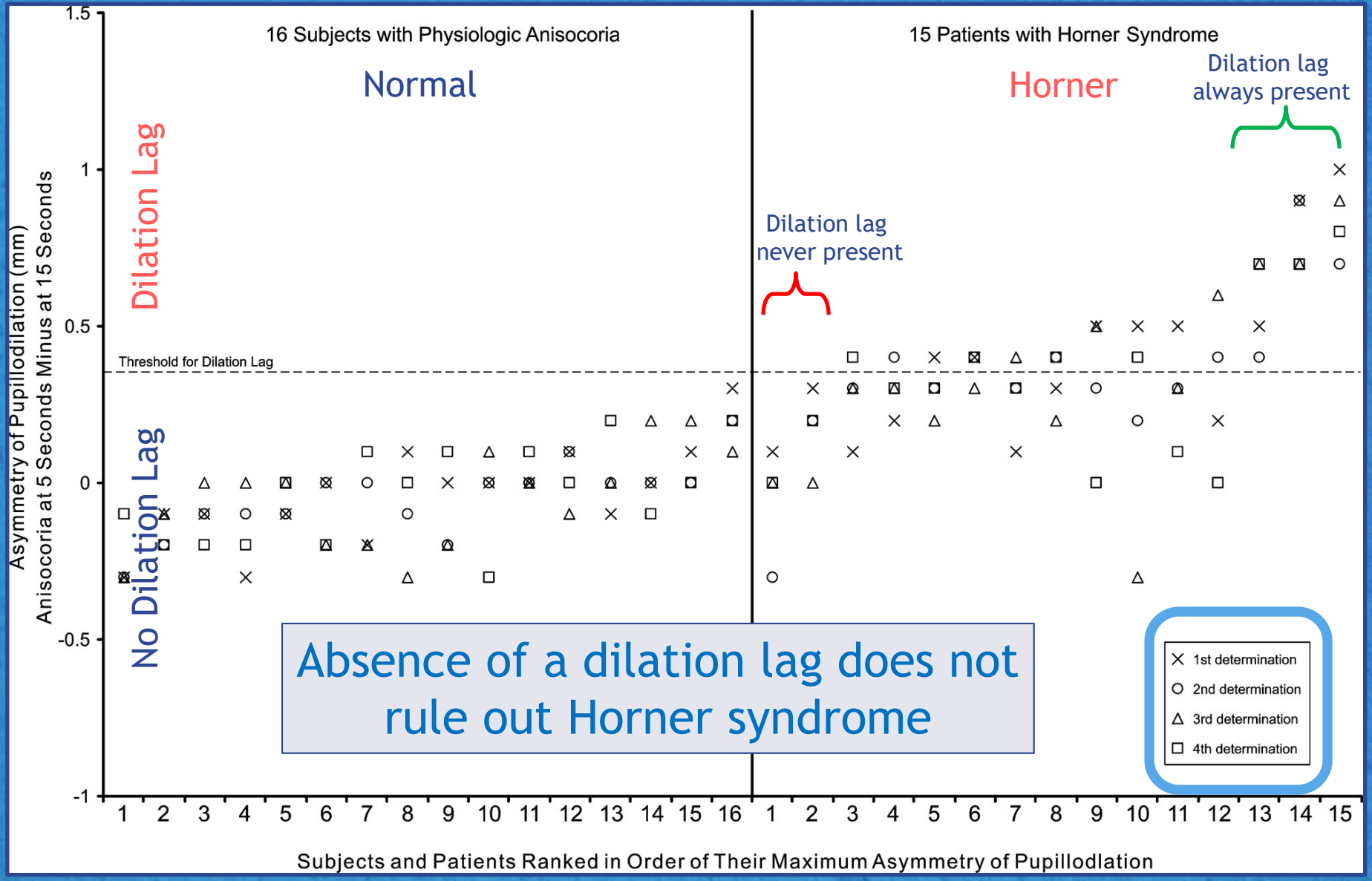
Horner syndrome →

    - Anisocoria greater in darkness: smaller pupil abnormal
    - Anisocoria greater in light: larger pupil abnormal

Anisocoria Evaluation

- Is the anisocoria pathologic?
  - ≈20% of normal individuals have anisocoria
  - Physiologic anisocoria is sometimes more apparent in dim light, simulating HS
  - ***Absence of a dilation lag is not evidence that the anisocoria is physiologic****
  - In the absence of dilation lag, use **pharmacologic testing** to differentiate physiologic anisocoria from HS

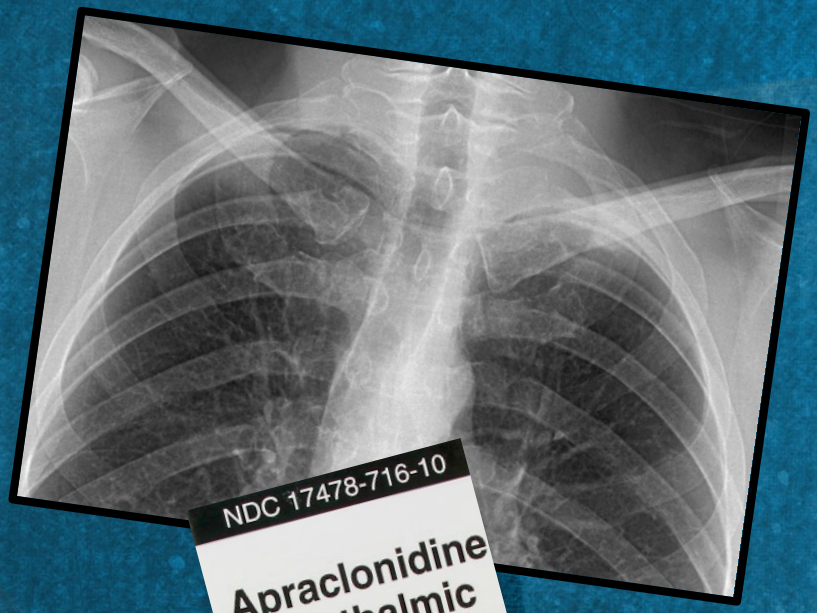
*PMID: 17386292

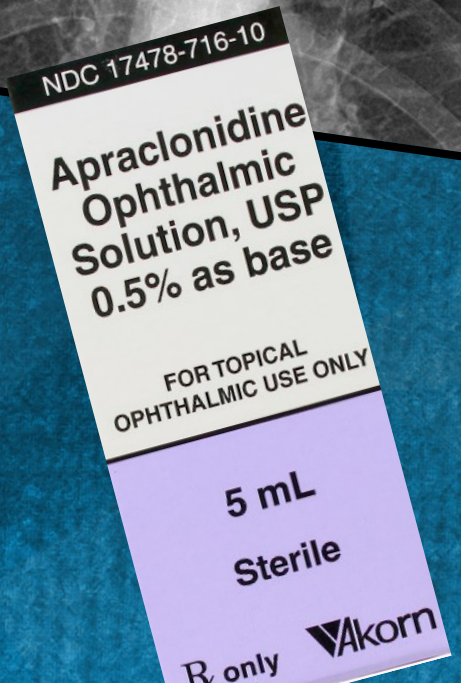


Crippa (2007): Scatterplot of calculated asymmetry of pupillodilation determined four times for 16 subjects with physiological anisocoria and 15 patients with Horner syndrome. Points above dotted line have asymmetry of >0.4 mm and thus meet criterion threshold used to define pupillary dilation lag. Dilation lag is only present among patients with Horner syndrome, but in most of these patients, it is only intermittently present over four recordings.

Diagnostic Evaluation

- History
- Physical exam
  - Pupils
  - Lids
- Pharmacologic studies
  - Diagnostic
  - Localization
- Radiographic evaluation
  - MRI or CT

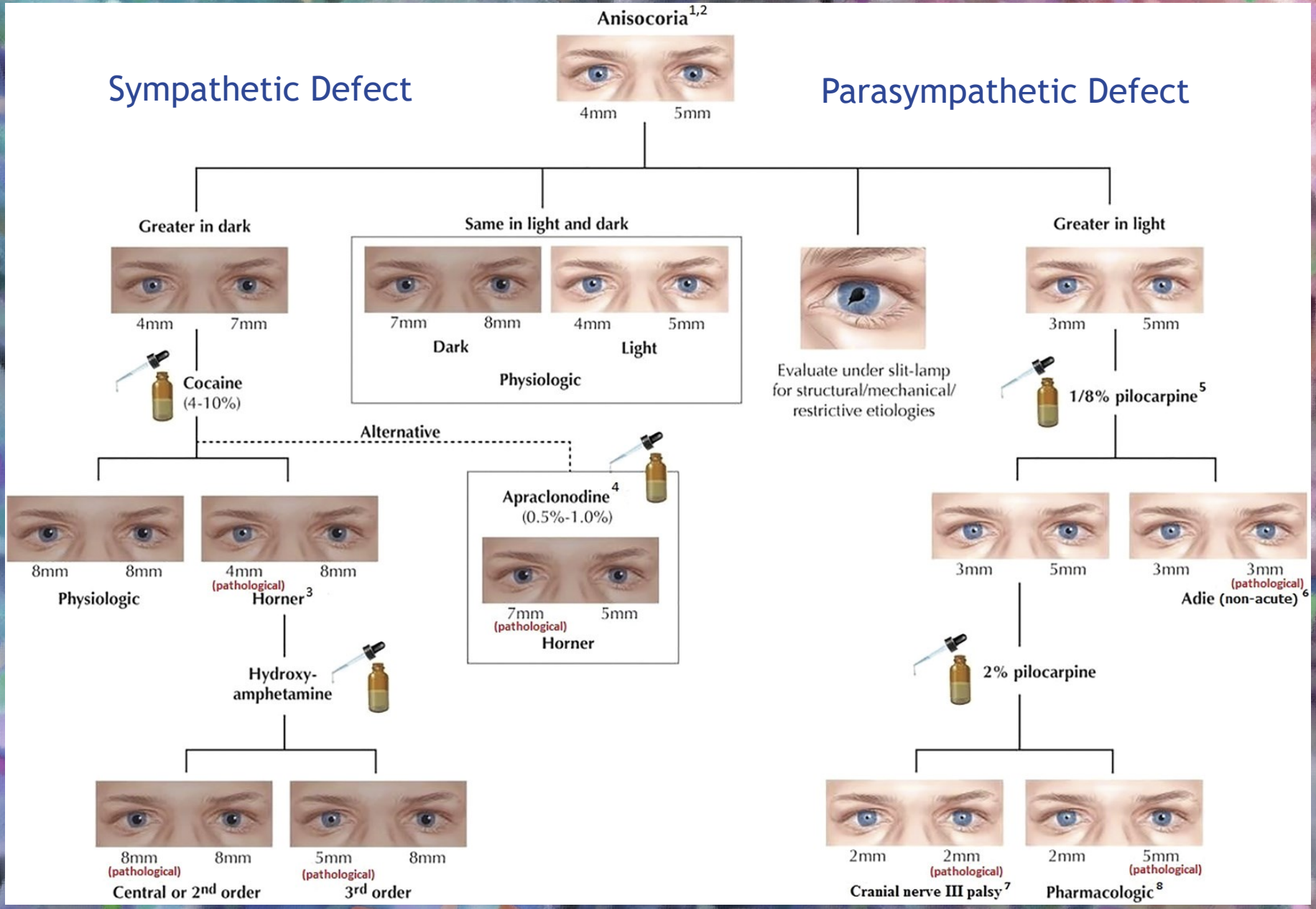




Pharmacologic Studies

- Used to confirm diagnosis and localize the lesion as preganglionic vs postganglionic
- **Shortcomings of pharmacologic studies**
  - Poor availability of reagents
    - Cocaine, hydroxyamphetamine
  - False positive and false negative rates
  - Time required for onset of denervation supersensitivity or depletion of neurotransmitter
  - Need for 1-2 day washout period between tests

