What if?... The Pupil Showed This

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- Adjunct Professor, University of Iowa Hospitals & Clinics, Iowa City, Iowa, Baylor COM, UTMB, UTMDACC







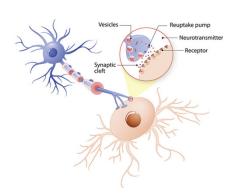


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What are we really covering?

- Anatomy
- Neurotransmitters
- Autonomic nervous system



https://qbi.uq.edu.au/files/27919/what-are-neurotransmitters-QBI.jpg

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Goal: you should be able to

- Describe the autonomic nervous system (ANS)
 - Sympathetic nervous system (SNS)
 - Parasympathetic nervous system (PNS)





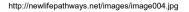
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Goal: you should be able to

- Give an overview of the pupil pathway
 - Differentiate Afferent from Efferent pathways







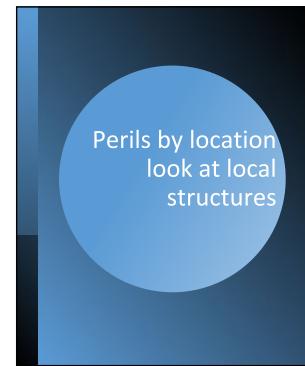
https://contemplativepathways.files.wordpress.com/2012/08/corn walls-glendurgan_1280x.jpg

5

Goal: You should be able to

Describe how location and local structures directs your differential diagnosis

List several causes of a "perilous pupil" tailored to the findings and location



• VITAMIN

 Vascular: aneurysm, malformation

• Infectious: Syphilis, TB

• Tumor: anything taking up space

 Anatomic: variation from the norm

• Metabolic: Thyroid

• Inflammatory: Sarcoid

• Neoplastic: primary or

metastatic

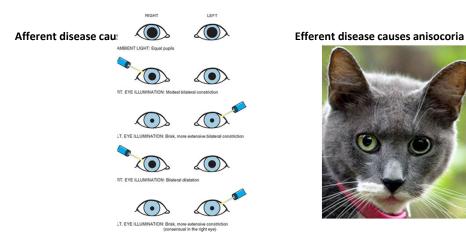
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To understand neural pathways, simplify...

- Stimulus (light) is received by the retina
- Retina transmits message to brain by neurons
 - "Relay station" between neurons is a synapse
- · Afferent neurons: eye to brain
- Efferent pathway: brain to end organ
 - Iris sphincter
 - Extra-ocular muscles



Afferent, Efferent: 2 different pathways



http://clinicalgate.com/wp-content/uploads/2015/04/B9780323033541500808_gr13.jpg https://vcahospitals.com/-/media/vca/images/lifelearn-images/anisocoria-in-cats-1.ashx?la=en&hash=7B633870616962F7E1016251E58B5971

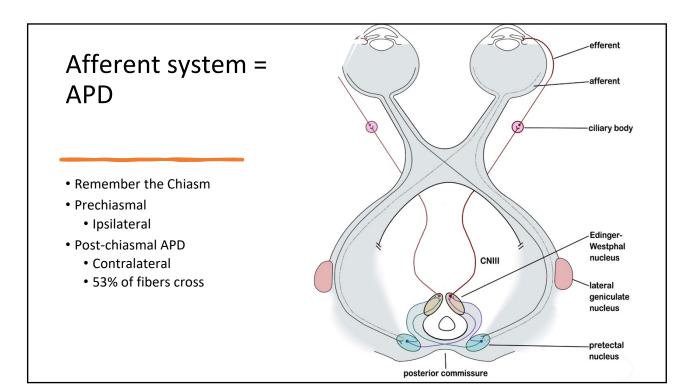
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If you find afferent and efferent, the patient has TWO lesions

• Repeat your pupil exam



 $\label{local-problem} $$ \frac{https://d2v9y0dukr6mq2.cloudfront.net/video/thumbnail/bOFIXnz/pupil-reaction-test-with-light_sgilxio4_F0000.png $$$



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Two types of Afferent fibers

- Vision fibers
- Pupil fibers



http://arts.brighton.ac.uk/__data/assets/image/0009/6201/yinyan g-1a.jpg

Afferents



Vision fibers

Synapse: lateral geniculate nucleus (LGN)





