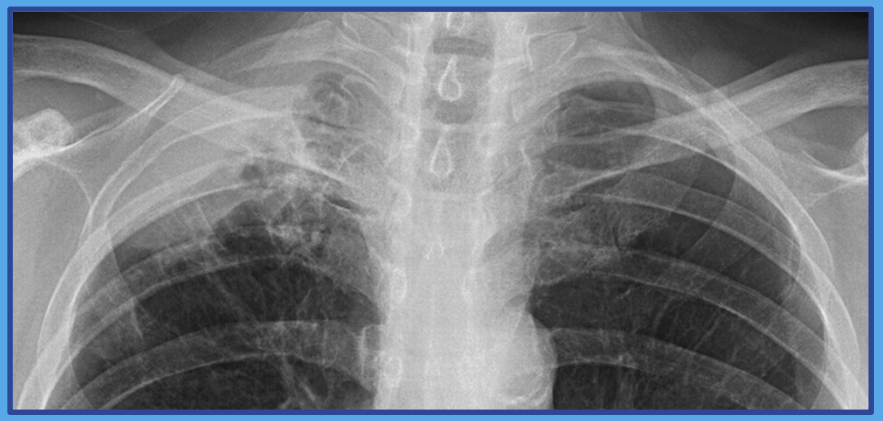

Horner Syndrome

Ptosis, miosis, and a whole lot more!

Rick Trevino, OD, FAAO
Rosenberg School of Optometry
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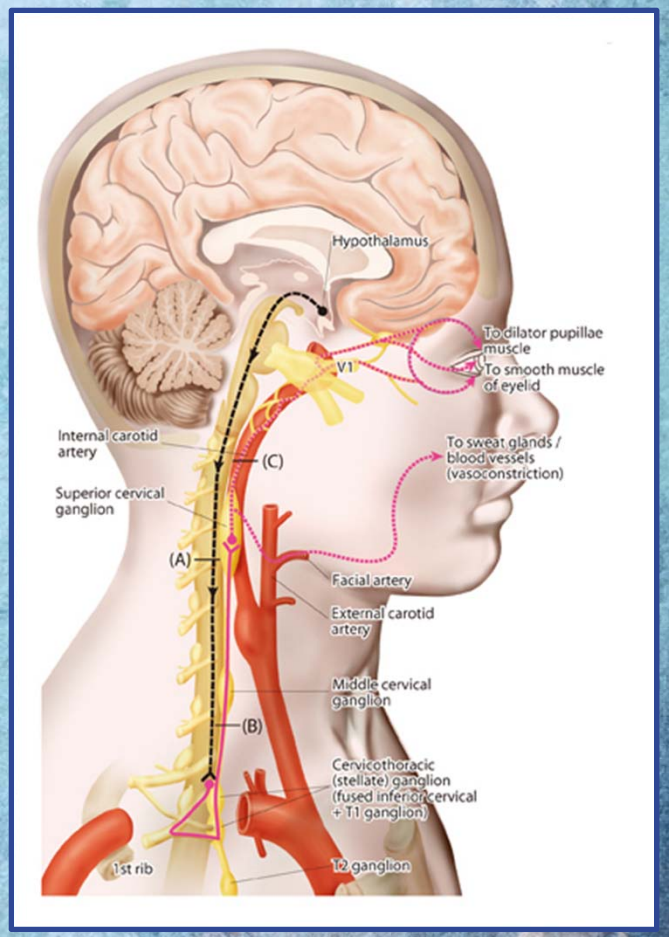
Horner Syndrome

- Online slides
  - slideshare.net/rhodopsin
- Online notes
  - richardtrevino.net
- Email me
  - rctrevin@uiwtx.edu
- Disclosures
  - None

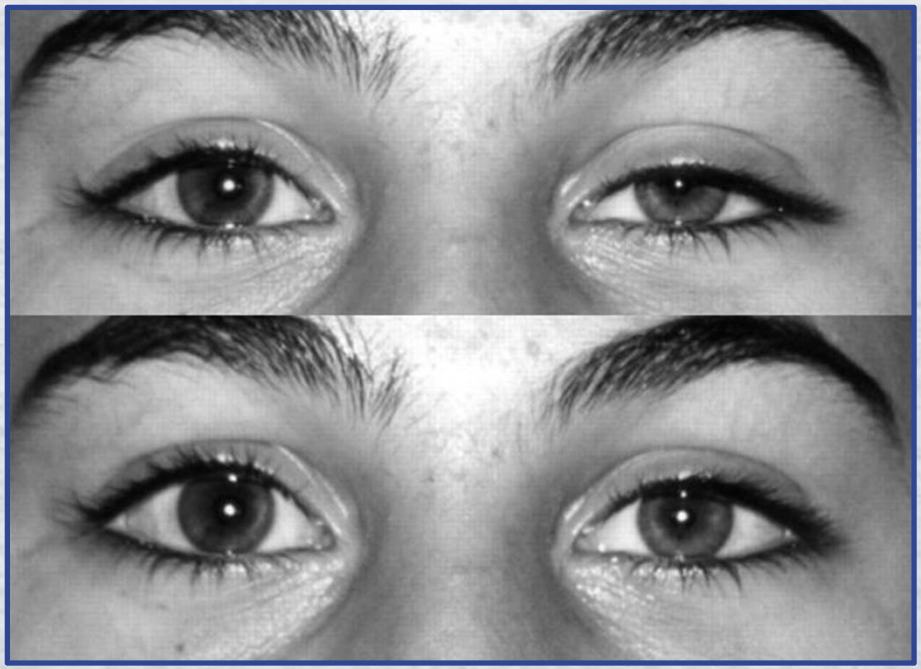


Horner Syndrome

- 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

- 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



Parsa CF, et al. Br J Ophthalmol. 1998;82(9):1095

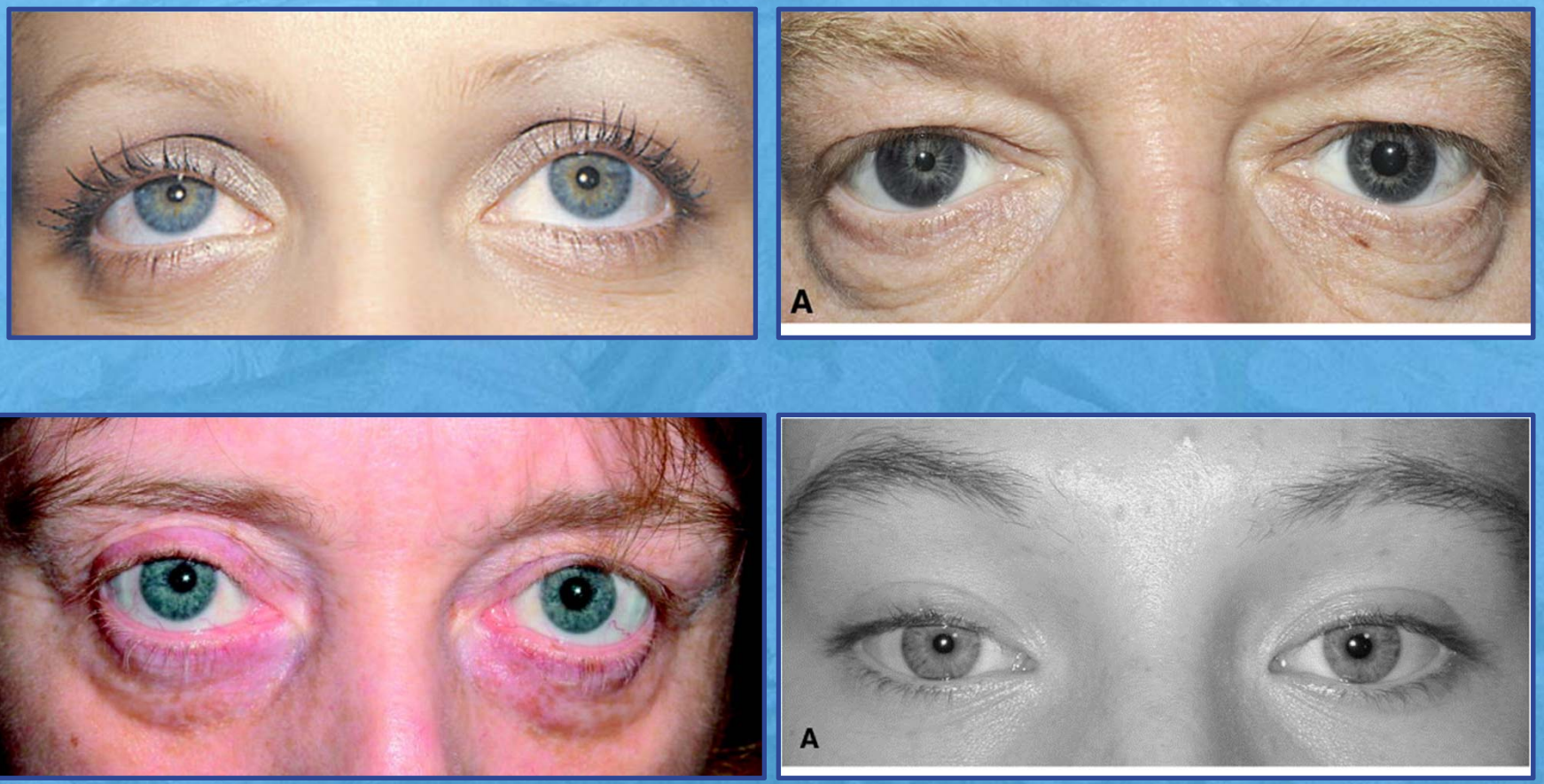
Features of HS

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***

* Smith SJ, et al. Arch Ophthalmol. 2010;128(3):324-9



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
  - Mild 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, and other factors
  - The miotic pupil is still within the range of normal pupil sizes – **the affected pupil is <u>not</u> abnormally small**

* Murphy MA, Hou LC. J Neuroophthalmol. 2006;26(4):296.

Features of HS

- Miosis
  - Loss of innervation of the iris dilator muscle
    - Anisocoria is greatest under dim illumination
  - **Dilation lag:** Slow dilation in dark[1]
    - Normal pupil: Takes 5-6s to dilate in darkness
    - HS pupil: Takes 10-12s to 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.Pilley SF, Thompson HS. Br J Ophthalmol. 1975;59(12):731–5.
2. Crippa SV, et al. Am J Ophthalmol. 2007;143(4):712–5.

How to test for dilation lag

1. With room lights off, adjust stand lamp such that there is dim and indirect ambient room illumination yet the patient's pupils are still clearly visible
2. Turn room lights up bright
3. Have patient fixate a distance target
4. Take baseline photos. Start video (if using video)
5. Technician turns off room lights and **blows a whistle**
6. After 5 sec take flash photo with "red eye" feature turned off (if not using video)
7. Wait 15-20 sec and take second photo
8. Repeat 2-3 times
9. Playback video or compare photos searching for slow dilation of affected eye compared to fellow eye

OPEN ACCESS Freely available online

PLoS one

The Eyes Have It: Sex and Sexual Orientation Differences in Pupil Dilation Patterns

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Department of Human Development, Cornell University, Ithaca, New York, United States of America

Abstract

Recent research suggests profound sex and sexual orientation differences in sexual response. These results, however, are based on measures of genital arousal, which have potential limitations such as volunteer bias and differential measures for the sexes. The present study introduces a measure less affected by these limitations. We assessed the' pupil dilation of 325 men and women of various sexual orientations to male and female erotic stimuli. Results supported hypotheses. In general, self-reported sexual orientation corresponded with pupil dilation to men and women. Among men, substantial dilation to both sexes was most common in bisexual-identified men. In contrast, among women, substantial dilation to both sexes was most common in heterosexual-identified women. Possible reasons for these differences are discussed. Because the measure of pupil dilation is less invasive than previous measures of sexual response, it allows for studying diverse age and cultural populations, usually not included in sexuality research.

Citation: Rieger G, Savin-Williams RC (2012) The Eyes Have It: Sex and Sexual Orientation Differences in Pupil Dilation Patterns. PLoS ONE 7(8): e40256. doi:10.1371/journal.pone.0040256

Editor: Andrew H. Kemp, University of Sydney, Australia

Received January 16, 2012; **Accepted** June 4, 2012; **Published** August 3, 2012

Funding: This research was funded by the American Institutes of Bisexuality (http://www.bisexual.org/home.html) and the United States Department of Agriculture's Federal Formula Funds (http://cuaes.cornell.edu/support/index.cfm) given to Cornell University for project NYC-321421. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing Interests: The authors have declared that no competing interests exist.

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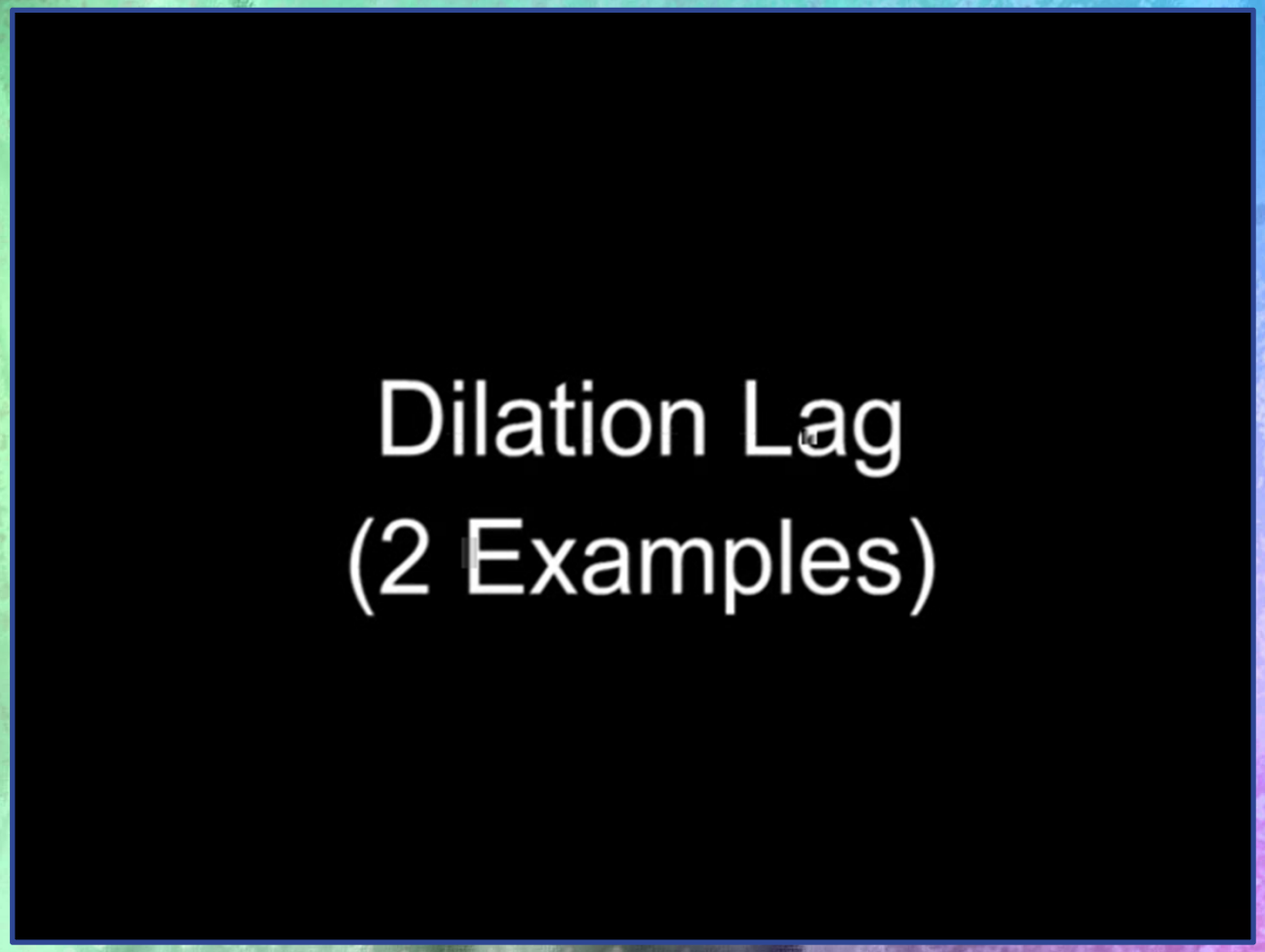
Rieger G, Savin-Williams RC. PloS one. 2012;7(8):e40256.