PMID: 23370415, 20182196



PMID: 33208545

Pharmacologic Studies

- Cocaine
  - The "**gold standard**" for diagnosis of HS*
    - Alternatives: apraclonidine, documentation of dilation lag plus heterochromia in congenital HS
  - 10% cocaine will dilate a normal eye but fail to dilate an eye with HS
  - *Normally only available in hospital settings*

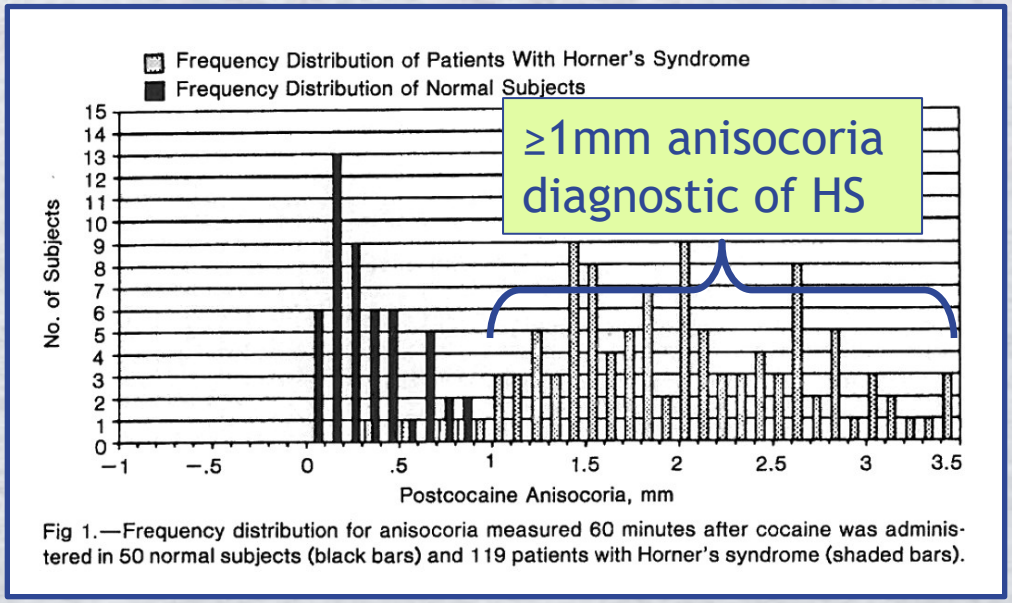
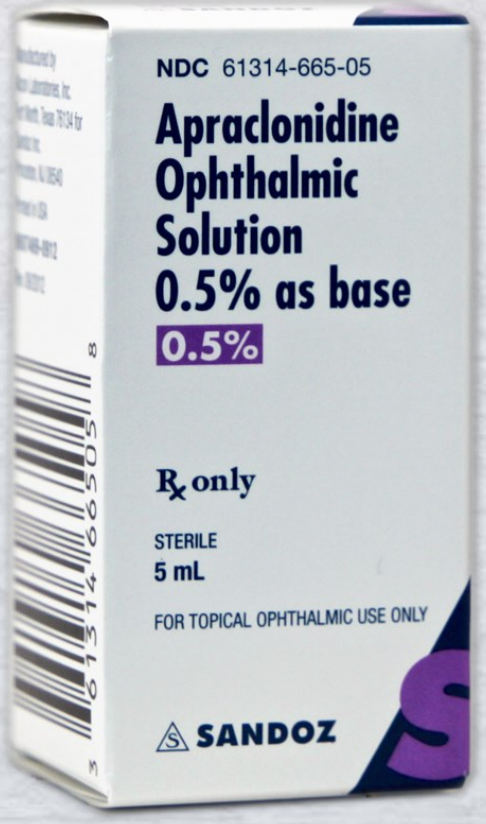


Fig 1.—Frequency distribution for anisocoria measured 60 minutes after cocaine was administered in 50 normal subjects (black bars) and 119 patients with Horner's syndrome (shaded bars).

*PMID: 2310339

Pharmacologic Studies

- Apraclonidine as alternative to cocaine
  - Sensitivity estimated to be similar to cocaine
  - Relies upon **supersensitivity**
    - May take ≥1 week to develop
    - Very weak mydriatic effect will not dilate normal eyes
  - May cause dysautonomia (excessive sleepiness) in infants[1]
  - Good alternative to cocaine[2]



1. PMID: 17572343
2. PMID: 15937425

The apraclonidine test

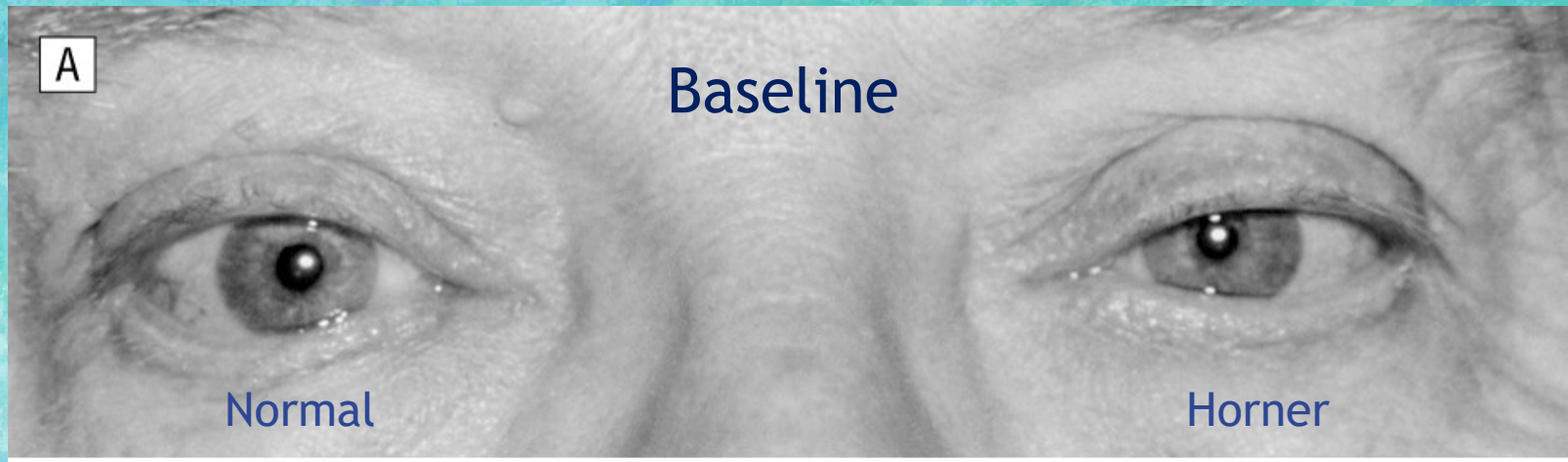
- Use 0.5% apraclonidine (Iopidine)
- May not be effective within 2 wks of HS onset
- **Virginal corneas** (no other drops, no other corneal contact, no epithelial defects)
- Take pretest photos
- Equal drops placed in inferior fornix; eyes closed 3 min; no eye wiping. Check at 60 min in the dark
- If patient has HS, dilation of affected eye will occur producing a **reversal of their anisocoria**
- Take photos at conclusion of test

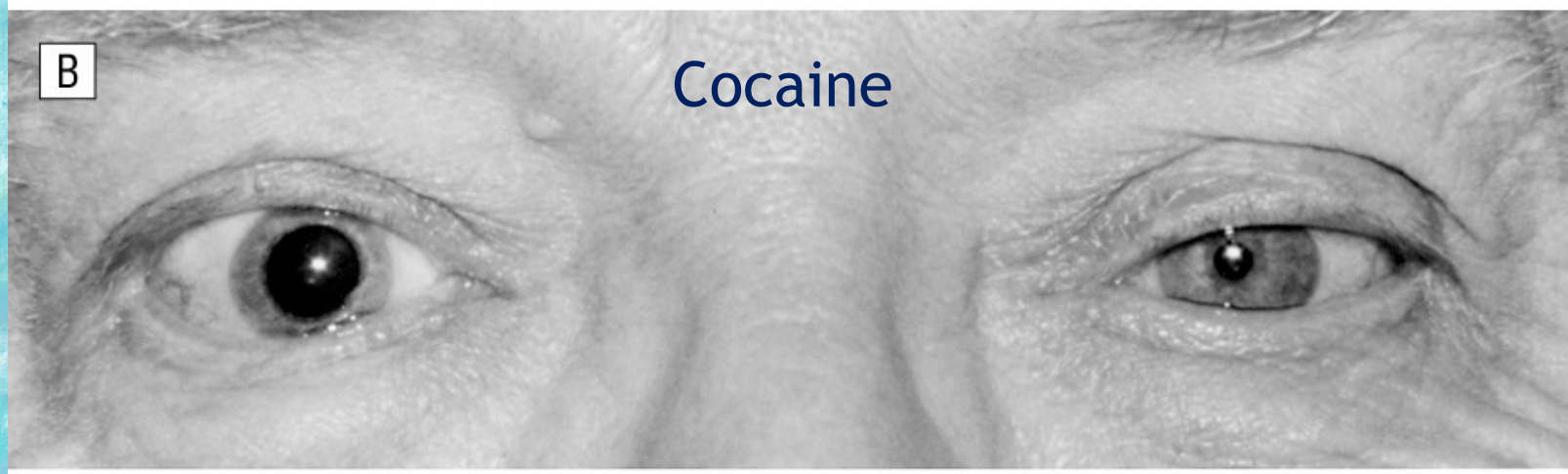
Morales (2000)

A. The patient at baseline, showing left ptosis and miosis

B. Forty-five minutes after instillation of 10% cocaine to each eye. Failure of the left pupil to dilate indicates Horner syndrome.