Pupil fibers

Bypass the LGN without synapse Synapse first in midbrain (pretectal nucleus)

Synapse again bilaterally

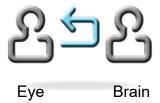
- Edinger-Westphal nuclei; CNIII
- Neuron between these synapses: interneuron

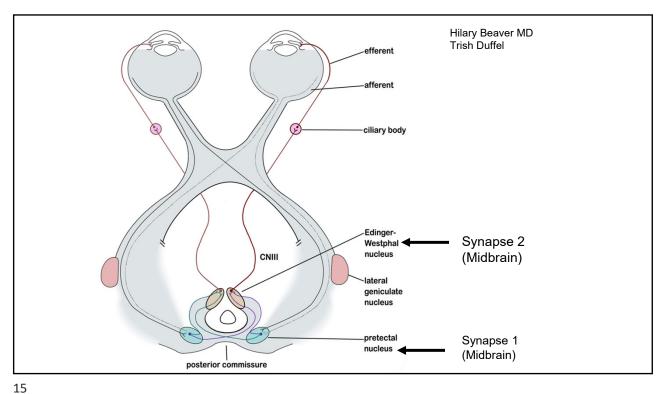
http://kidsblogs.nationalgeographic.com/globalbros/images/skipping-stones-at-avalanche-lake.jpg

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After the interneuron: Efferent fibers

- Bilateral post-synaptic fibers return to both eyes
 - Same impulse sent to both pupils
 - Explains the equal direct and consensual response
- Neural impulse causes pupil response



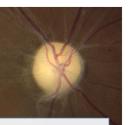


Afferent disease: sites for pupil perils

- Interruption of impulse from retina to midbrain
- Damage causes afferent pupillary defect (APD)
 - · Large retinal lesion
 - Lesion of optic nerves, optic tracts
 - Lesion of isolated pupil fibers all the way to midbrain
- May retain good vision or have vision loss
- RAPD not covered in PERRLA!
 - You must test for and document relative afferent pupillary defect (RAPD)

5mm 3mm No
P< D(ark) L(ight) APD
5mm 3mm No

Afferent pupil perils:



Large retinal lesion

Lesions of the optic nerve

• Macula

Optic nerve disease

- Tumor: Optic nerve glioma or meningioma
- Demyelinating disease
 - Multiple sclerosis
- Ischemia
 - Giant cell arteritis

http://medcnrome.com/wp-content/uploads/2012/04/saltatory.jpg

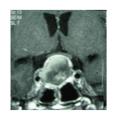
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Pupil perils: nerve compression



- Orbital disease
 - Graves disease
 - Tumors
- Brain tumors: malignant or benign
 - Meningioma
 - Frontal, olfactory groove, sphenoid ridge
 - Foster-Kennedy Syndrome
 - Pituitary (apoplexy, tumor)





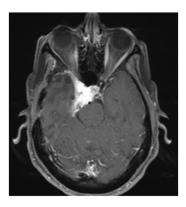
Courtesy of AG Lee, MD

http://webeye.ophth.uiowa.edu/eyeforum/atlas/pages/Thyroid-Eye/fig2-TED-LRG.jpg http://www.oculist.net/downaton502/prof/ebook/duanes/graphics/figures/v2/0240/010f.jpg

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Pupil perils: Inflammatory/ infectious involvement to chiasm

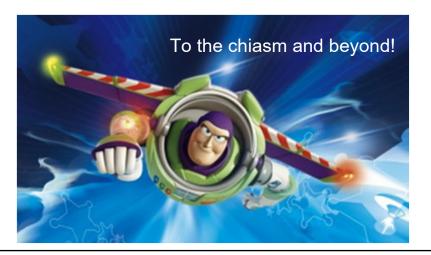
Sarcoidosis



Courtesy of AG Lee, MD

The forgotten afferents

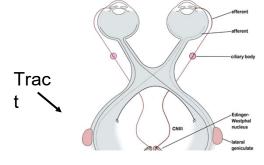
• Optic tracts, Midbrain



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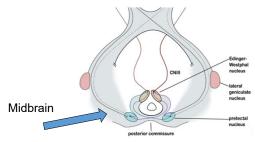
The forgotten afferents