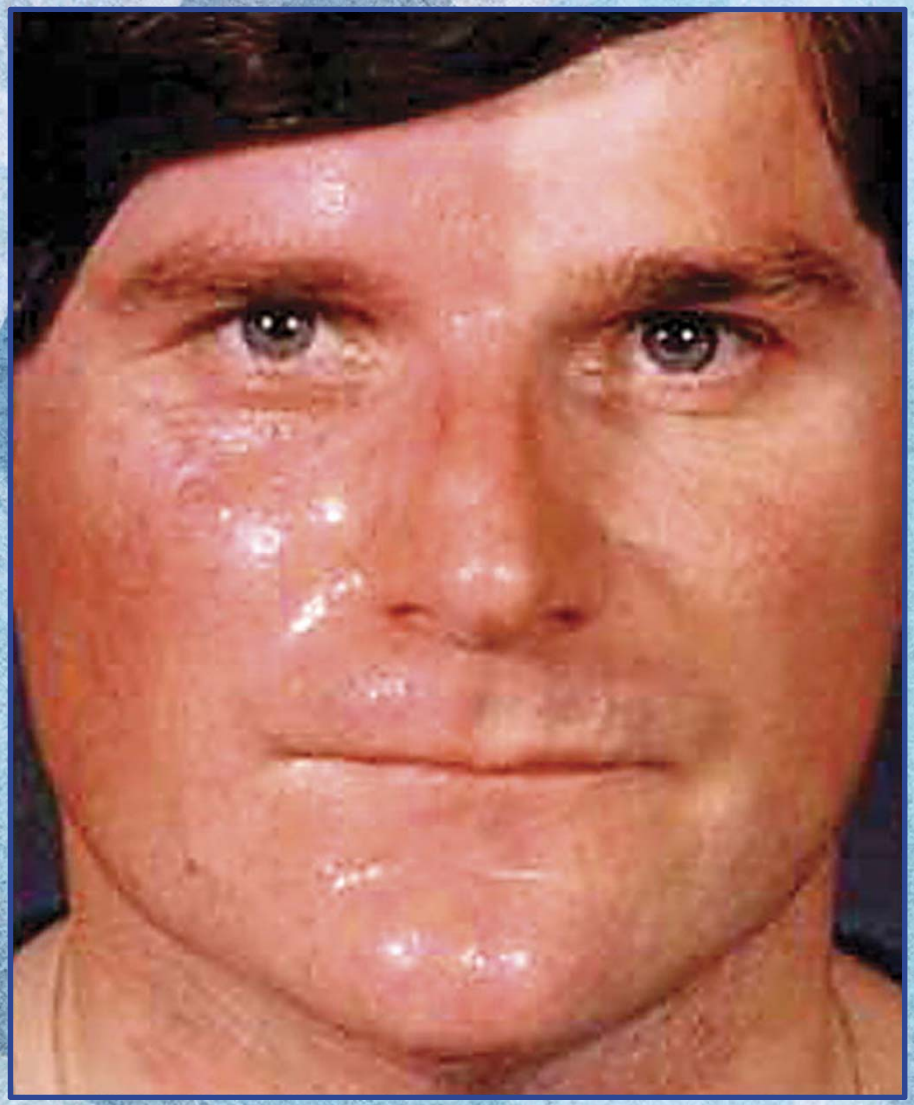
Dilation Lag

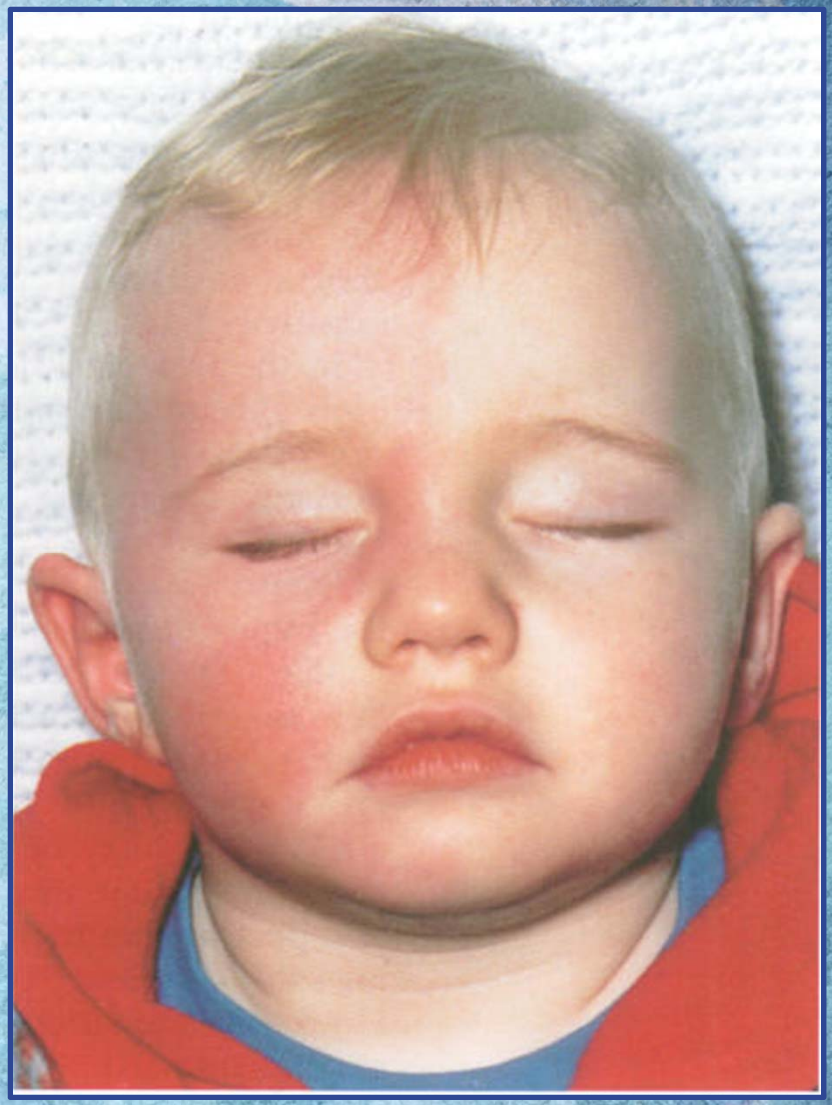


Features of HS

- Facial anhidrosis
  - Decreased or absent sweating of all or part 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

* Bremner F, Smith S. J Neuroophthalmol. 2008;28(3):171–7.





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

Thompson HS. Trans Am Acad Ophthalmol Otolaryngol. 1977;83(5):840–2.

Features of HS

- Increased amplitude of accommodation
  - 0.5 to 1.5 D greater accommodation
  - Mechanism may be loss of sympathetic inhibitory accommodative inputs
- 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 an acquired HS*
  - Sympathetic innervation required for normal melanin production in the iris melanocytes

* Byrne P, Clough C. J Neurol Neurosurg Psych. 1992;55(5):413.

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

Gesundheit B, Greenberg M. NEJM. 2005;353(22):2409–10

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

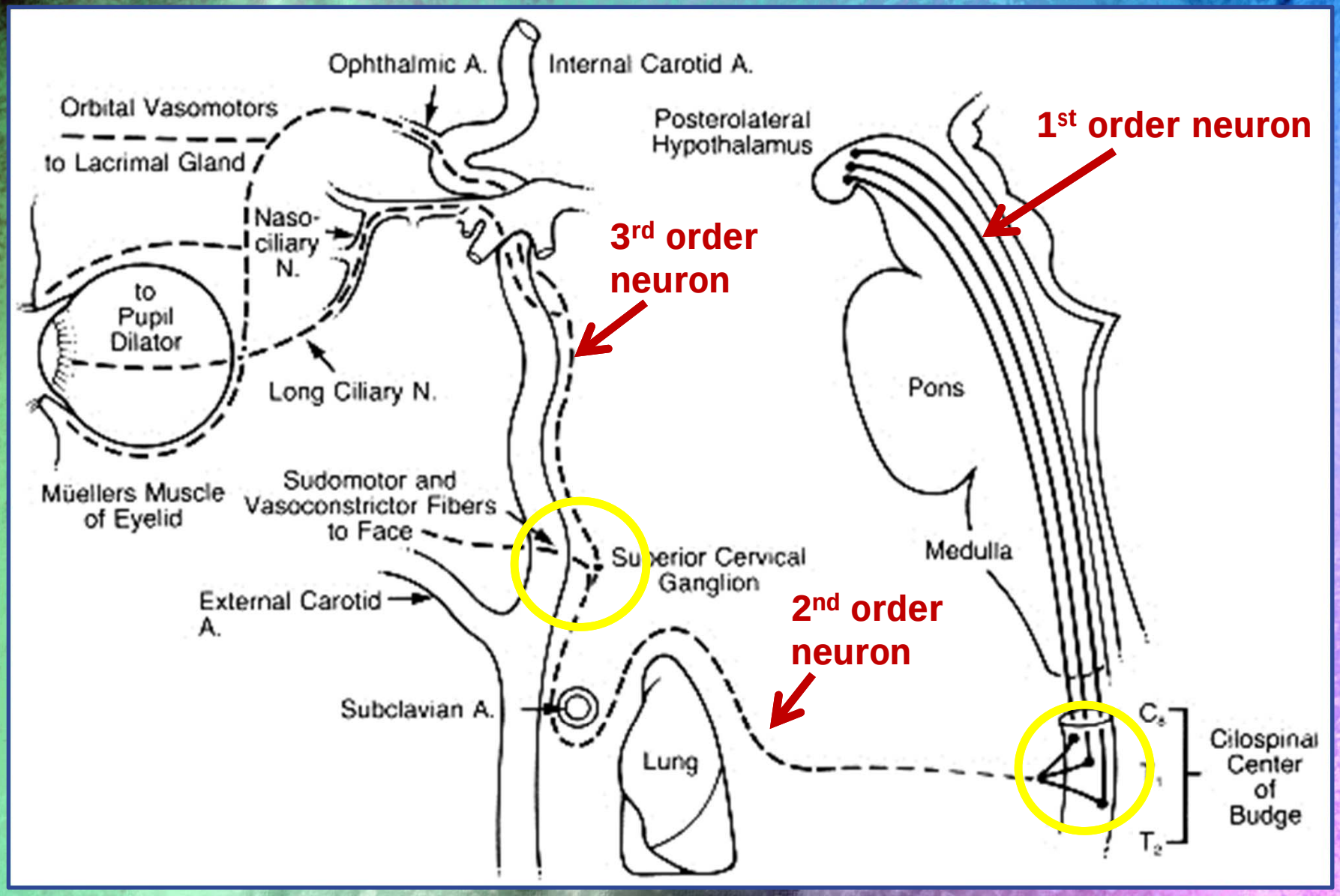
Thompson HS. Trans Am Acad Ophthalmol Otolaryngol. 1977;83(5):840–2.

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

Sympathetic Pathway

- First order neuron (FON) ← *Central HS*
  - Hypothalamus to the Ciliospinal center of Budge
- Second order neuron (SON) ← *Preganglionic HS*
  - Ciliospinal center of Budge to superior cervical gangion
  - Passes over **apex of lung** before reaching superior cervical ganglion
- Third order neuron (TON) ← *Postganglionic HS*
  - Superior cervical ganglion to iris dilator
  - Joins **carotid plexus** after emerging from superior cervical ganglion



Adapted from: Weinstein JM, et al. Arch Ophthalmol. 1980;98(6):1074-8.

Sympathetic Pathway

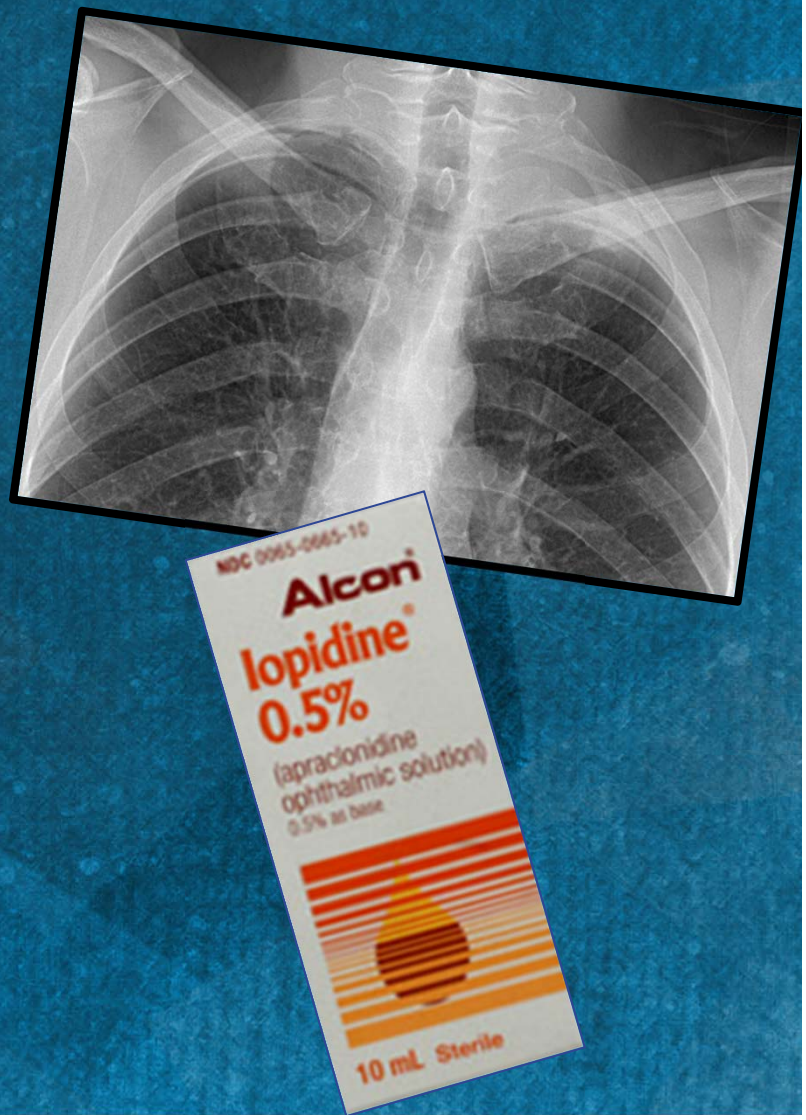
Least common Most common

Study	#	FON (%)	SON (%)	TON (%)
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 (SON) lesions tend to be the most common. Central lesions tend to be the least common, except in hospitalized settings (Keane). In general, **about 30%-40% 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**

* Al-Moosa A, Eggenberger E. Curr Opin Ophthalmol. 2011;22(6):468–71.