C. Several weeks later, appearance 1 hour after instillation of 1 drop of 1% apraclonidine. Note reversal of baseline anisocoria.





Pharmacologic Studies

What if you perform the apraclonidine test and neither pupil dilates?

A. The patient does not have HS
B. The patient has HS, but supersensitivity has not (yet) developed
C. The patient has HS, but you failed to instill a sufficient amount of drug

- **Always repeat a negative test**

  Or consider proceeding to imaging*

*PMID: 15937427

Pharmacologic Studies

- Localizing tests
  - **Hydroxyamphetamine and phenylephrine 1%** may aid in differentiating preganglionic from postganglionic HS
  - More narrowly targeted imaging studies
  - **Concerns**: questionable reliability, poor availability of the reagents
  - ***Rarely performed today* due to wide availability of highly sensitive, minimally invasive digital imaging modalities***

*PMID: 20182196

Diagnostic Evaluation

- History
- Physical exam
  - Pupils
  - Lids
- Pharmacologic studies
  - Diagnostic
  - Localization
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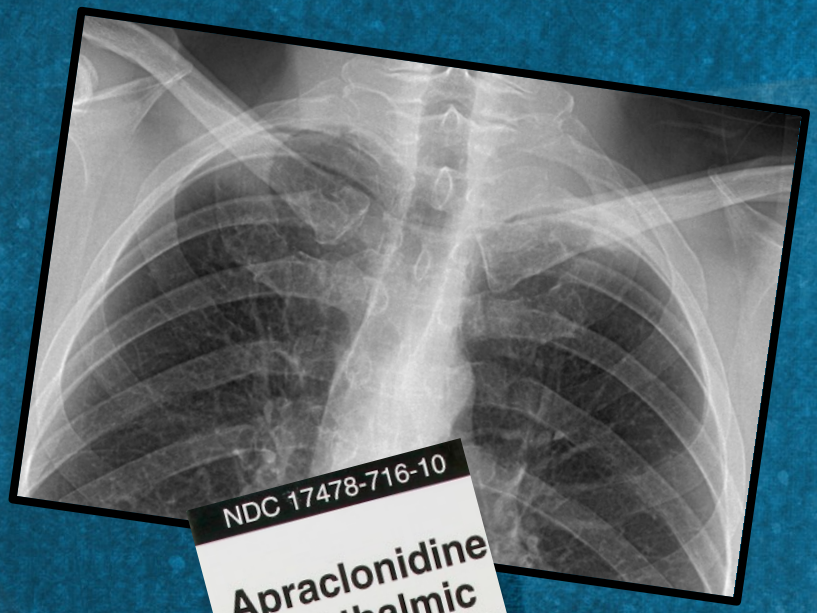
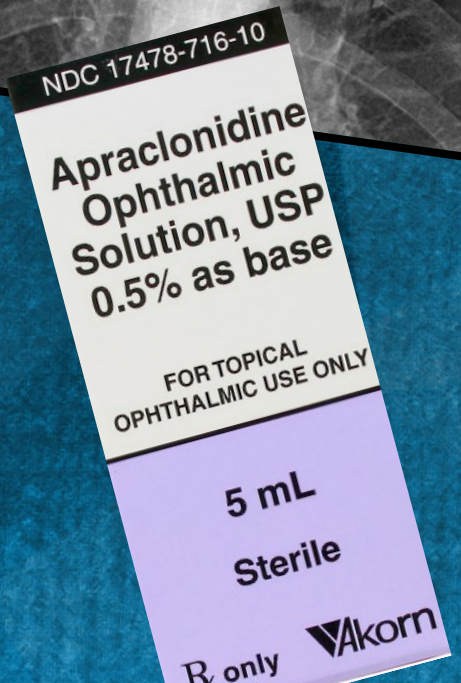
  - MRI or CT

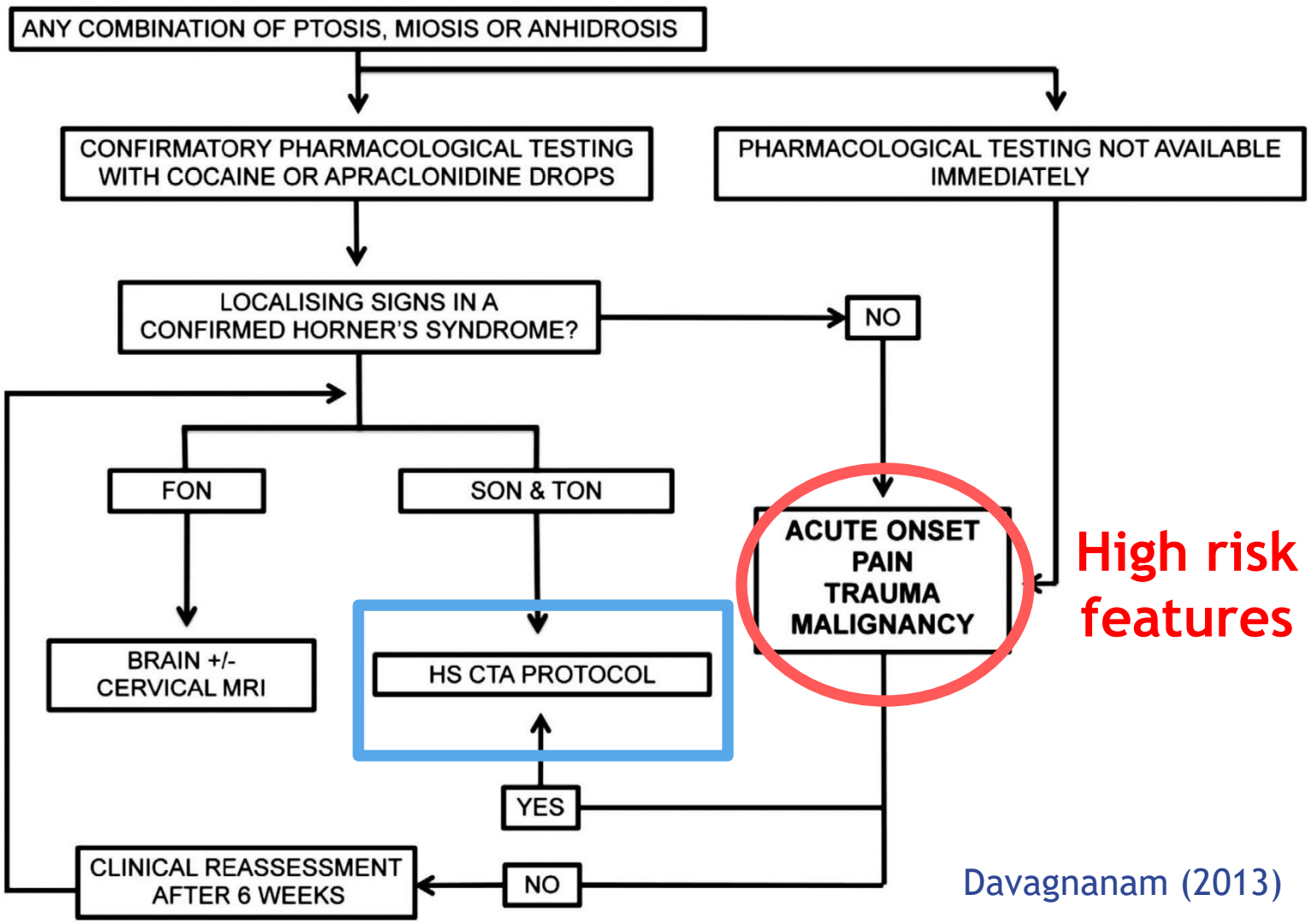




Radiographic Studies

- Important role in identifying the underlying cause of HS
- No firm consensus on imaging guidelines
- **Differentiate 1st neuron lesions from other lesions on clinical grounds***
  - 1st: Midbrain studies ←*MRI*
  - 2nd/3rd: Chest, neck, cavernous sinus ←*CTA*

*PMID: 23370415

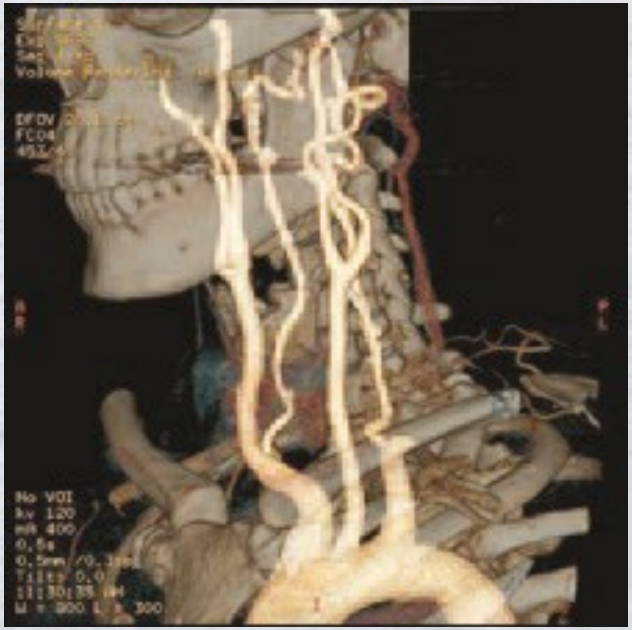


High risk features

Davagnanam (2013)

CT Angiogram Protocol

- Davagnanam (2013)*
  - **CT angiogram from Circle of Willis to aortic arch with visualization of the orbits and lung apices**
  - Advantages
    - Widely available
    - Excellent visualization of lung apices and carotids
  - Disadvantages
    - Ionizing radiation
    - Iodinated contrast agent