- Optic tracts
 - 53% pupil fibers cross (vs 47% = 6% difference)
 - Unequal crossing = unequal tract innervation
 - 53% Tract lesion causes contralateral APD
 - Post chiasmal lesion
 - If Visual defect, then homonymous hemianopsia



The most forgotten pretectal afferents

- Lesion as far back as the midbrain
 - Pupil fibers don't synapse until midbrain
 - Presynaptic damage causes APD
 - Pupil fibers have separated from vision fibers
 - Bypass the LGN
 - Therefore no associated vision loss



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Afferent pupillary defect anywhere along afferent pathway Optic nerve lesion causes ipsilateral APD and vision loss Optic tract lesion causes contralateral APD and Homonymous hemianopsia Midbrain lesions cause APD without vision loss

Enough with the Afferents

• On to the Efferents!



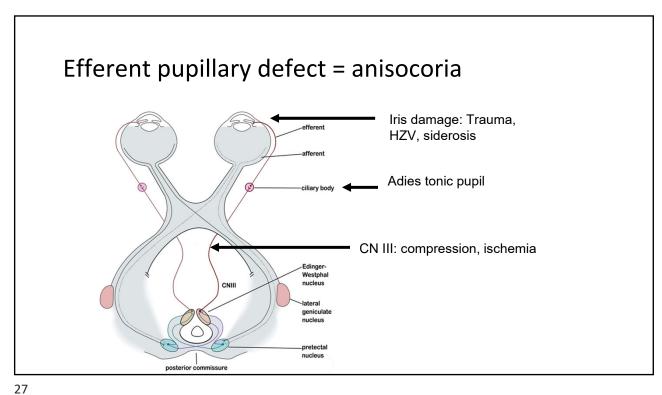
http://davidlwilliams.org.uk/wp-content/uploads/2011/08/Barn-owl-anisocoria-in-light.jpg

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Efferent disease

- Iris innervated by Autonomic Nervous System
 - Constrictor muscle
 - Parasympathetic fibers: midbrain to pupil
 - Dilator muscle
 - Sympathetics, covered later
- Present with anisocoria
- Patients have good vision, intact retinas and normal optic nerves (no RAPD)





Pupil path is autonomic nervous system

Autonomics are automatic

- You don't have to think for them to function
- Autonomic nervous system works while you don't

Components

- Sympathetic nervous system (SNS)
- Parasympathetic nervous system (PNS)

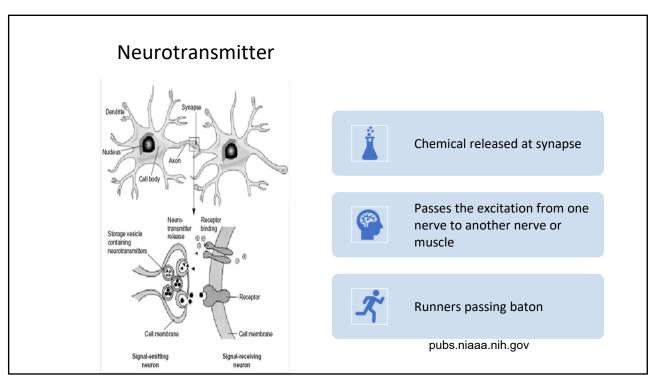
Balance of power within each system

- Activation (stimulation)
- Suppression (inhibition)

Components of the ANS

- Sympathetic nervous system
 - Neurotransmitter: epinephrine, norepinephrine
 - Ex.: Fight or flight response
 - Increased heart rate and blood pressure
 - "Wide eyed with fright" opens pupil and lid
- Parasympathetic nervous system
 - Neurotransmitter: acetylcholine
 - Ex.: Digestion
 - Pupil constriction

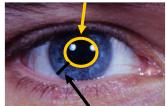
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Parasympathetics constrict pupil

- Sphincter muscle
 - Contraction constricts pupil
 - Purse string effect
- PNS defect = dilated pupil

Constrictor muscle



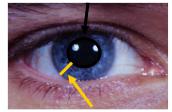
Dilator muscle

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Sympathetics dilate pupil

- Dilator muscle- like spokes on wheel
 - Contraction dilates pupil
- SNS defect = small pupil