History

- Past medical history may provide clues as to the underlying cause
  - Surgery of neck/chest, stroke, malignancy
  - Neck injury may trigger carotid dissection
- **Localizing signs and symptoms***
  - Ataxia or nystagmus (FON)
  - Arm pain, weakness or numbness (SON)
  - Acute neck or facial pain (TON)
  - Ear pain or hearing loss (TON)
  - Sixth CN palsy (TON)

* Trobe JD. J Neuroophthalmol. 2010;30(1):1–2

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

* Davagnanam I, et al. Eye. 2013;27(3):291-8.

Physical Exam

- HS is often a very subtle condition
- **Some patients with HS may not present with simultaneously occurring ptosis and miosis[1,2]**
- *It is important to <u>not</u> eliminate the possibility of HS when only miosis or only mild ptosis is seen*

1. Peterson JD, et al. Surv Ophthalmol. 2012 Jul 9. [Epub ahead of print]
2. Pollard ZF, et al. Arch Ophthalmol. 2010;128(7):937–40.

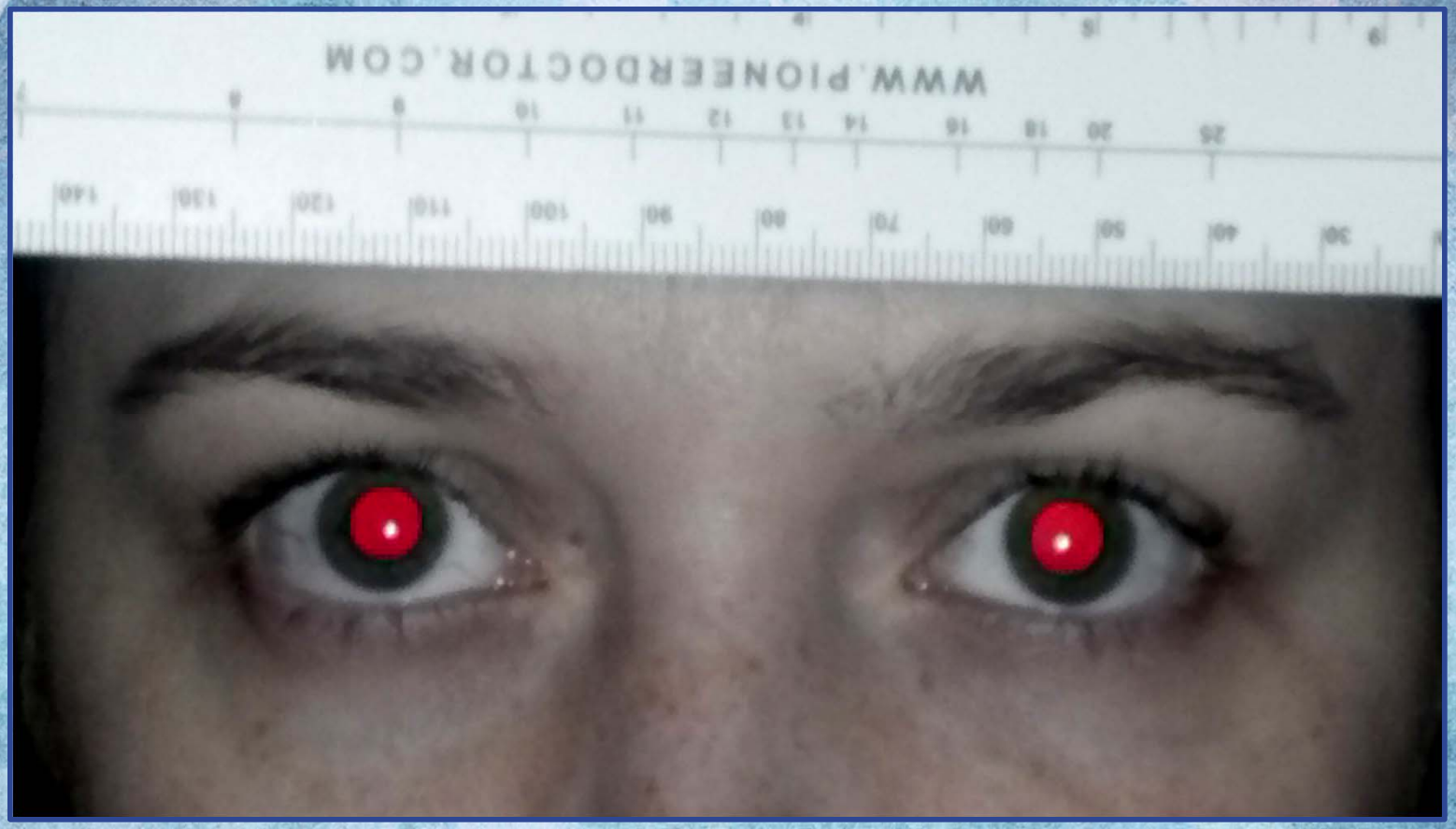
Physical Exam

- *Findings are highly variable and may be transient[1] or intermittent[2]*
- Ptosis
  - May vary with state of fatigue or alertness
  - May be masked by facial features (eg. dermatochalasis)
- Anisocoria
  - May vary from day to day, and time of day
  - Will vary with ambient illumination (>dim)

1. Leira EC, et al. Neurology. 1998;50(1):289-90.
2. Murphy MA, Hou LC. J Neuroophthalmol. 2006;26(4):296.

Anisocoria Evaluation

- Assess iris integrity with biomicroscope
  - R/O synechia, sphincter tears, etc
- Measure pupil size in light & dim illumination
  - *Use photos or video*
- Assess lid position
  - Measure vertical palpebral fissure width
- Response to light and near stimuli
- Swinging flashlight test



Measuring pupils photographically with PD rule and cell phone

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

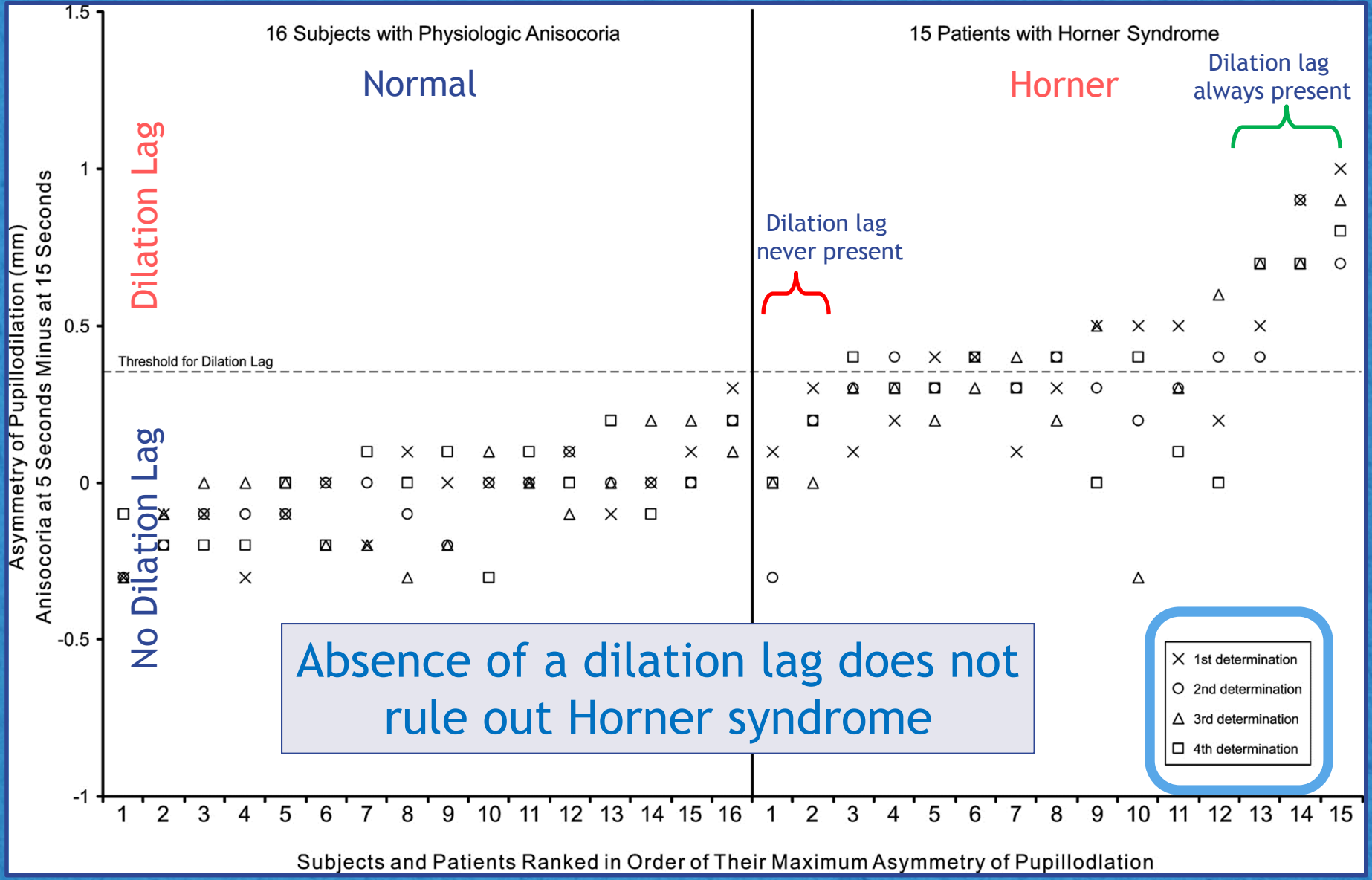
Horner syndrome →

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

Anisocoria Evaluation

- Is the anisocoria pathologic?
  - At any given moment, about 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

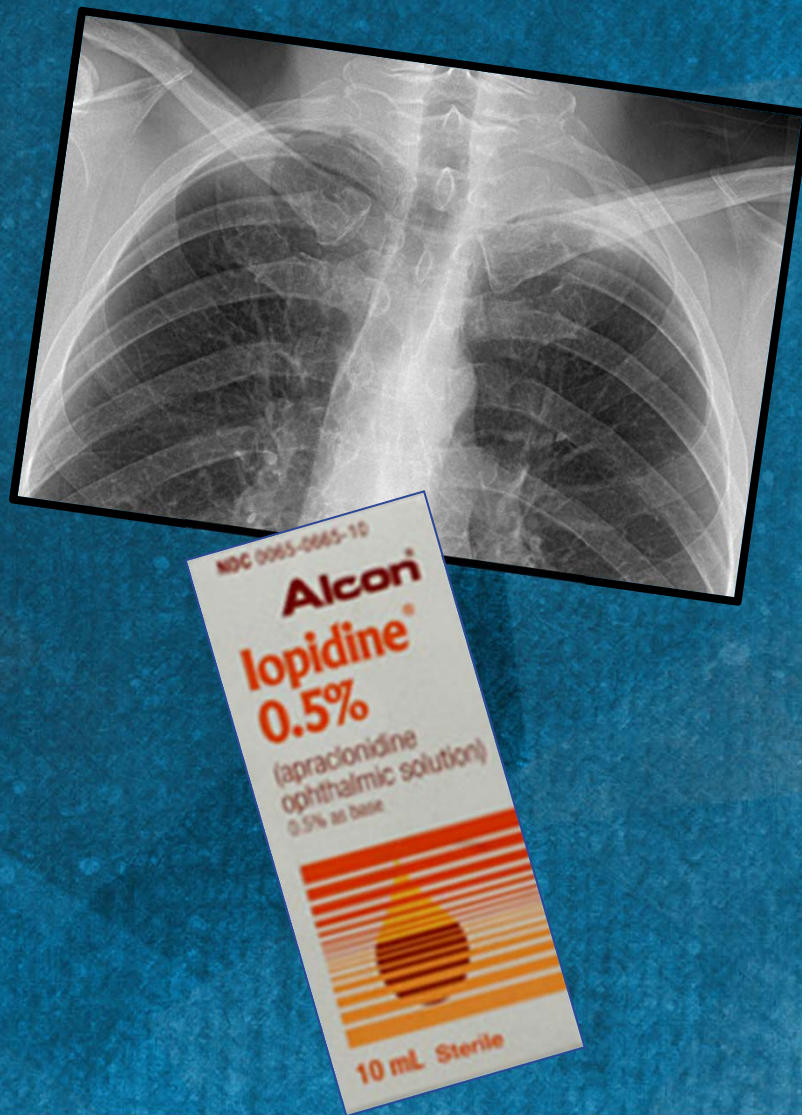
* Crippa SV, et al. Am J Ophthalmol. 2007;143(4):712-5.