*PMID: 23370415

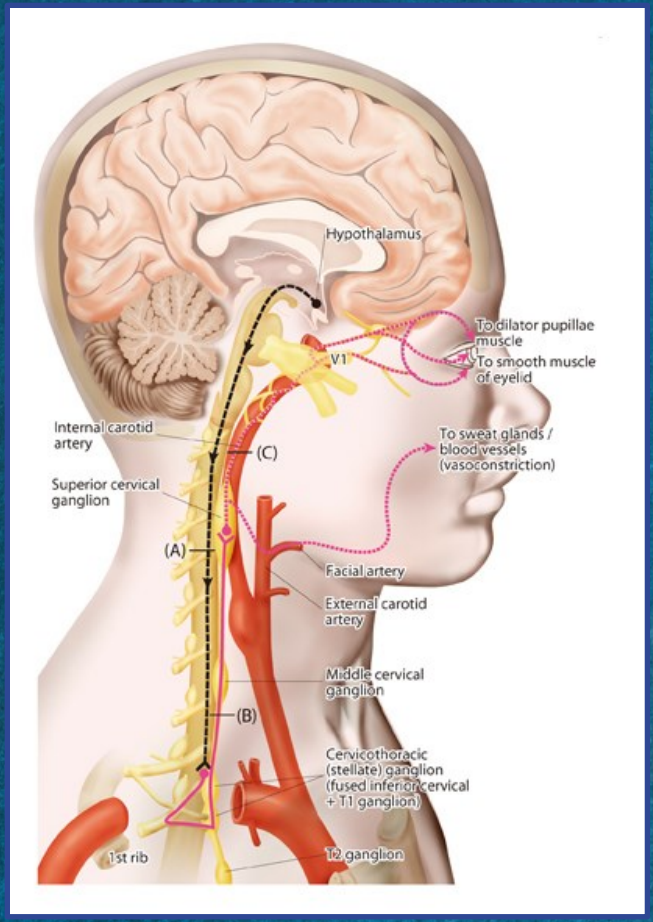
Horner Syndrome

Stepwise approach to suspected HS

1. Aniso in light/dark
2. Ask about high risk features
   (shoulder pain, neck pain, headache, TIA, smoker, etc)
3. Dilation lag
4. Apraclonidine
5. CT/MRI Angiography

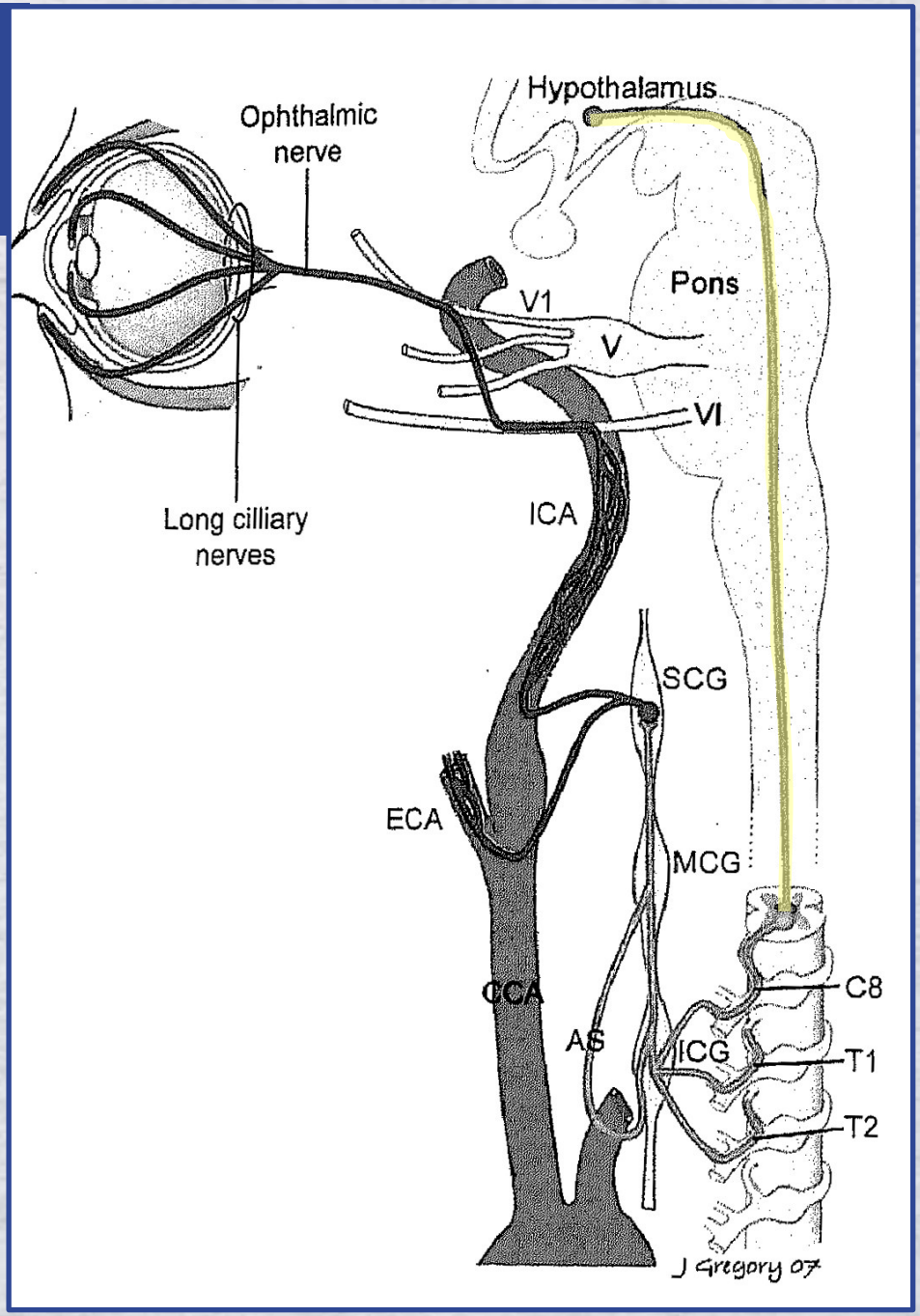
Major Causes of HS

- Wallenberg syndrome
  - Central HS (1st neuron)
- Pancoast syndrome
  - Preganglionic (2nd neuron)
- Carotid artery dissection
  - Postganglionic (3rd neuron)
- Pediatric HS
  - Neuroblastoma



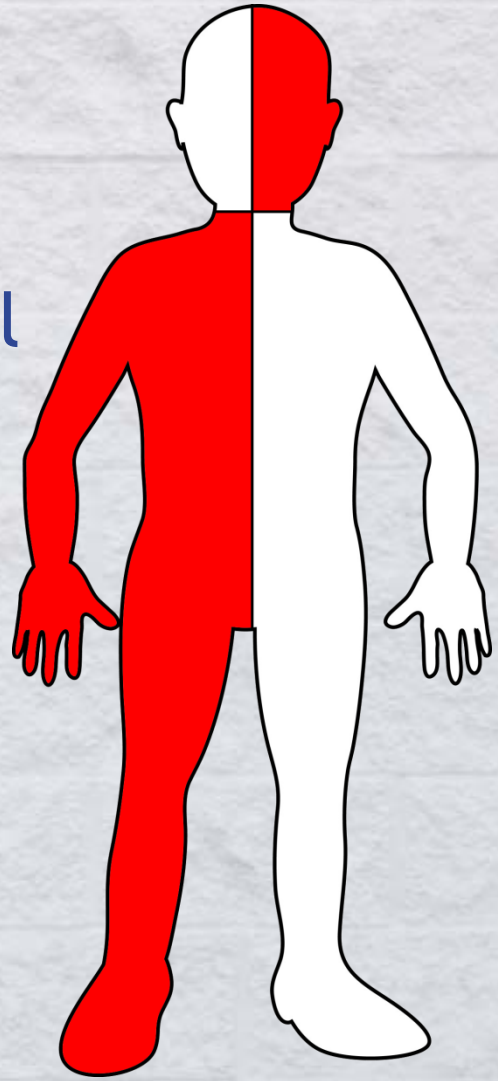
Central HS

- Relatively uncommon
- Typically easy to localize due to associated signs and symptoms
- **Wallenberg syndrome** is most common clinical presentation of a central HS



Wallenberg Lateral Medullary Syndrome

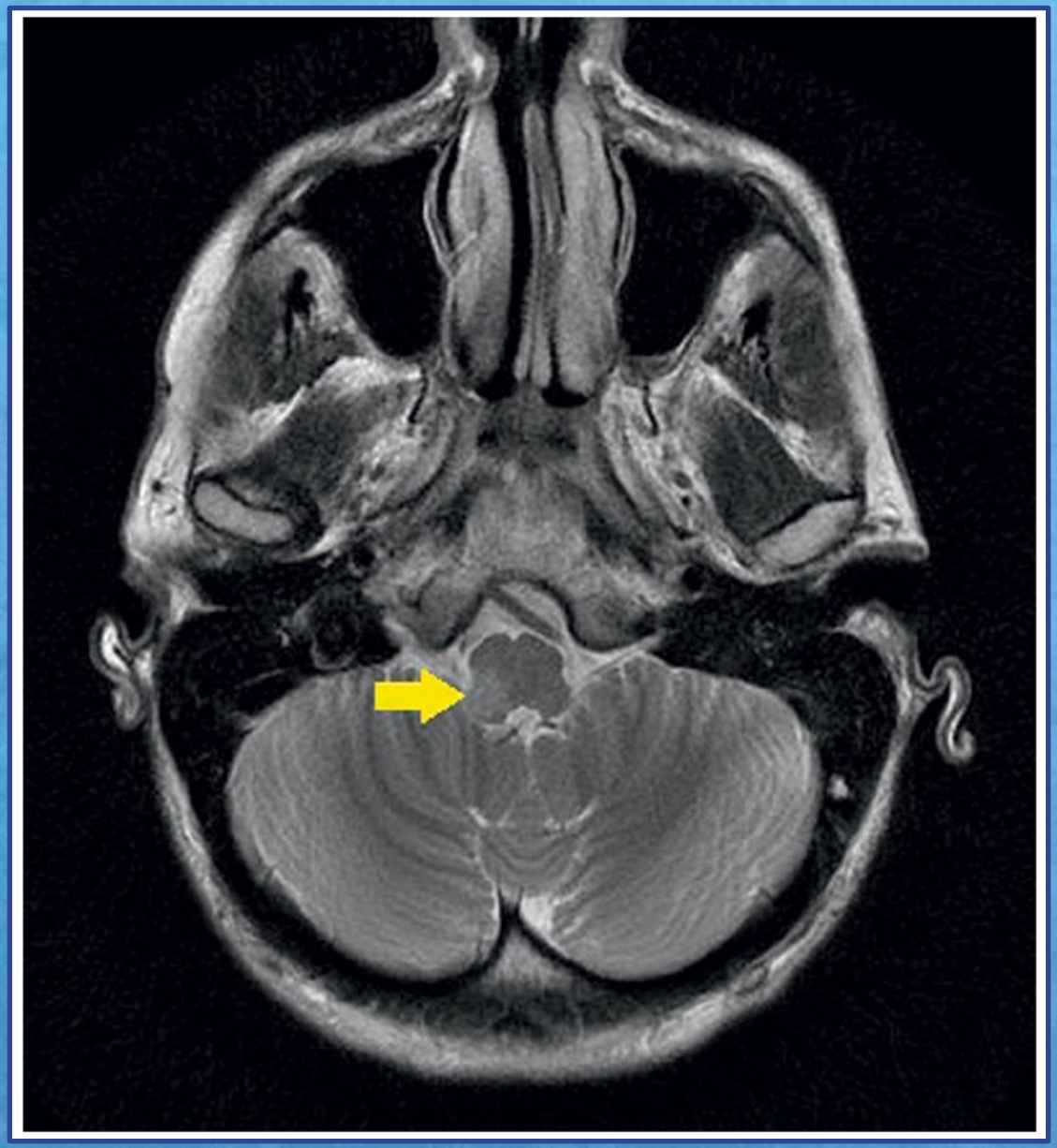
- Brainstem stroke syndrome
- Typical findings*
  - **Crossed sensory deficit**: ipsilateral facial analgesia, contralateral analgesia of the trunk
  - Ataxia: Loss of motor coordination
  - Dysarthria: Speech disorder caused by loss of control
  - Dysphagia: Difficulty swallowing



* Kim JS, et al. Stroke. 1994;25(7):1405–10.