Constrictor muscle



Dilator muscle





Applied science: Locate lesion using anisocoria

 Pinpoint which neuron by pharmacologic testing



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Localize anisocoria by pupil responses: 3 choices

- Asymmetry equal in light and dark
- Asymmetry greater in dark
 - One pupil cannot dilate
- · Asymmetry greater in light
 - One pupil cannot contract

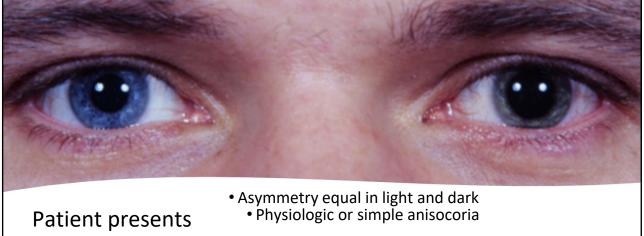
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Asymmetry equal in light and dark

- Physiologic or simple anisocoria
- •20% of normal people
- Benign, variable by day
- Example
 - Dark: 5 mm OD, 4 mm OS
 - Light: 4 mm OD, 3 mm OS







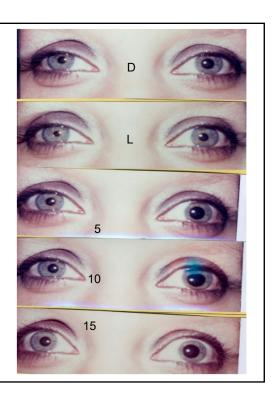
with anisocoria: Localize by the pupil responses

- Asymmetry greater in darkPupil cannot dilate
- Asymmetry greater in light

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Asymmetry greater in dark: the little pupil is abnormal

- Pupil cannot dilate
 - Dilator not being stimulated (SNS problem)
 - Most marked immediately after lights out
 - Dilation lag



SNS does more then just pupils

- Elevates lid (Mueller's muscle)
- Dilates pupil
- Facial sweating
- Loss of these function = Horner syndrome
 - Ptosis, miosis, anhydrosis



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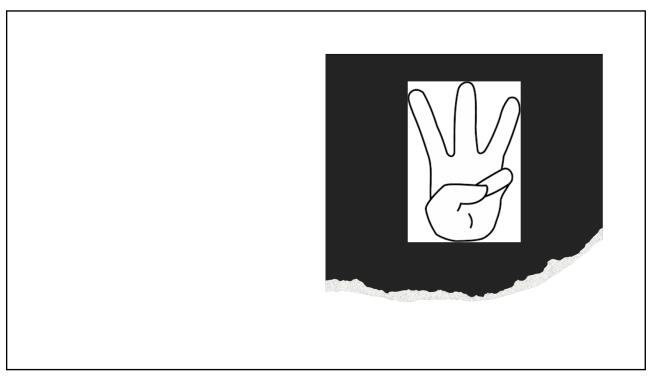
Don't forget upside down ptosis





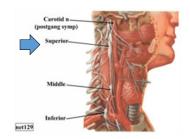


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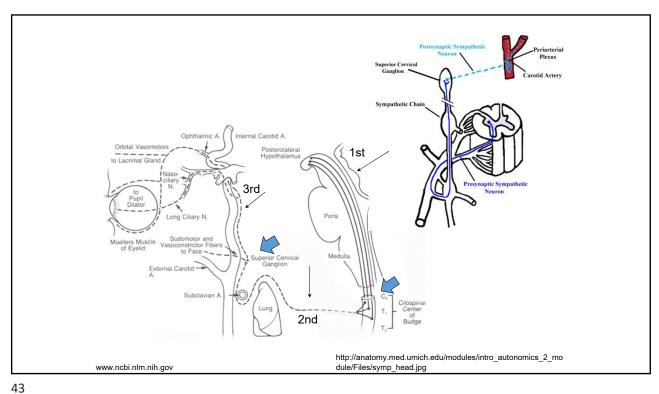


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- First order neuron
 - Hypothalmus, runs down spinal column
 - Synapse in C7-T2 cord
- Second order neuron
 - Leaves spine, ascend outside spine
 - Over lung apex
 - Synapse near jaw
 - Superior cervical ganglion
- Third order neuron
 - Within wall of carotid into skull

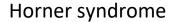


 $https://o.quizlet.com/F.oiYbWeAxIIIwTgqNUP2g_m.jpg$



Sympathetic third order neuron

- External carotid- sweat glands of lower face
- Internal carotid- Into skull
 - Cavernous sinus- rides CN VI then CN III
 - In orbit on ciliary nerves
 - Pupil dilator muscle
 - On ophthalmic artery branches
 - Muller's muscle (lid)
 - Lower eyelid retractors
 - Frontal sweat glands





Issue: where is the lesion



Location, location



Indicates likely differential diagnosis

1st, 2nd, 3rd order neuron?