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



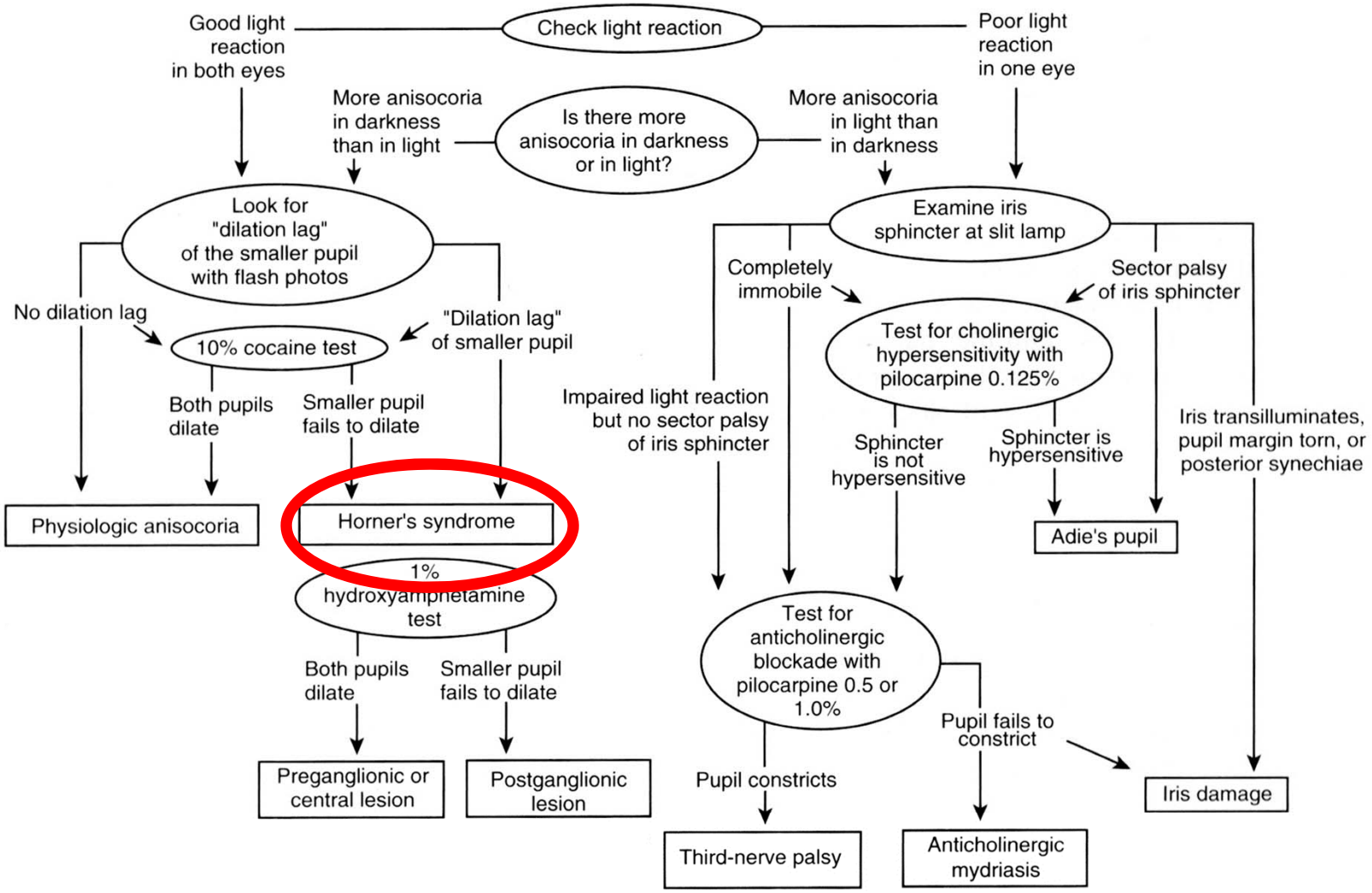


Figure 22-11 Flow chart for the clinical and pharmacologic evaluation of a patient with anisocoria in which only one pupil is affected. (Modified from Thompson HS, Pilley SFJ. Unequal pupils. A flow chart for sorting out the anisocoria. Surv Ophthalmol 1976;21:45–48.)

Pharmacologic Studies

- Used to confirm diagnosis and localize the lesion as preganglionic vs postganglionic
- **Shortcomings of pharmacologic studies[1,2]**
  - 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

1. Davagnanam I, et al. Eye. 2013;27(3):291–8.
2. Trobe JD. J Neuroophthalmol. 2010;30(1):1–2.

Pharmacologic Studies

- Cocaine
  - The "**gold standard**" for diagnosis of HS*
    - Alternatives: apraclonidine, documentation of dilation lag and 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*

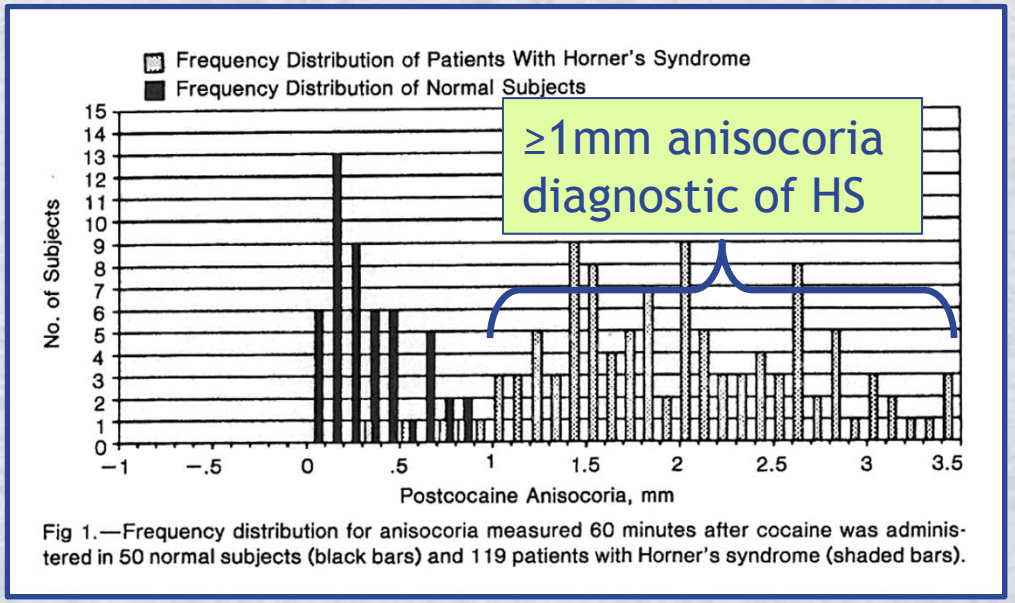


Fig 1.—Frequency distribution for anisocoria measured 60 minutes after cocaine was administered in 50 normal subjects (black bars) and 119 patients with Horner's syndrome (shaded bars).

* Kardon RH, et al. Arch Ophthalmol. 1990;108(3):384–7.

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]
  - Promising alternative to cocaine[2]

1. Watts P, et al. J AAPOS. 2007;11(3):282–3.
2. Kardon R. J Neuroophthalmol. 2005;25(2):69–70.

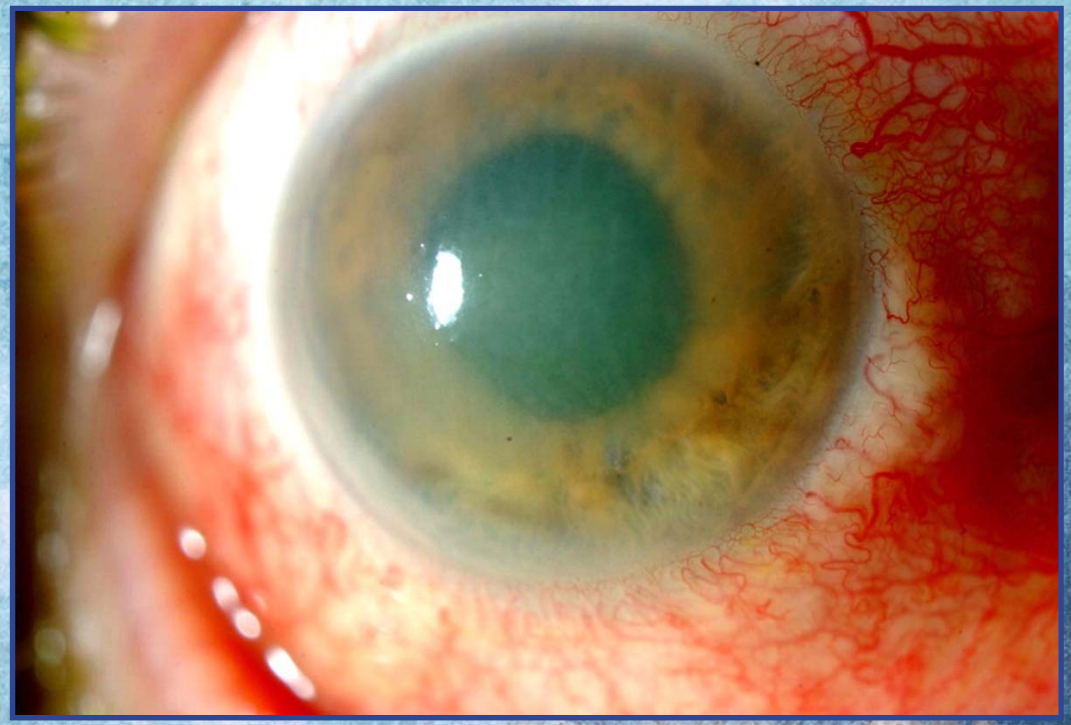
Angle Closure Kit

0·5% apraclonidine (Iopidine)

0.5% timolol maleate

2% pilocarpine

250mg tablets acetazolamide



How to do the apraclonidine test

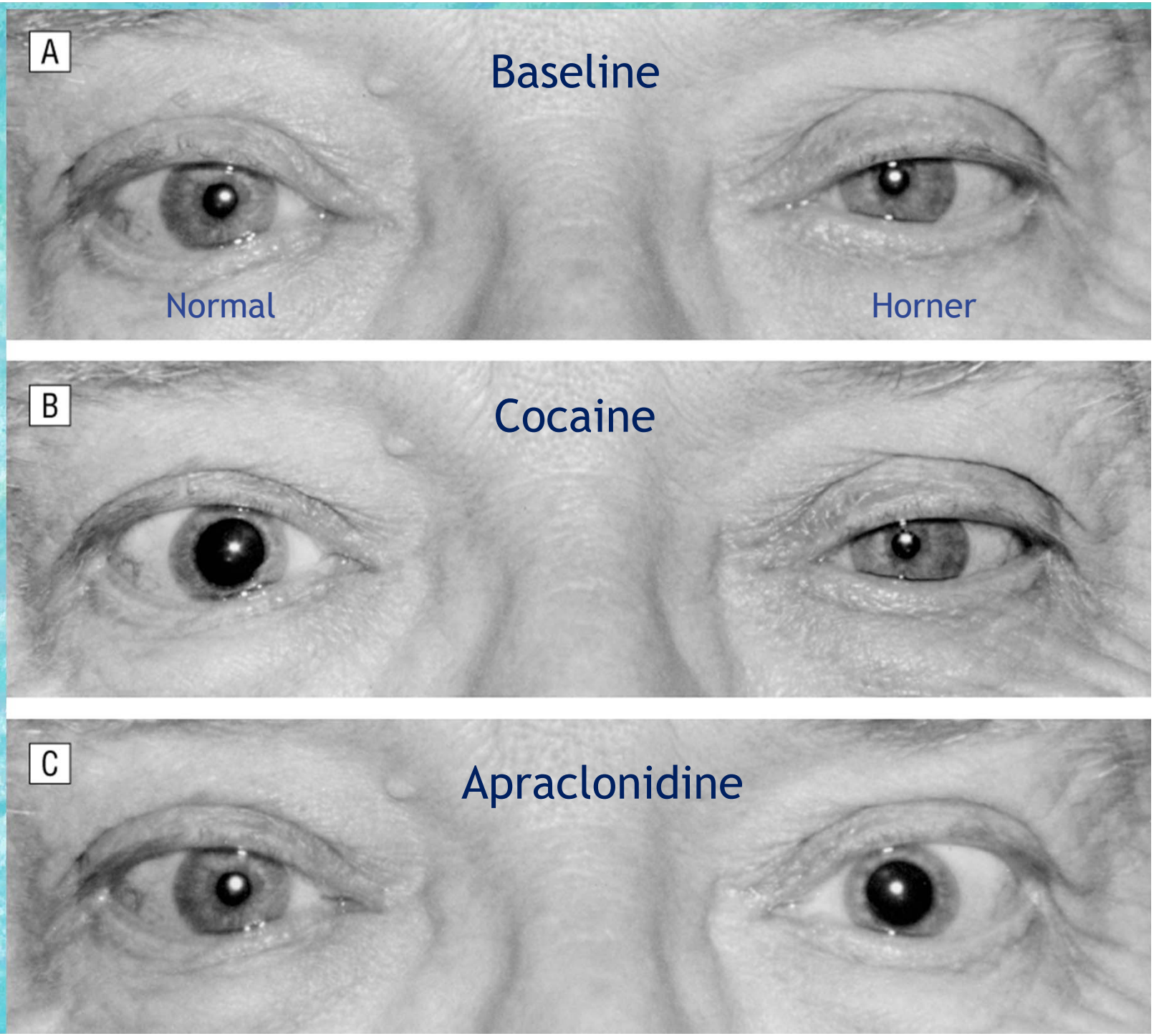
- Use 0.5% apraclonidine (Iopidine)
- May not be effective within 2 wks of HS onset
- **Virginal corneas** (no other drops, no other corneal contact, no epithelial defects)
- Take pretest photos
- Equal drops placed in inferior fornix; eyes closed 3 min; no eye wiping. Check at 60 min.
- If patient has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

* Freedman KA, Brown SM. J Neuro-ophthalmol. 2005;25(2):83-5.

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*

* Trobe JD. J Neuro-ophthalmol. 2010;30(1):1–2.