1st neuron lesions are best visualized with MRI*

Axial T2-weighted MRI showing an infarct (arrow) in the midbrain supplied by the right posterior inferior cerebellar artery causing a Wallenberg syndrome.



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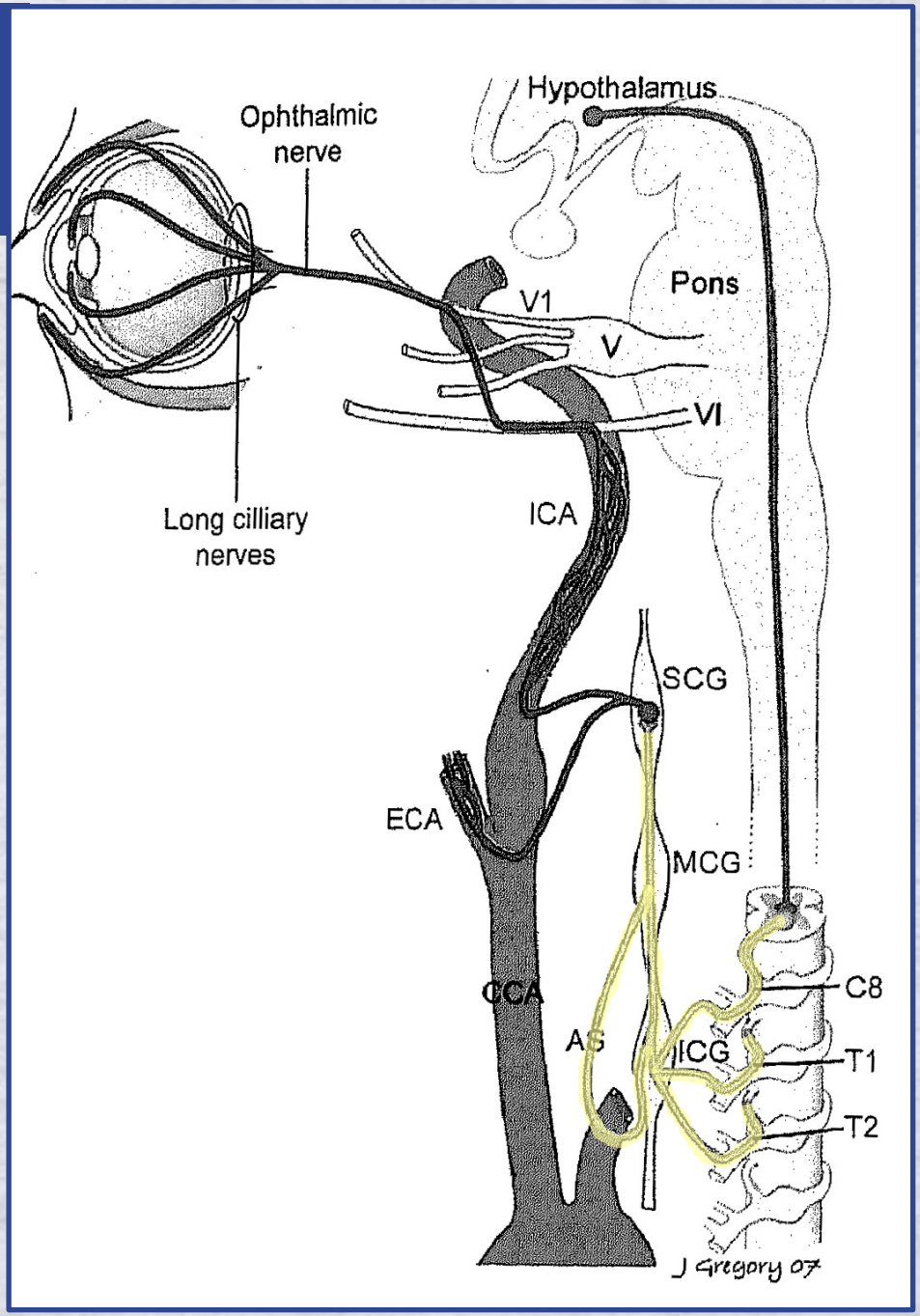
Preganglionic HS

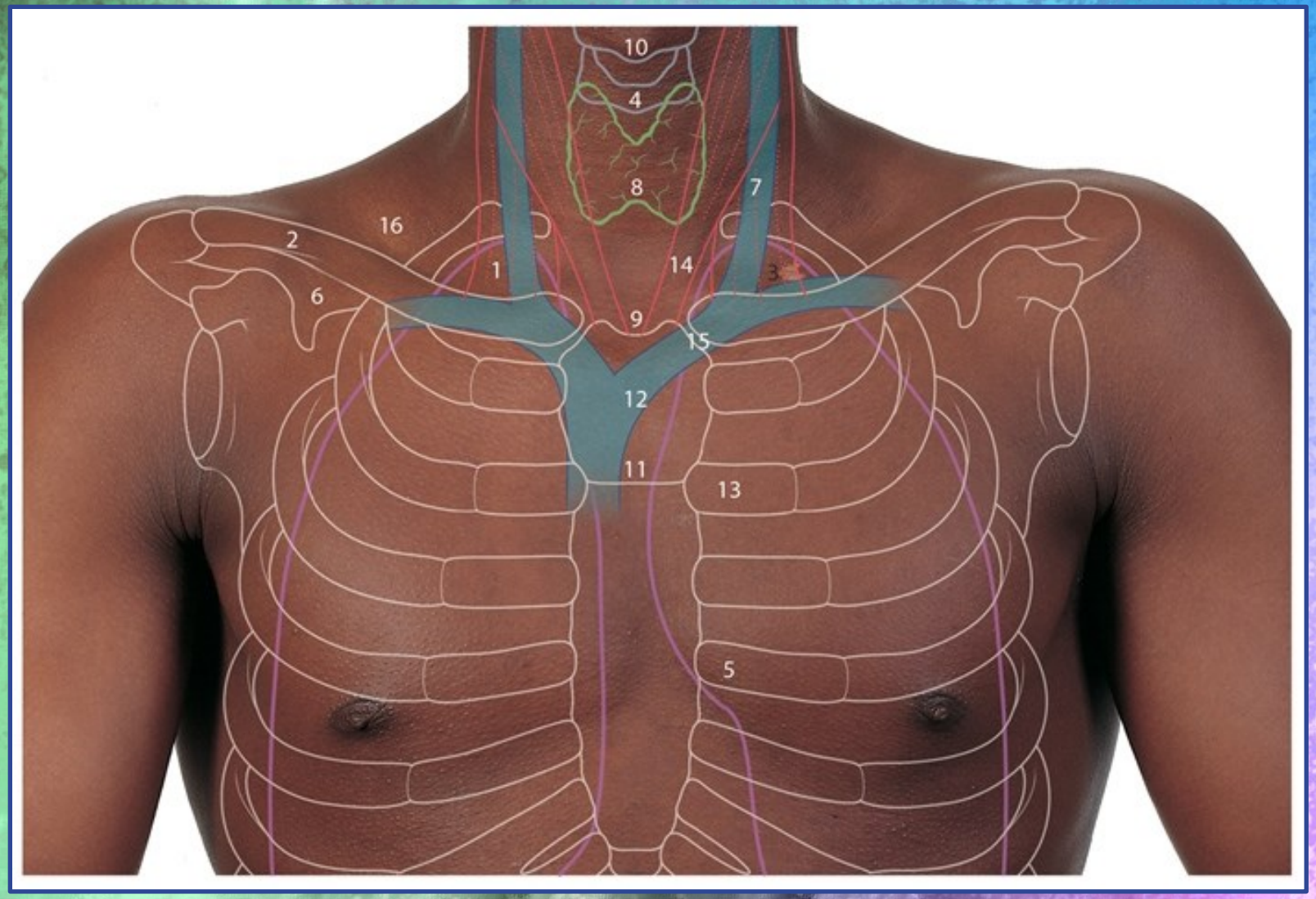
- Often presents as a clinically isolated finding
- Frequently idiopathic (~40%)
- Most common identified causes are **trauma and tumor** (Pancoast syndrome)



Pancoast Syndrome

- Clinical presentation
  - **Shoulder and arm pain** *(90% in one series*)*
  - Weakness of the muscles of the hand
  - Horner syndrome
- Most commonly caused by extension of **apical lung tumors** (Pancoast tumor) at the superior thoracic inlet
  - Invasion of the brachial plexus, vertebrae, subclavian vessels and sympathetic ganglia