Ptosis

Miosis

Upside down ptosis

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Traditional (multistep)
Horner test Step one

- Do not touch or drop the eye!
 - Makes subsequent testing unreliable
- Cocaine 10% (Compounding pharmacy)
 - Prevents synaptic reuptake of norepinephrine
 - Iris dilator muscle
 - Excess norepinephrine floods iris dilator receptors
 - Normal pupil dilates
 - ***If SNS not functioning, no baseline release of norepinephrine so no dilation = Horner syndrome
 - Postcocaine anisocoria > 1mm is Horner



Traditional: Step two

- Go home- you've had step one, which makes further same day testing unreliable
- Hydroxyamphetamine 1% (Compounding pharmacy)
 - Stimulates intact nerve to release norepinephrine
 - Released norepinephrine stimulates dilator muscle
 - Pupil dilates
 - If pupil dilates, then 3rd order nerve is intact
 - Thus 3rd order not the problem
 - Therefore is a 1st or 2nd order lesion

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New kid on the block: apraclonidine (lopidine)

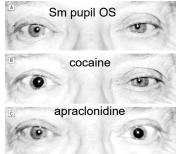


- Alpha 1: dilates
- Alpha 2: constricts
- Apraclonidine primarily alpha-2 agonist
 - Constricts normal pupils (glare post lasik)
 - Weak alpha-1 activity
- But....Horner syndrome
 - Denervation supersensitivity after 5-7 day



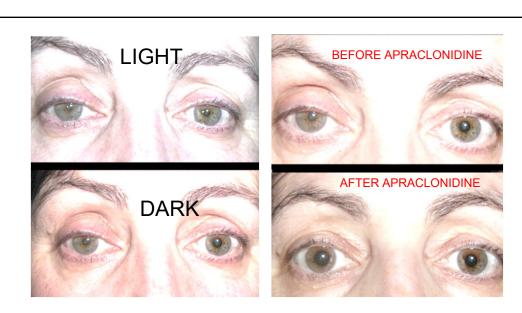
Denervation supersensitivity

- Apraclonidine normally alpha-2 agonist
 - Constricts normal pupil
- Horner: denervation supersensitivity (α -1)
 - Small pupil dilates (alpha-1)
 - Ptotic lid elevates (alpha-1)
- · Reversal of anisocoria
 - Easy to obtain drop
 - · Easy to read result



Ocular Effects of Apraclonidine in Horner Syndrome
Jose Morales, MD; Sandra M. Brown, MD; Aziz S. Abdul-Rahim, MD; Craig E. Crosson, PhD
Arch Ophthalmol. 2000;118(7):951-954. doi:10-1001/pubs.Ophthalmol.-ISSN-0003-9950-118-7-ecs90240

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Apraclonidine test (inferior image) confirmed suspected diagnosis of Horner syndrome. *González Martín-Moro et al. Horner Syndrome, a New Complication. J Oral Maxillofac Surg 2009.*

• All you can prove pharmacologically
• It is/not Horner syndrome
• It is/not last nerve in the sympathetic pathway

30 year old WF presents with 4 months of anisocoria

No PMH, no headache, no neck surgery

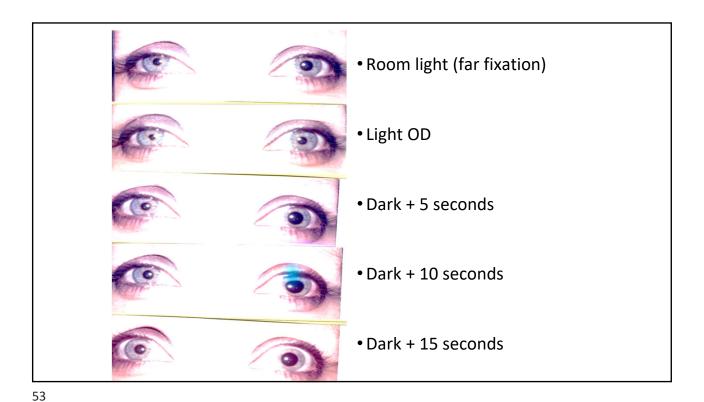
6 years s/p bike accident "clothslined"