Diagnostic Evaluation

- History
- Physical exam
  - Pupils
  - Lids
- Pharmacologic studies
  - Diagnostic
  - Localization
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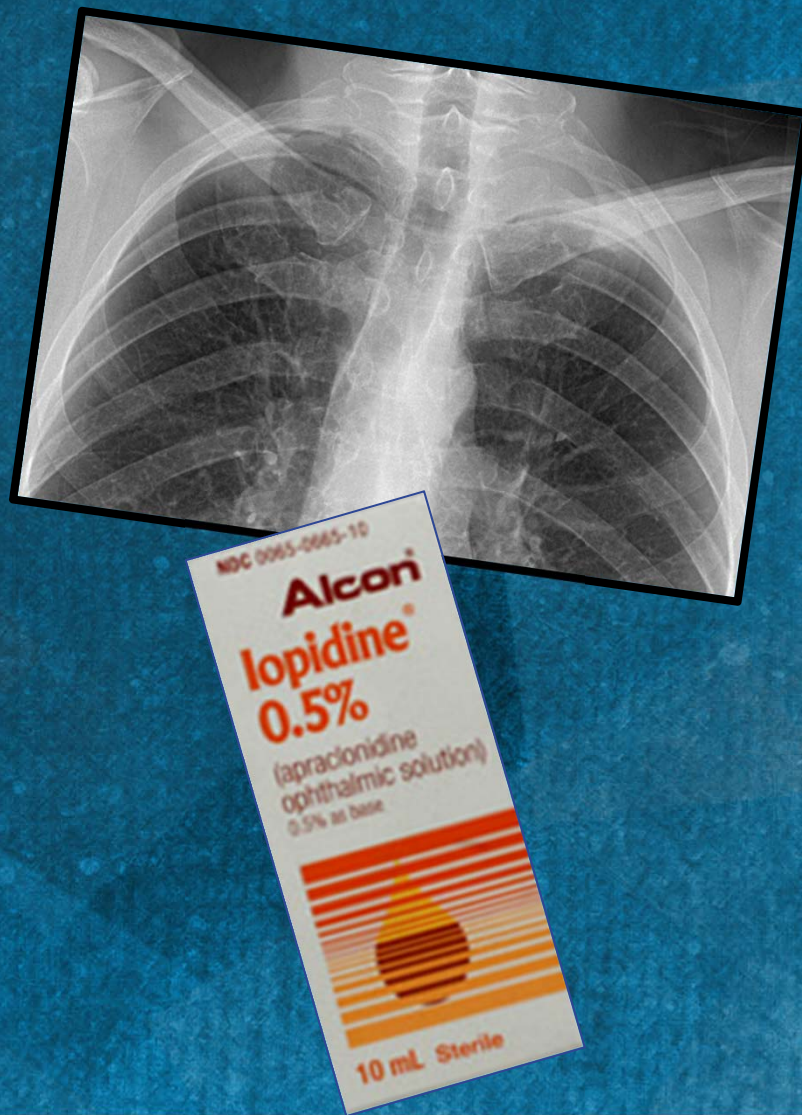
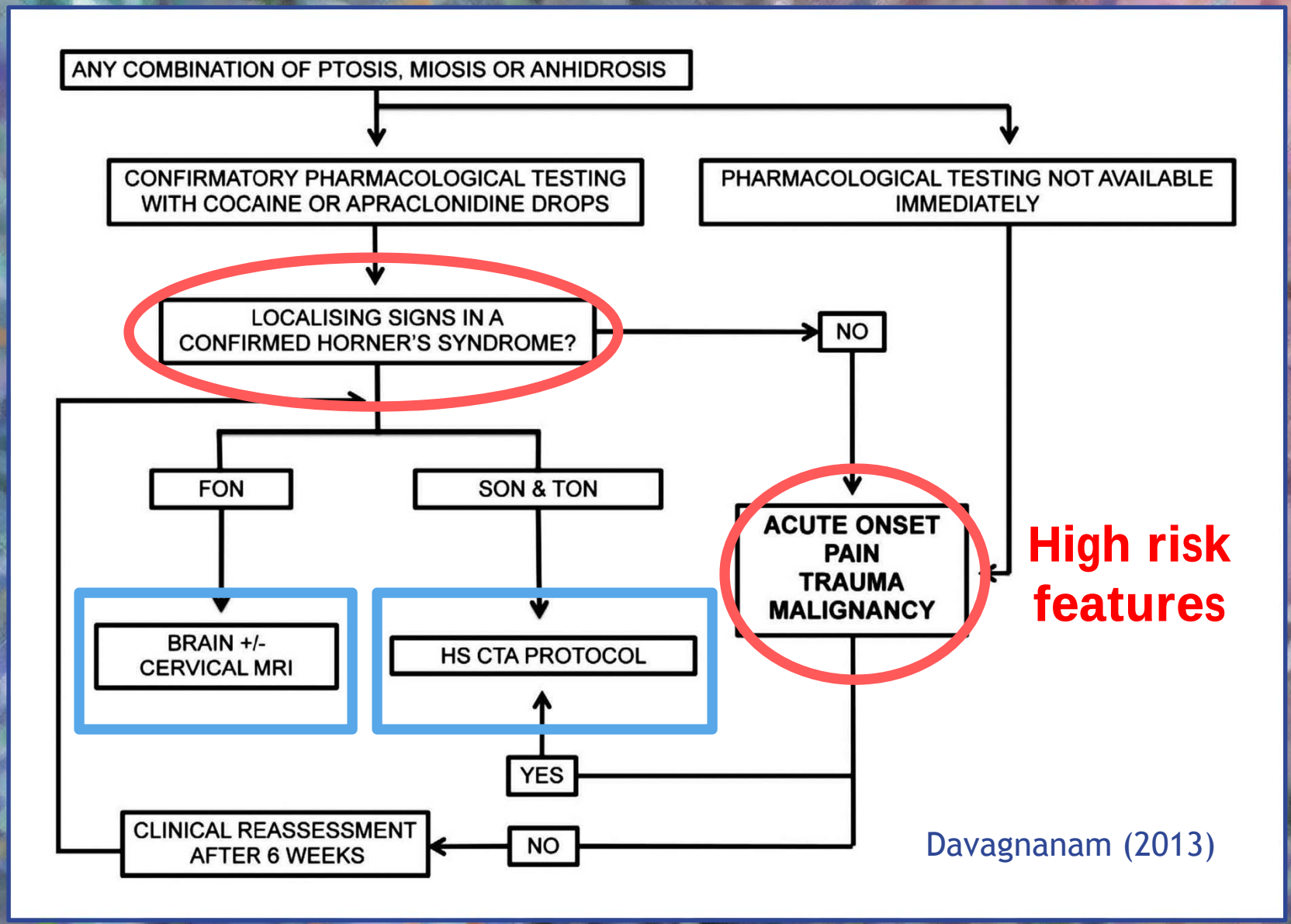


Radiographic Studies

- Important role in identifying the underlying cause of HS
- No firm consensus on imaging guidelines
- **Can often differentiate FON lesions from SON/TON lesions on clinical grounds***
  - FON: Midbrain studies ←*MRI*
  - SON/TON: Chest, neck, cavernous sinus ←*CTA*

* Davagnanam I, et al. Eye. 2013;27(3):291-8.

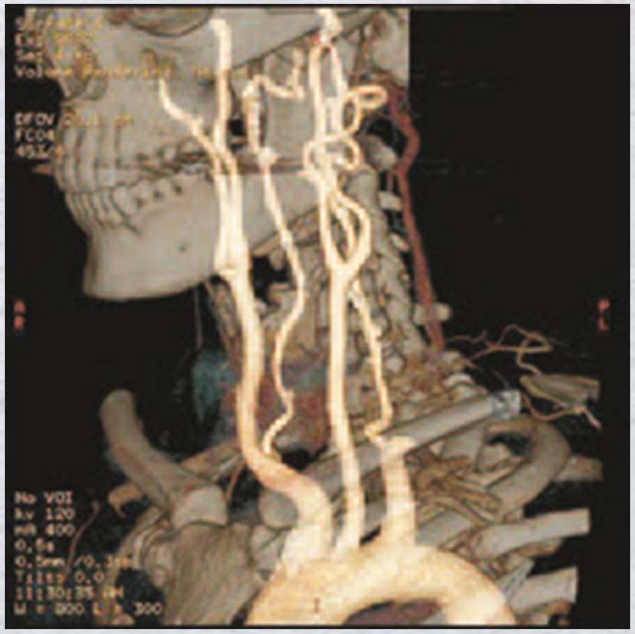


High risk features

Davagnanam (2013)

CT Angiogram Protocol

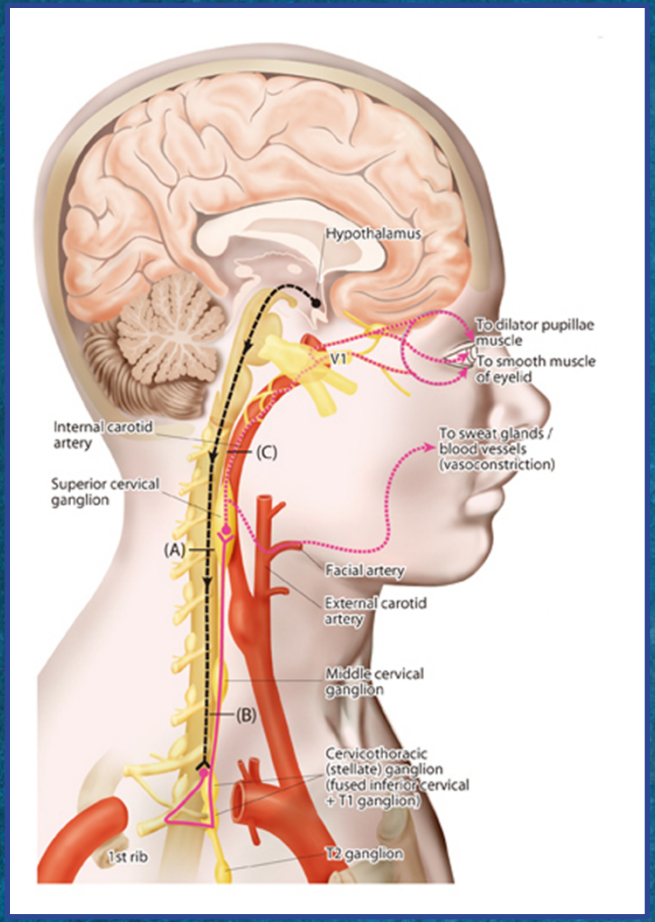
- Davagnanam (2013)*
  - **CT angiogram from Circle of Willis to aortic arch with visualization of the orbits and lung apices**
  - Advantages
    - Widely available
    - Excellent visualization of lung apices and carotids
  - Disadvantages
    - Ionizing radiation
    - Iodinated contrast agent



* Davagnanam I, et al. Eye. 2013;27(3):291–8.

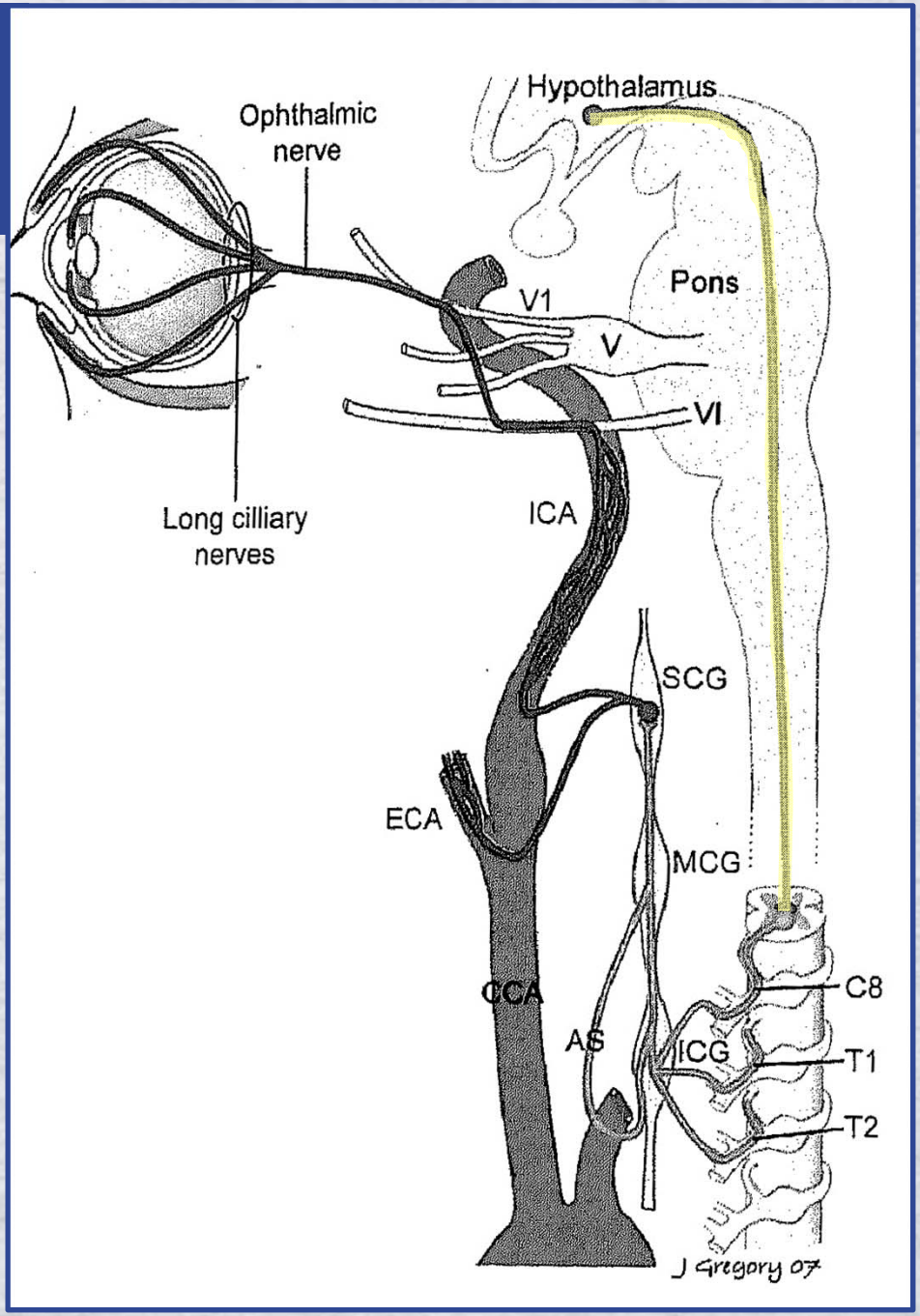
Major Causes of HS

- Wallenberg syndrome
  - Central HS (FON)
- Pancoast syndrome
  - Preganglionic (SON)
- Carotid artery dissection
  - Postganglionic (TON)
- Pediatric HS
  - Neuroblastoma