*PMID: 7425056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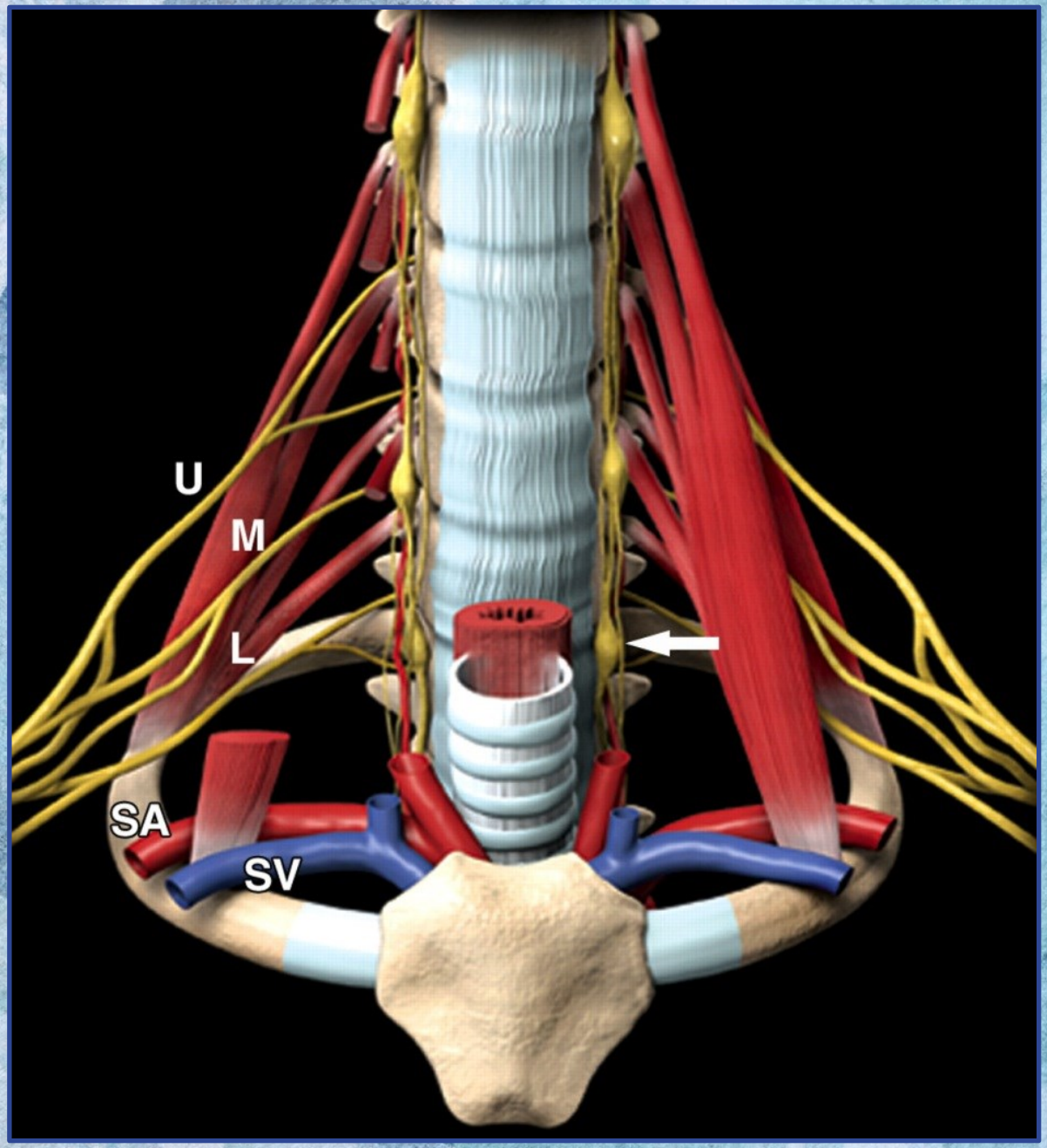
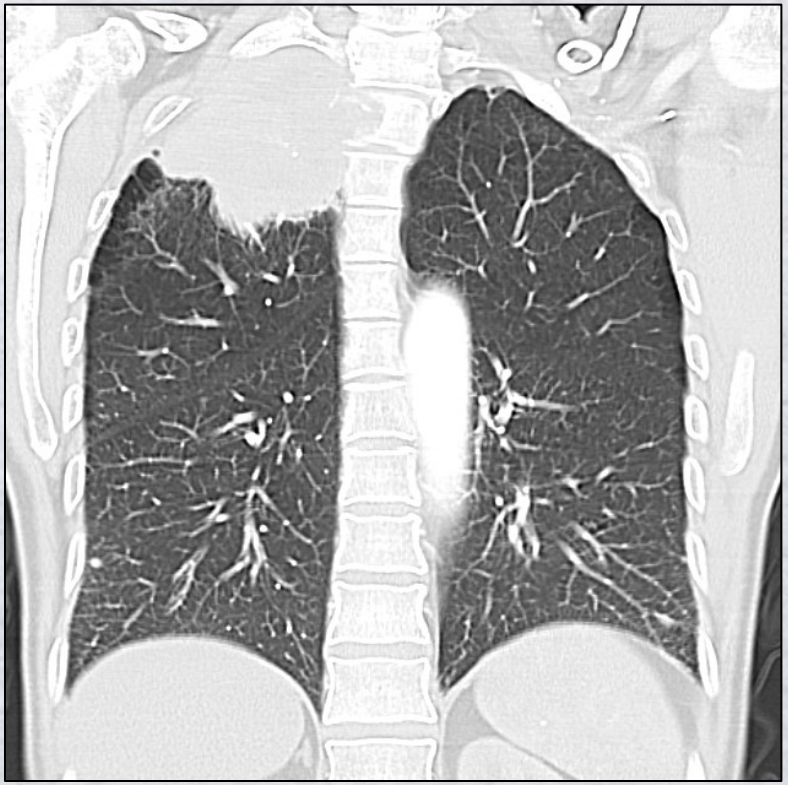


Apical lung tumors may invade the **brachial plexus** (U, M, L), the subclavian vessels (SA & SV) and the sympathetic ganglia that lie along the vertebral column (**white arrow**)

Pancoast Syndrome

- Diagnosis
  - Contrast-enhanced CT scan effective for lesion identification
  - MRI for greater information about spatial relationships
  - Needle biopsy for definitive diagnosis
  - *Easily missed on a regular chest X-ray*



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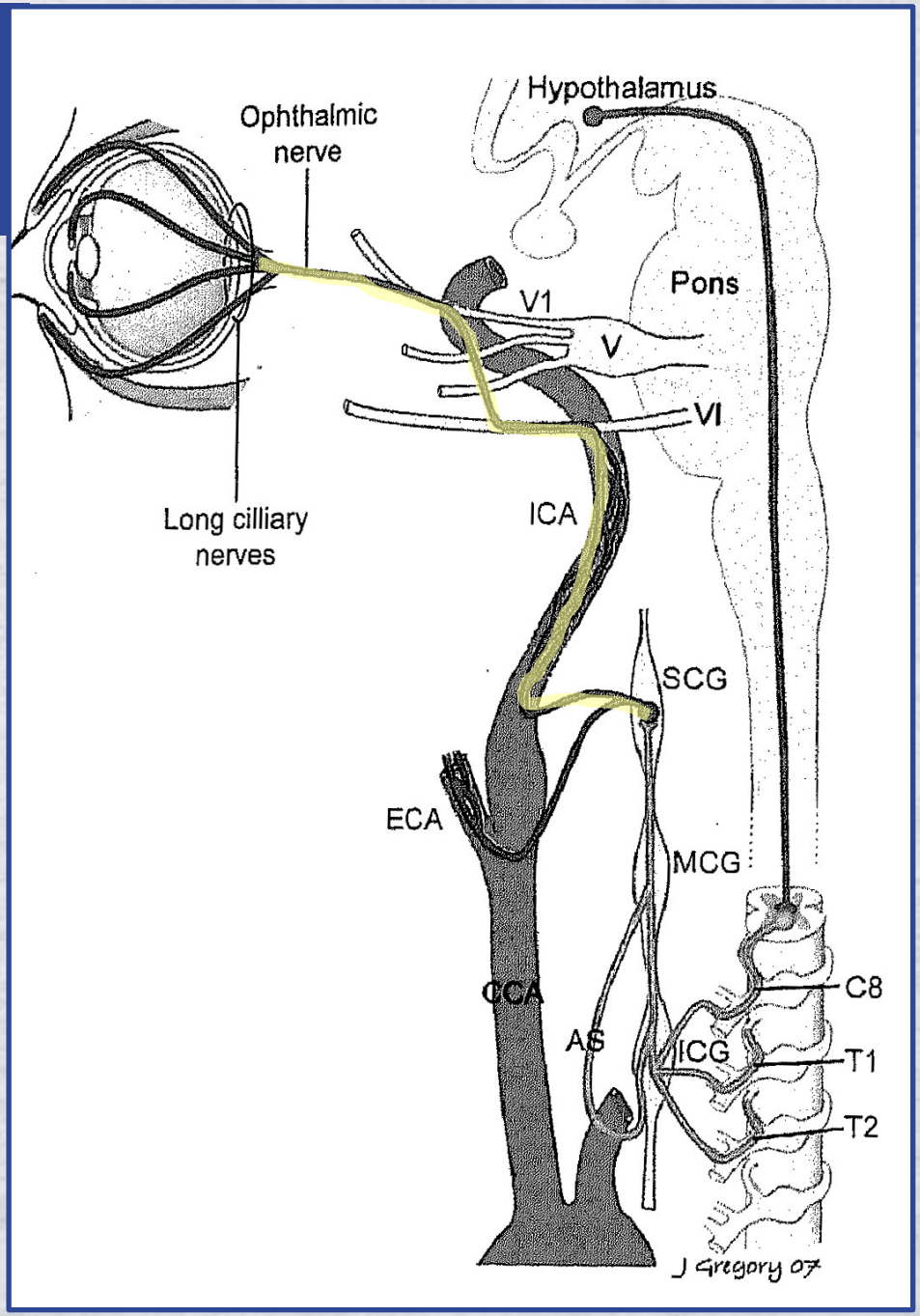
Postganglionic HS