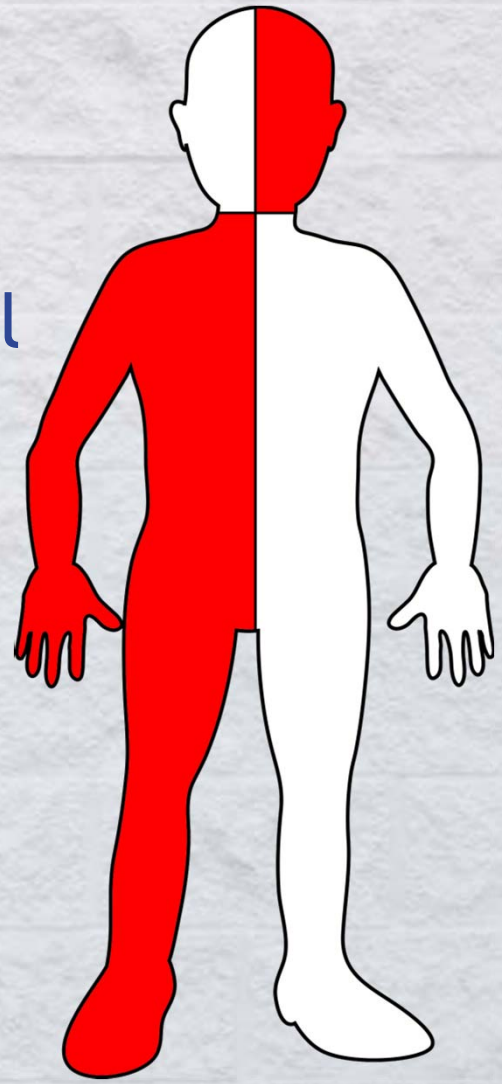
Central HS

- 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

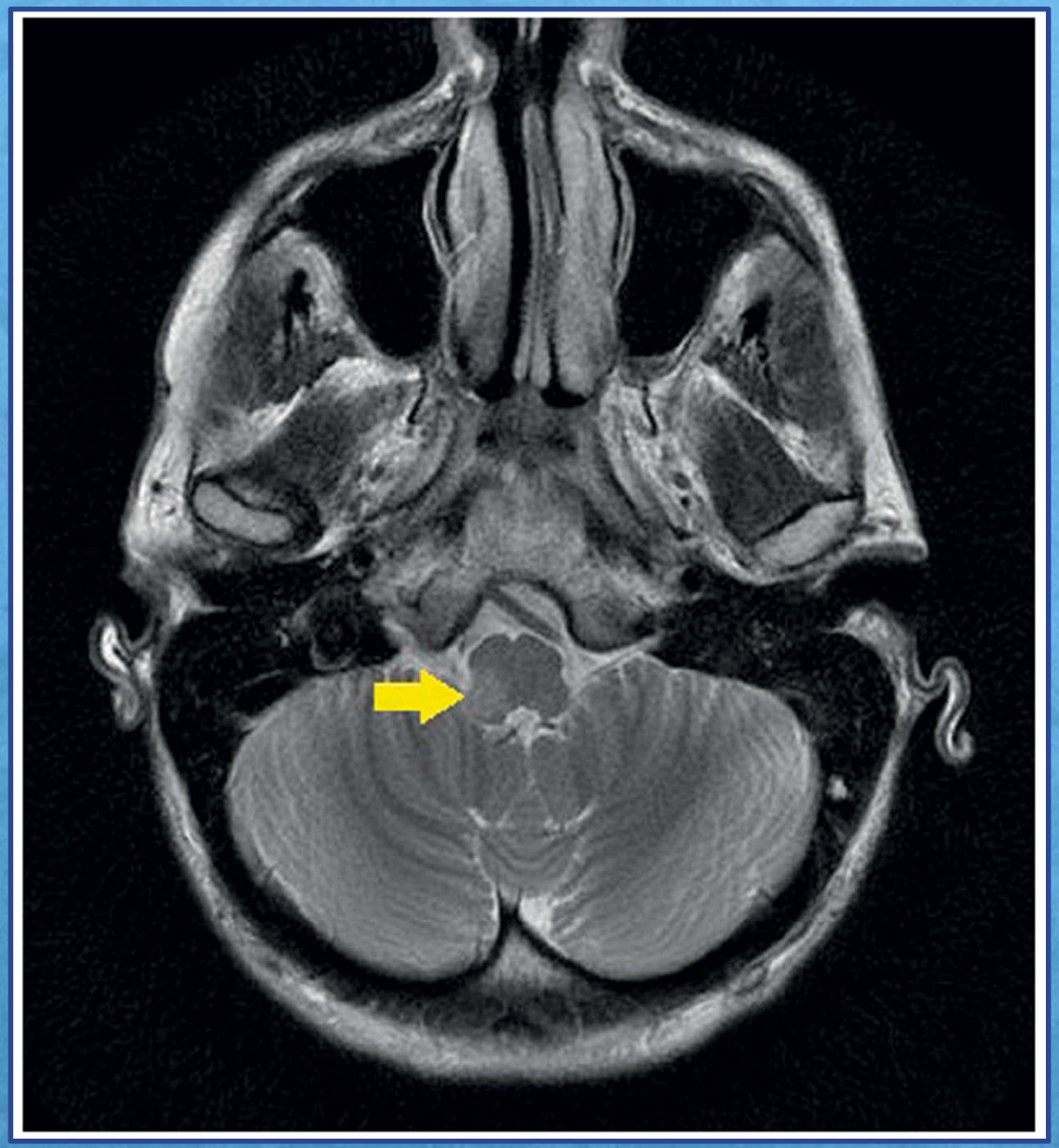
- Brainstem stroke syndrome
- Typical findings*
  - **Crossed sensory deficit**: ipsilateral facial analgesia, contralateral analgesia of the trunk
  - Ataxia: Loss of motor coordination
  - Dysarthria: Speech disorder caused by loss of control
  - Dysphagia: Difficulty swallowing



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

FON lesions are best visualized with MRI*

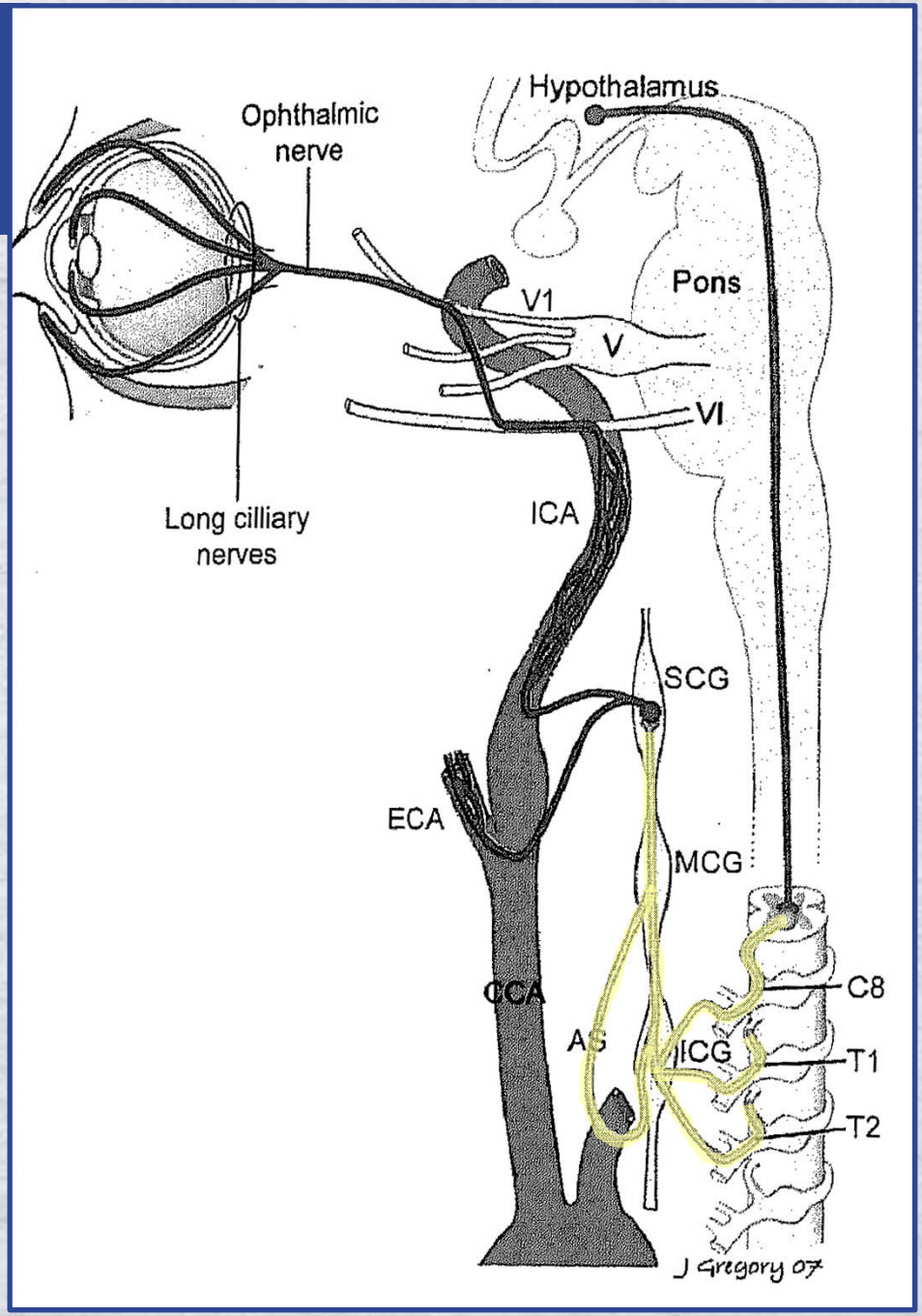
Axial T2-weighted MRI showing an infarct (arrow) in the midbrain supplied by the right posterior inferior cerebellar artery causing a Wallenberg syndrome.



* Ross MA. et al. Stroke. 1986;17(3):542–5.

Preganglionic HS

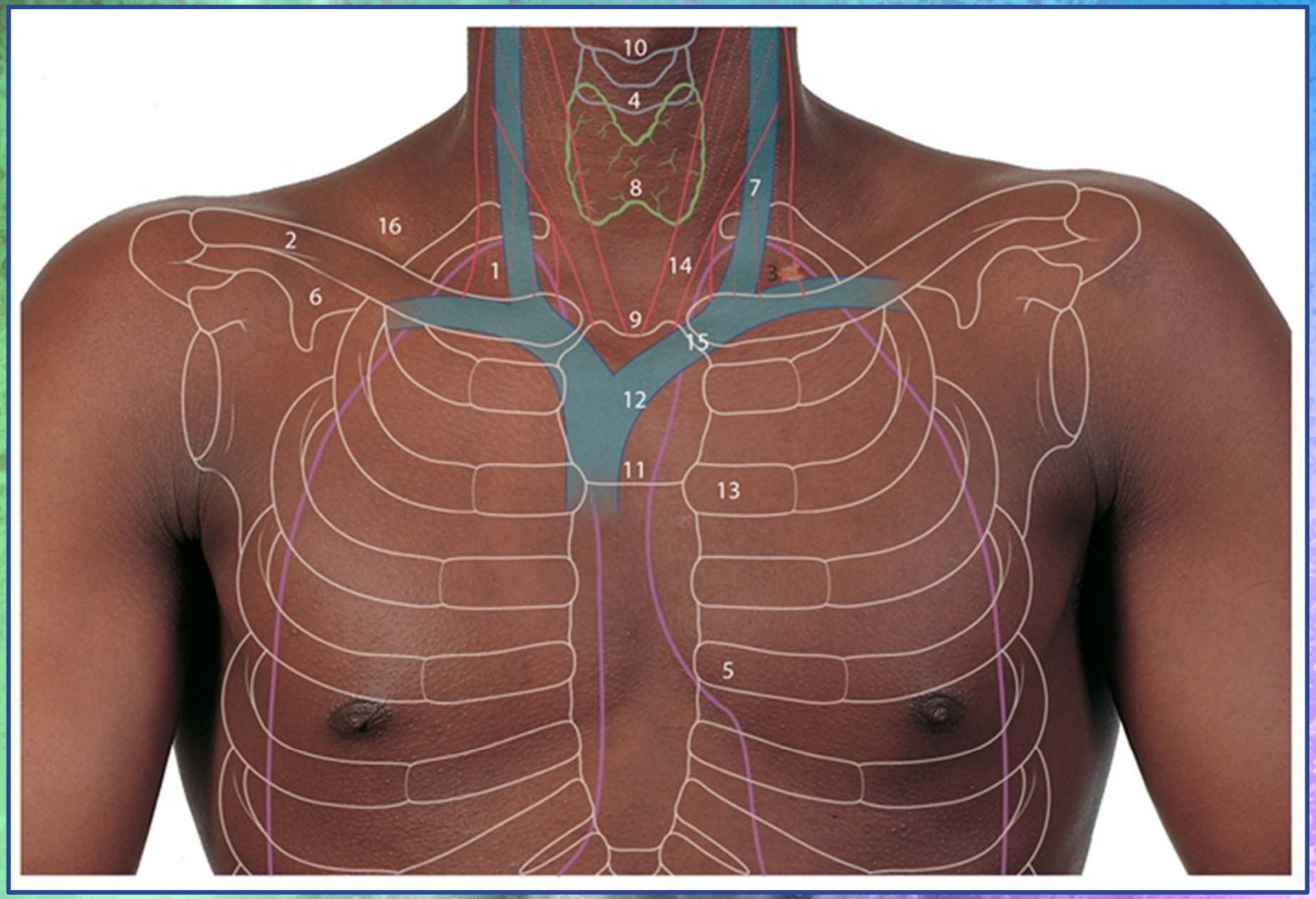
- Often presents as a clinically isolated finding
- Frequently idiopathic (~28%)
- Most common identified causes are **trauma and tumor** (Pancoast syndrome)



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

* Maloney WF, et al. Am J Ophthalmol. 1980;90(3):394-402.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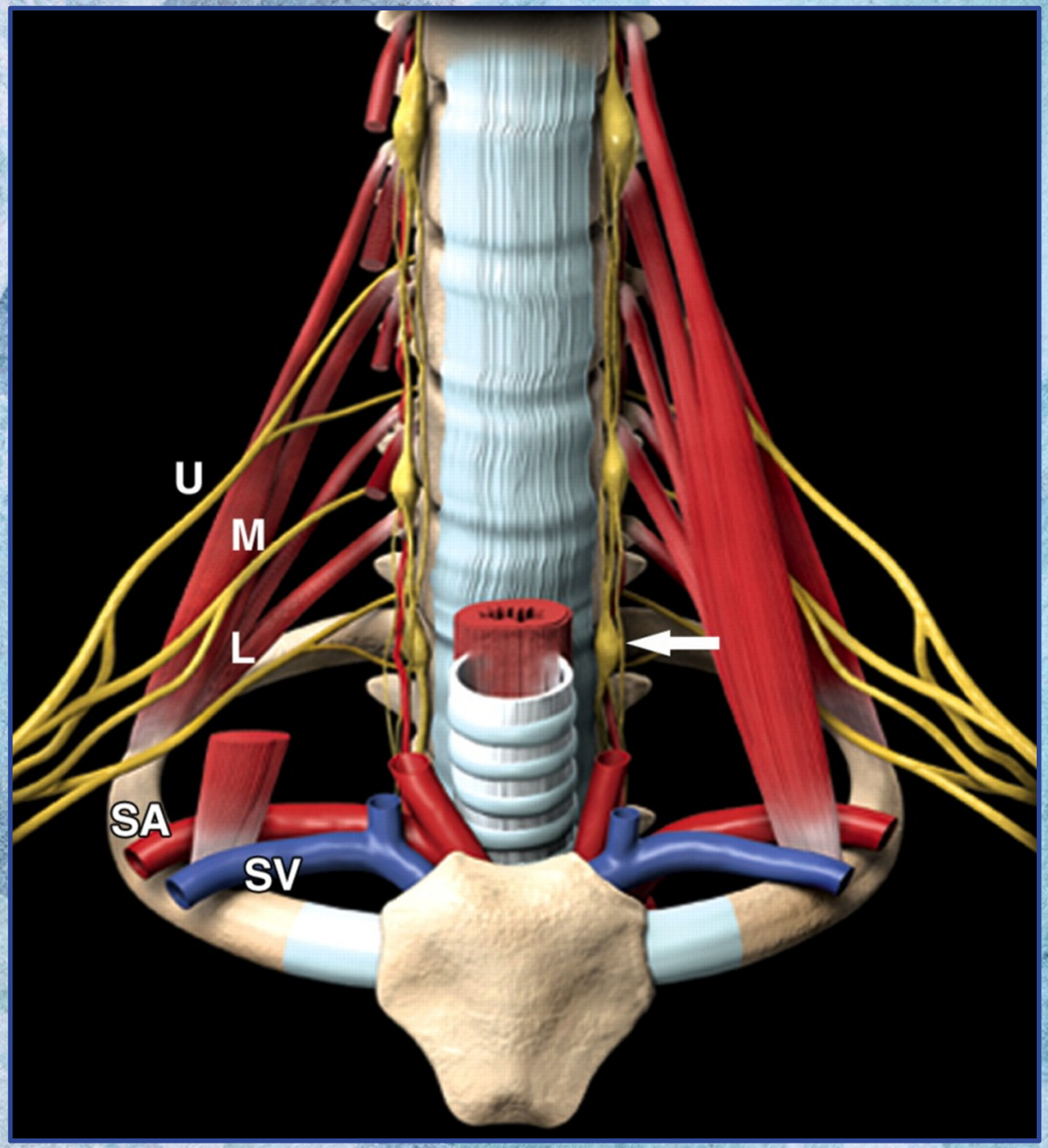
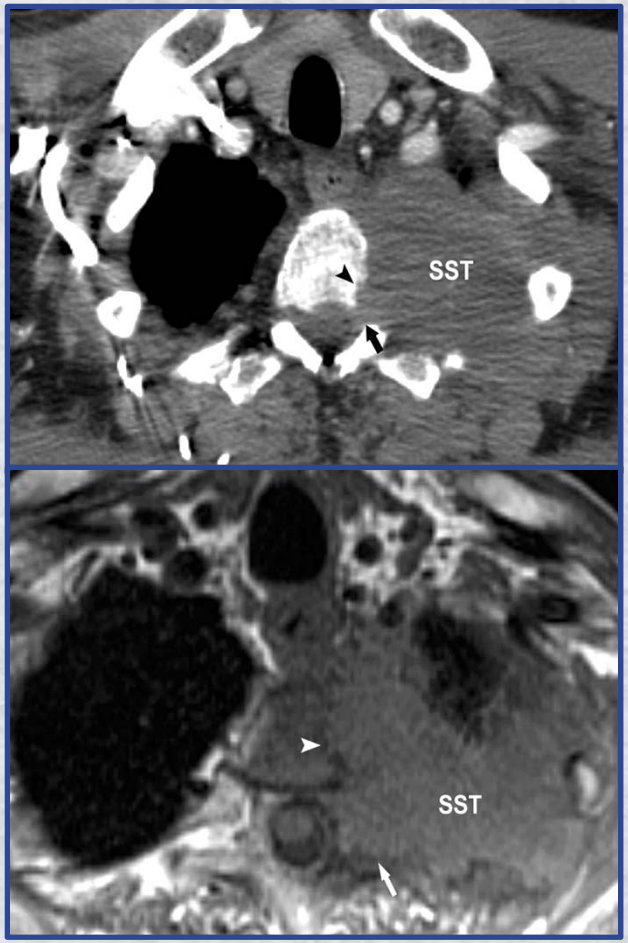


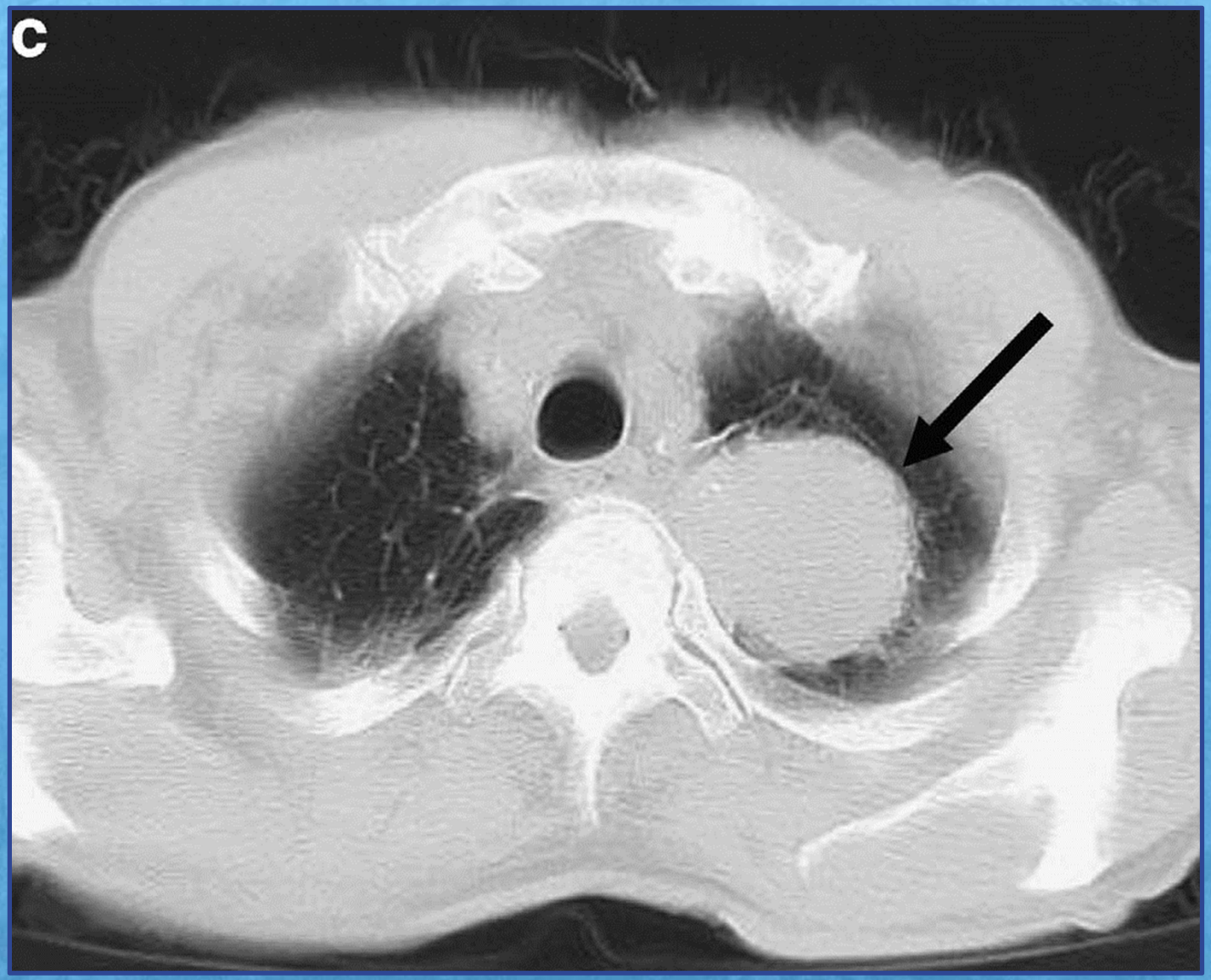
Apical lung tumors may invade the brachial plexus (U, M, L), the subclavian vessels (SA & SV) and the sympathetic ganglia that lie along the vertebral column (white arrow)

Pancoast Syndrome

- Diagnosis*
  - **Contrast-enhanced axial CT** effective for identification of the lesion
  - MRI for greater information about spatial relationships
  - Percutaneous needle biopsy for definitive histologic diagnosis
  - *Easily missed on a regular chest X-ray*



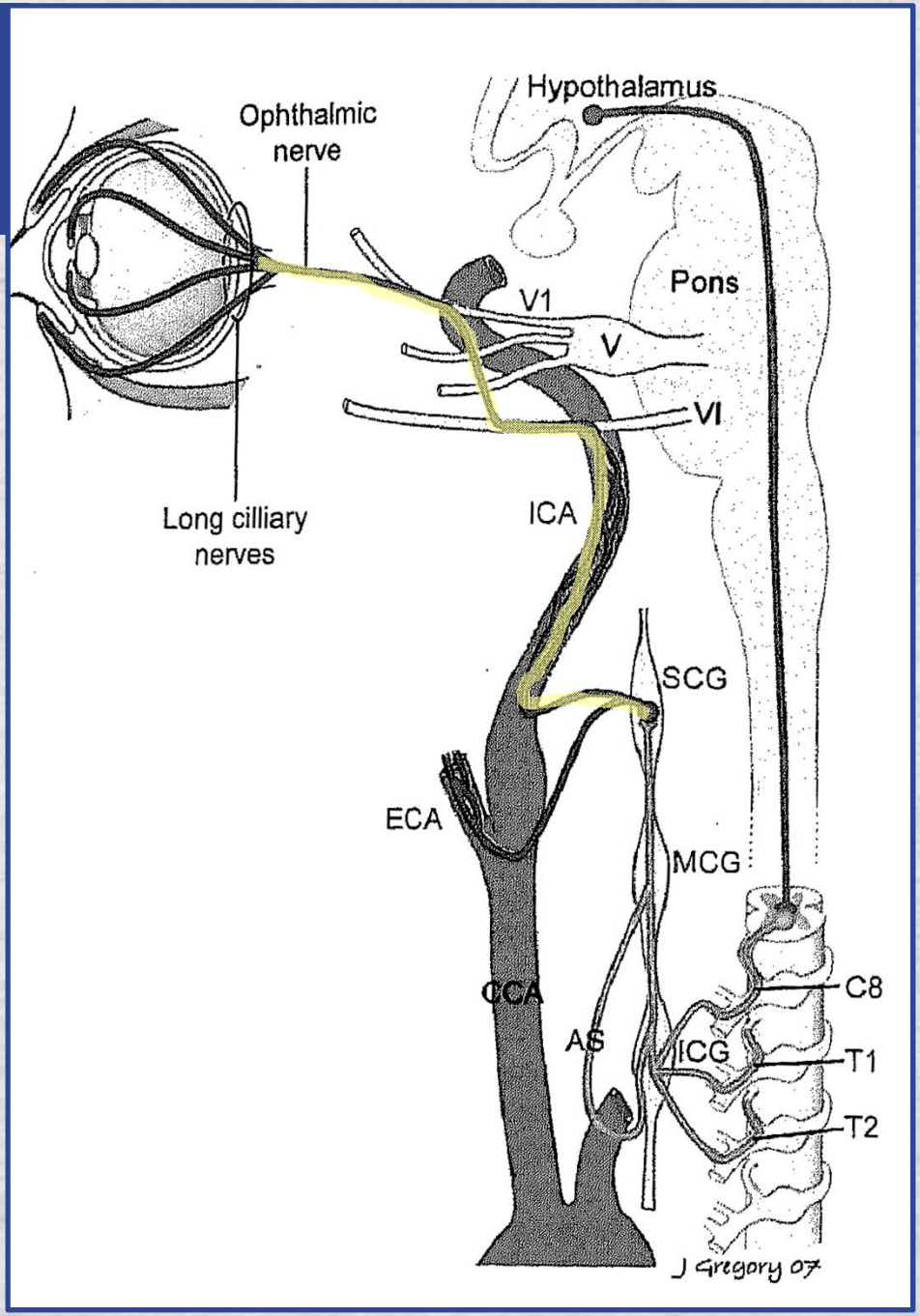
* Bruzzi JF, et al. Radiographics. 2008;28(2):551-60



CT angiogram axial image showing a left apical bronchogenic carcinoma (black arrow) (Davagnanam, 2013)

Postganglionic HS

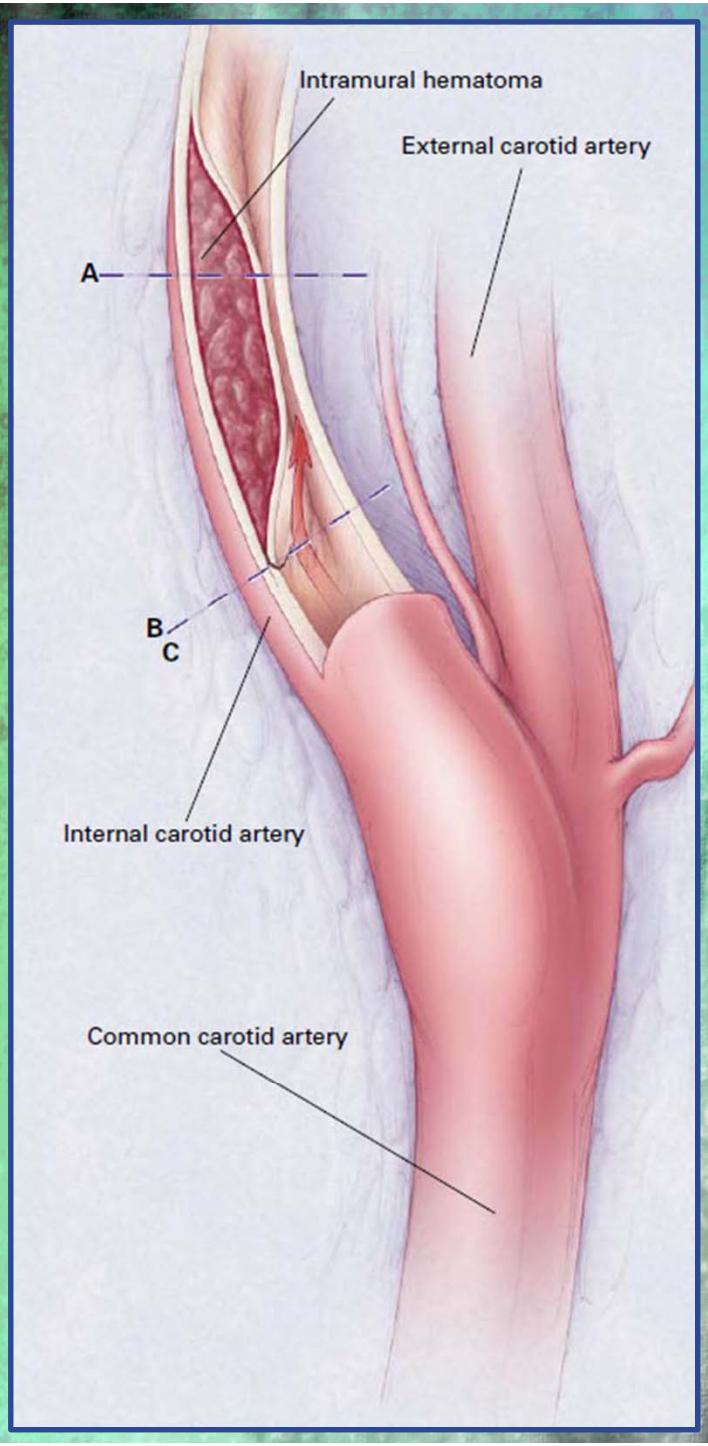
- Three types of lesions
  - Carotid artery lesions
  - Skull base tumors
  - Cavernous sinus & orbital apex disease
- **Carotid artery dissection** is an important cause of HS because it may have few other clinical manifestations and can rapidly lead to stroke

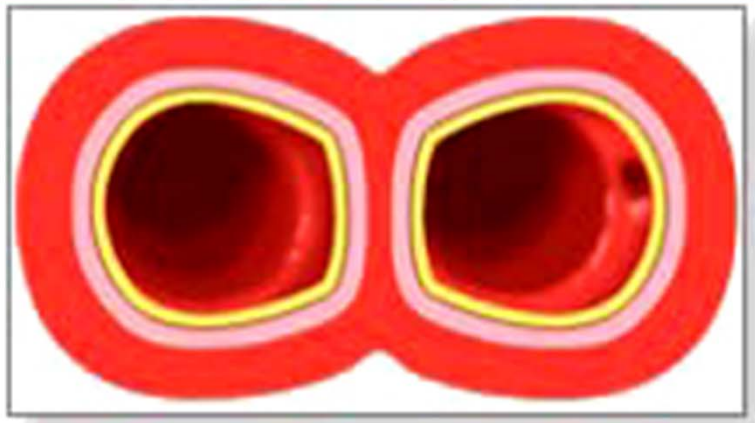


Carotid Artery Dissection

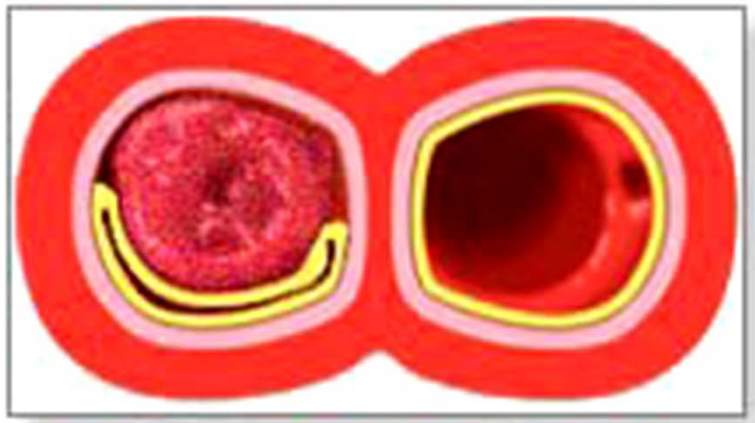
- An intimal tear in the arterial wall allows blood to enter the wall of the vessel and form an intramural hematoma
- Results in either stenosis or aneurysmal dilatation of the vessel.
- Spontaneous dissections affect all age groups, but are most common in the fifth decade of life
- **A major cause of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

* Schievink WI. NEJM. 2001;344(12):898-906.