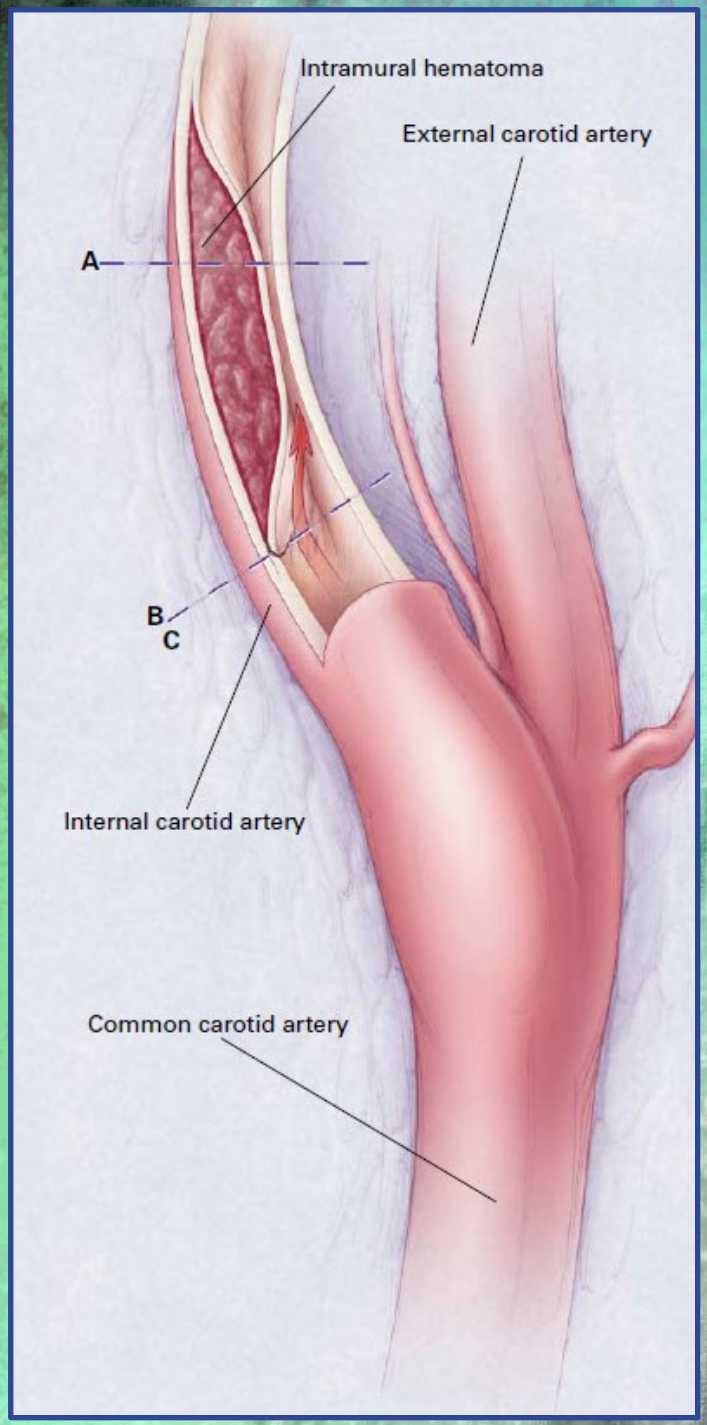
- Lesions include:
  - Carotid artery lesions
  - Thyroid disease
  - Cavernous sinus & orbital apex disease
- **Carotid artery dissection** is an important cause of HS because it may have few other clinical manifestations and can rapidly lead to stroke

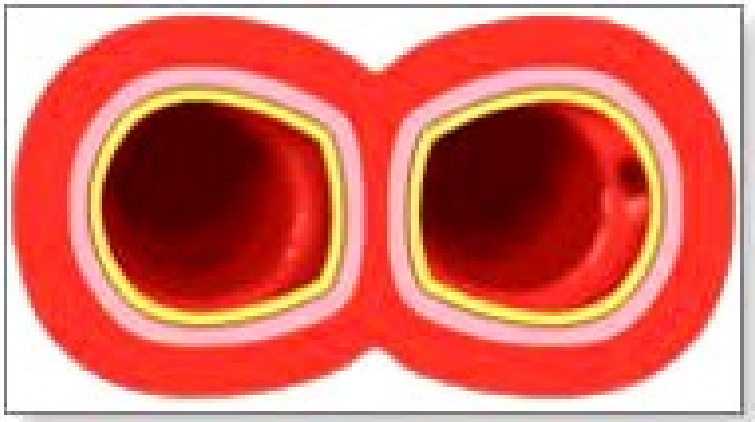


Carotid Artery Dissection

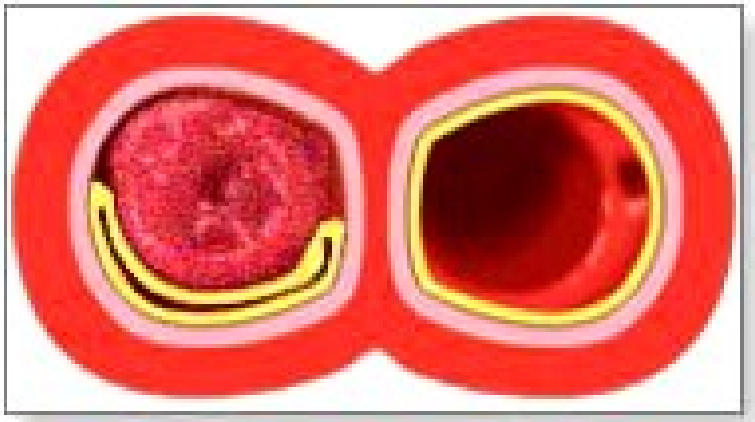
- A defect in the arterial wall allows blood to enter and form an intramural hematoma
- Results in either stenosis or aneurysmal dilation of the vessel.
- Spontaneous dissections affect all age groups, but are most common in the fifth decade of life
- **A major cause of ischemic stroke** in young to middle aged individuals*

*PMID: 11259724





Normal carotid artery



Lining of artery compressed due to blood dissecting up from a tear

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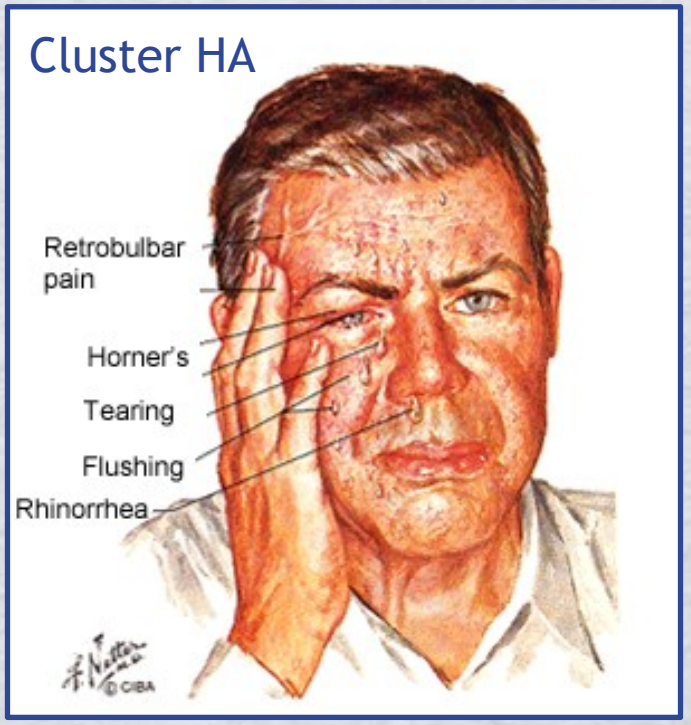
Carotid Artery Dissection

- Presentation
  - Classic triad of clinical findings[1]:
    - **Pain on one side of the head**, face, or neck
    - Horner's syndrome
    - Cerebral or retinal ischemia (TIA)
  - Classic triad found in <33% of patients
  - ***Can perfectly mimic cluster headache[2]***



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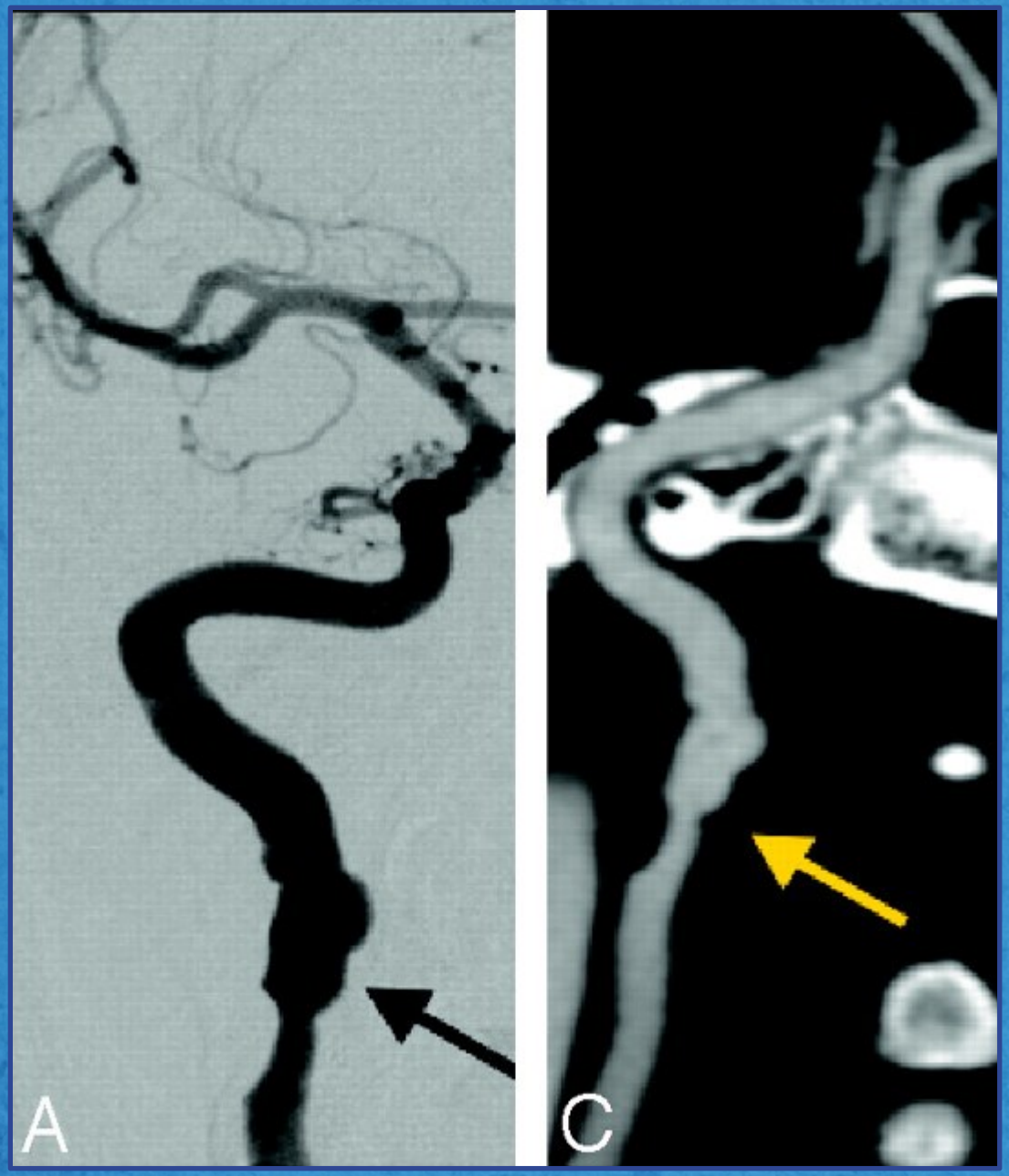


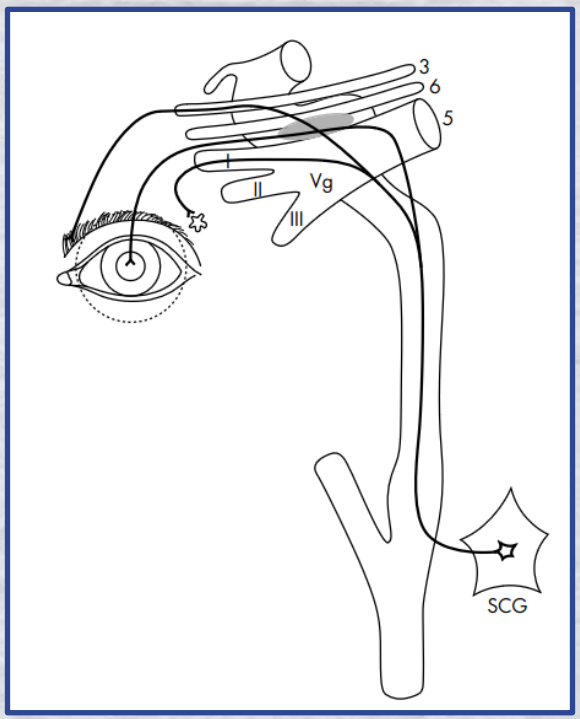
CT and magnetic resonance angiography appear to have nearly equal sensitivity and specificity in detecting dissections

Conventional cerebral angiographic images of the right ICA (left) and CTA of the same lesion (right).