Normal carotid artery

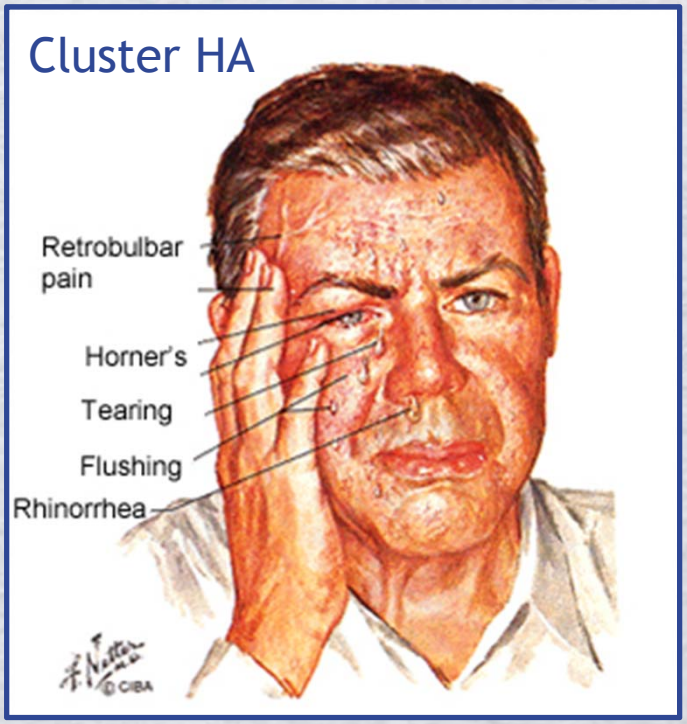


Lining of artery compressed due to blood dissecting up from a tear

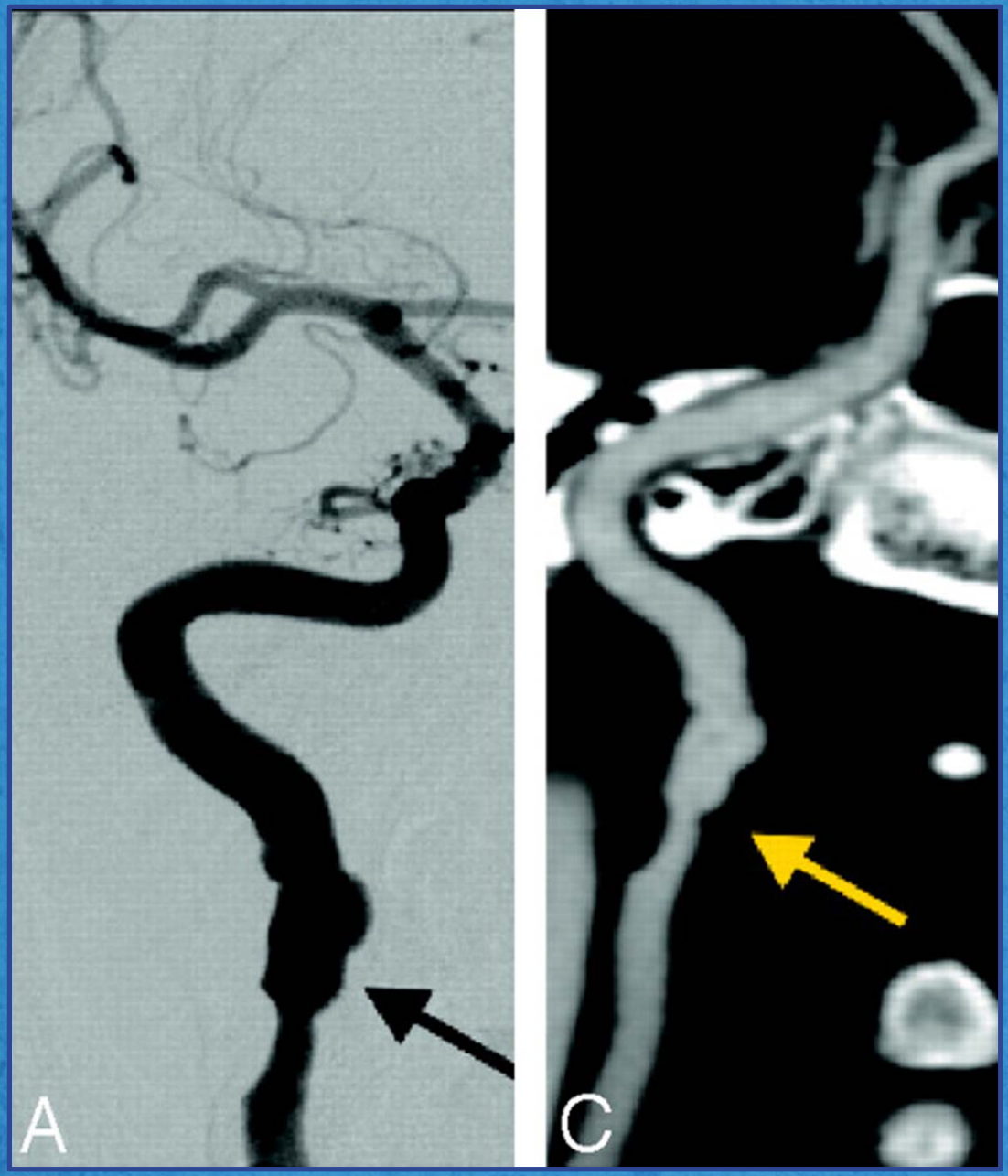
Schievink WI. NEJM. 2001;344(12):898-906.

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]



1. Schievink WI. NEJM. 2001;344(12):898-906.
2. Trobe JD. J Neuro-ophthalmol. 2010;30(1):1-2.



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).

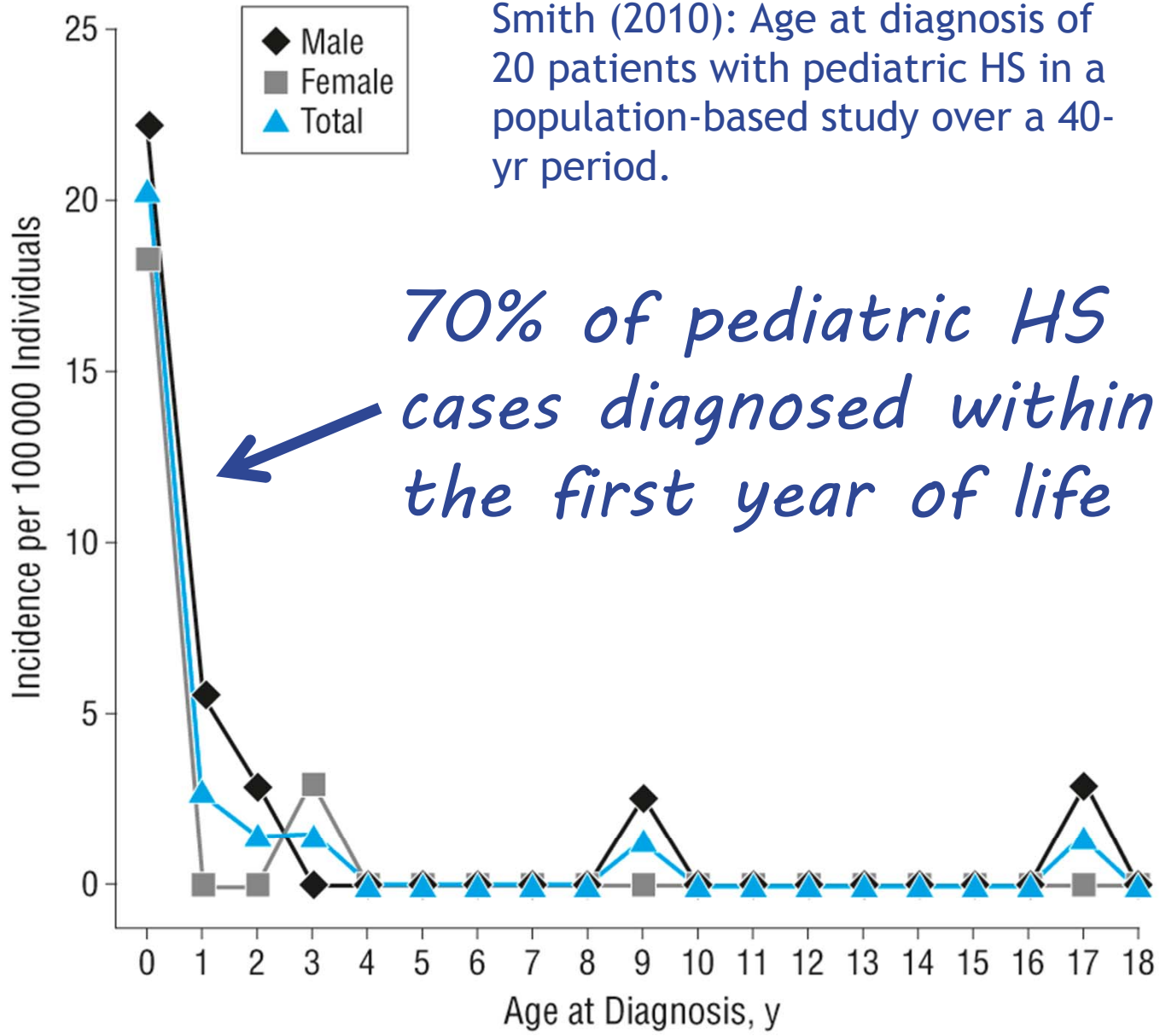
Vertinsky AT, et al. Am J Neuroradiol. 2008;29(9):1753-60.

Pediatric Horner Syndrome

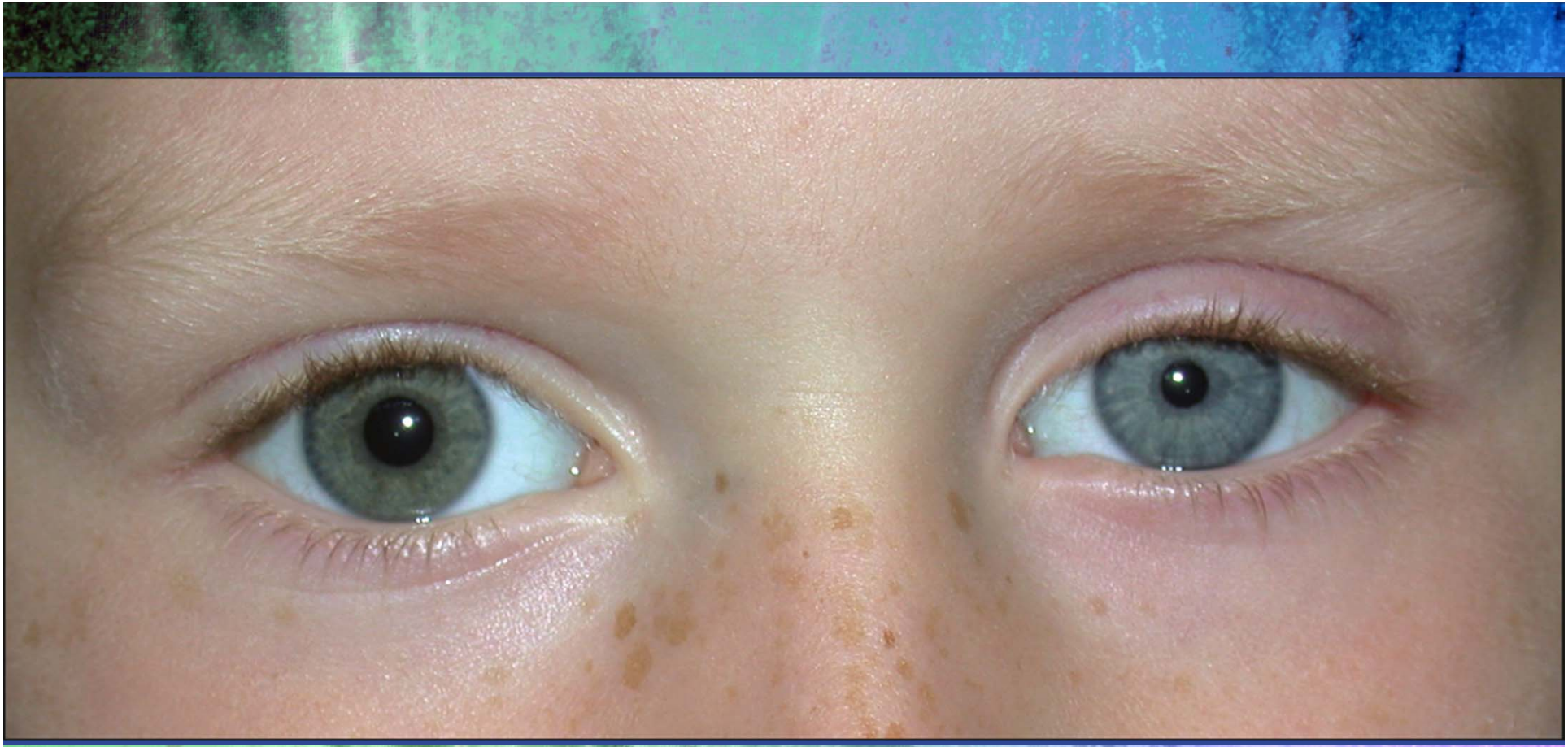
- Pediatric HS may be acquired or congenital
  - Congenital: birth trauma, neoplasm, others
  - Acquired: surgery, neoplasm, others
  - Often no underlying lesion can be found
- The most common neoplasm associated with pediatric HS is **neuroblastoma***
  - Most common tumor of the 1st year of life
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

* Smith SJ, et al. Arch Ophthalmol. 2010;128(3):324-9.

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*

Mahoney NR, et al. Am J Ophthalmol. 2006;142(4):651–9.

Key Points

- HS is a subtle, easily missed condition
- May be caused by hundreds of possible lesions, some life-threatening
- Search for localizing symptoms (eg. arm weakness) and high risk findings (eg. pain)
- Diagnosis can be clinical (dilation lag) or pharmacologic (apraclonidine)
- CT/MRI of the head, neck and chest is the best means of identifying a causative lesion

Thank you!