PMID: 18635617

Raeder's Syndrome

- Definition: HS with ipsilateral headache
- Classification
  - Idiopathic/Benign: Typical cluster HA or occult carotid artery disease
  - Organic Disease: Carotid artery or middle cranial fossa lesion
- Neurology consult
- MRI/MRA of head and neck



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Prognosis of Idiopathic HS

- Most HS cases are idiopathic
  - Must undergo imaging before condition can be considered idiopathic
- Bellego (2021)*: Long-term (avg: 8yrs) follow-up of idiopathic HS
  - HS is stable or improves in most patients
  - Not associated with onset of any systemic dx
  - Conclude ***condition is benign*** and **no long-term follow-up is needed**

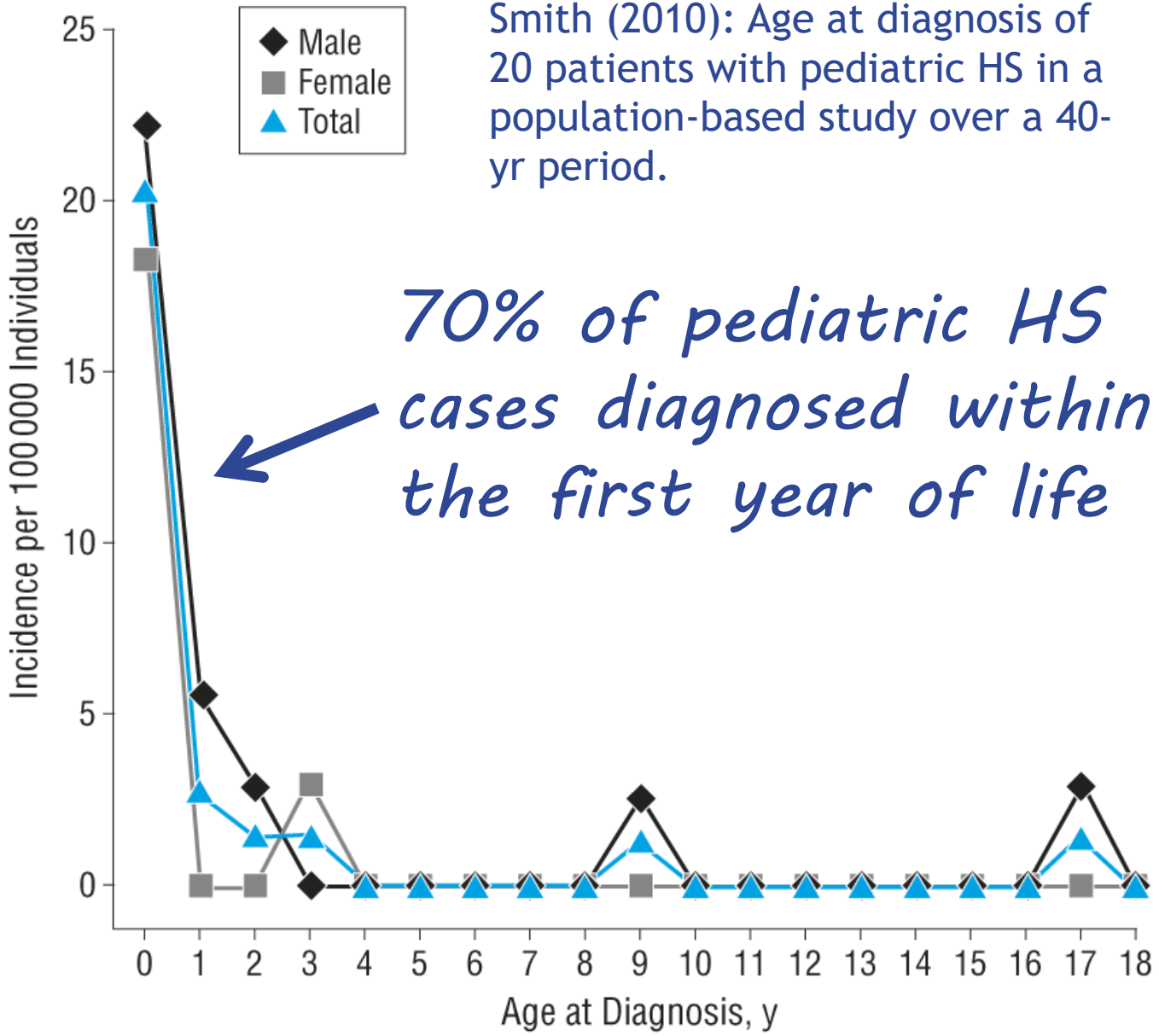
*PMID: 34839389

Pediatric Horner Syndrome

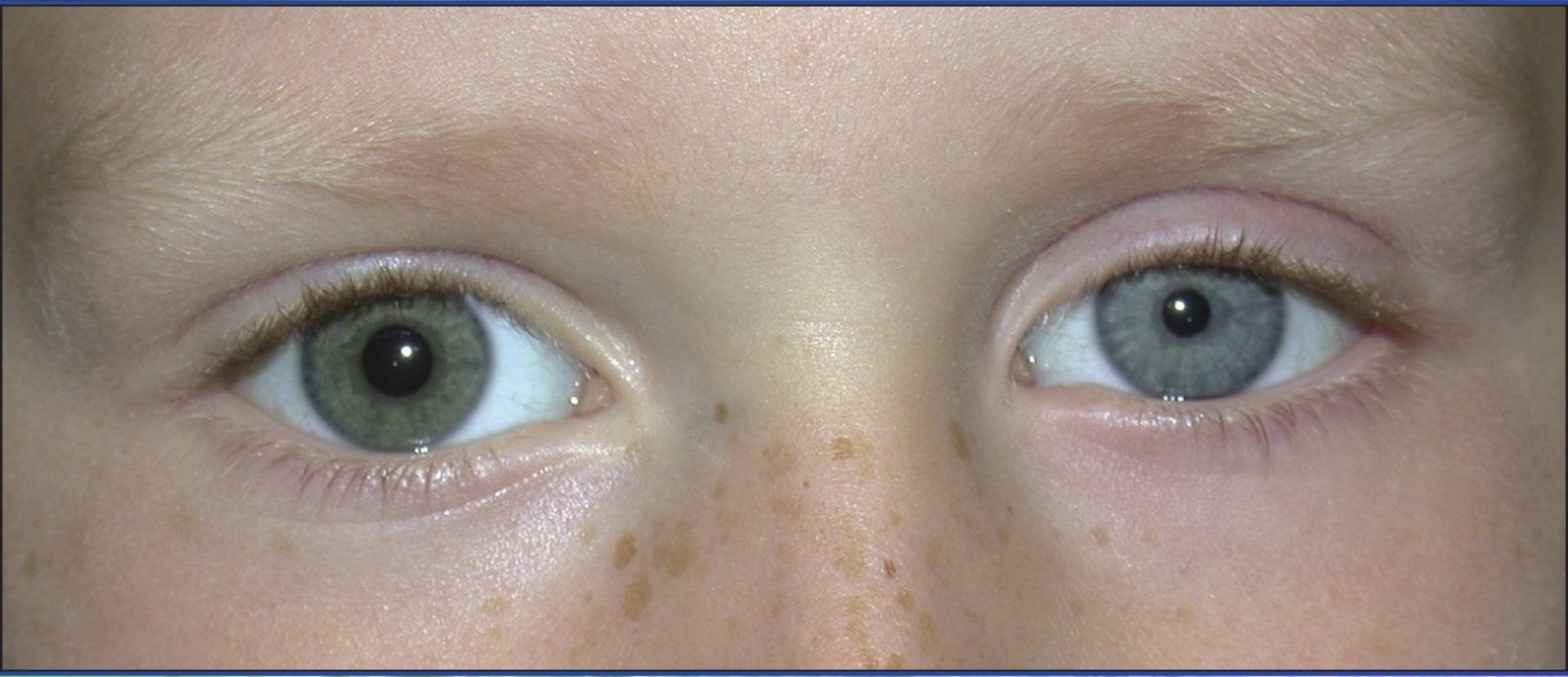
- Pediatric HS may be acquired or congenital
  - Congenital: birth trauma, neoplasm, others
  - Acquired: surgery, neoplasm, others
  - Often no underlying lesion can be found
- The most common neoplasm associated with pediatric HS is **neuroblastoma***
  - Most common tumor of the 1st year of life
  - 5% arise in the cervical sympathetic chain

*PMID: 20212203

Smith (2010): Age at diagnosis of 20 patients with pediatric HS in a population-based study over a 40-yr period.



70% of pediatric HS cases diagnosed within the first year of life



Congenital HS showing a lighter iris on the affected left side. (Pollard, 2010)

Pediatric Horner Syndrome

- Mahoney (2006): Recommended work-up for idiopathic HS in child
  - General physical examination
    - Palpation of the neck, axilla, and abdomen for mass lesions
  - If HS is clinically (dilation lag, heterochromia) or pharmacologically (cocaine) confirmed
    - Brain, neck, and upper chest MRI
    - Urinary catecholamine metabolite levels
- *Avoid apraclonidine in infants <6mos old*

PMID: 17011859

Key Points

- HS is a subtle, easily missed condition
- Hundreds of possible causes, some are life-threatening
- Search for localizing symptoms (eg. arm weakness) and high risk findings (eg. pain)
- Diagnosis can be clinical (dilation lag) or pharmacologic (apraclonidine)
- CTA is the imaging study of choice to identify causative lesion

Thank you!