Seen in ER, arm x-ray and exam (–)

2 years later: left arm, dorsal hand pain, arm "cold"

• Saw chiropractor- resolved

Was noted to have anisocoria



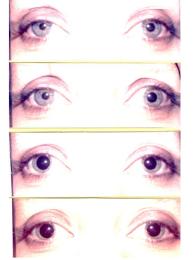
1 hour after cocaine 10%

• Room light

• Dark room

• Mild ptosis, miosis, dilation lag, poor response to cocaine = Horner syndrome

Hydroxyamphetamine 1%



- Room light
- Dark room

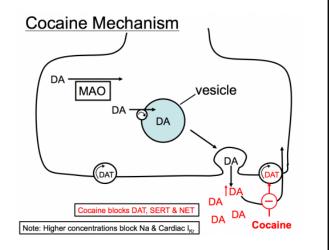
(45 minutes after HA1%)

- Room light
- Dark room
- DX: Preganglionic Horner (brachial plexus trauma)

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How to remember the sympathetics?

- People like stimulation
 - Cocaine and amphetamine thus drugs of abuse
 - Stimulation dilates pupil (wide eyed with fright)
- Cocaine is a stimulant and will dilate pupils
 - Inhibits reuptake of neurotransmitter
 - Sympathetic pathway must be intact
- Amphetamine forces release of neurotransmitter <u>if</u> third order neuron is intact



Where is the "Peril"? 3rd order neuron lesion



Carotid artery damage

- Dissection (splitting apart)
 - Blood within wall
- Post traumatic
 - Roller coaster, whiplash, chiropractic manipulation
- Stroke risk: Carotid occlusion or clot

Post surgical

• Neck dissection, endarterectomy

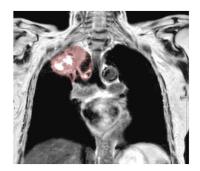
Cavernous sinus tumor

http://www.pyroenergen.com/articles13/images/carotid-artery-dissection.jpg

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Preganglionic "Perils"?

- 2nd order neuron lesion
 - Apical lung cancer (Pancoast tumor)
 - Beware Horner in smokers!
 - Metastasis- Sentinel nodes in neck
 - Chest lesion: aortic aneurysms, brachial plexus syndrome, surgery
- 1st order neuron lesion
 - Brain and spinal cord- stroke, tumor, disc dx
 - Rarely isolated as is tight space



https://moffitt.org/media/4633/bc_pancoast_mr.jpg

Infant with Horner syndrome

- Congenital lesion along the sympathetic chain
- Birth trauma to brachial plexus
- Associated with iris heterochromia
- Neuroblastoma
 - Malignant but treatable childhood tumor
 - "Baby gram" MRI scan of the sympathetic chain
 - Chest lesion

http://image.slidesharecdn.com/hornerfonts3-130619193933-phpapp02/95/horner-syndrome-15-638.jpg?cb=1371672820193933-phpapp02/95/horner-syndrome-15-638.jpg?cb=1371672820193933-phpapp02/95/horner-syndrome-15-638.jpg?cb=1371672820193933-phpapp02/95/horner-syndrome-15-638.jpg?cb=137167282019393-phpapp02/95/horner-syndrome-15-638.jpg?cb=137167282019393-phpapp02/95/horner-syndrome-15-638.jpg?cb=137167282019393-phpapp02/95/horner-syndrome-15-638.jpg?cb=137167282019393-phpapp02/95/horner-syndrome-15-638.jpg?cb=137167282019393-phpapp02/95/horner-syndrome-15-638.jpg?cb=137167282019393-phpapp02/95/horner-syndrome-15-638.jpg?cb=137167282019393-phpapp02/95/horner-syndrome-15-638.jpg?cb=13716728201939-phpapp02/95/horner-syndrome-15-638.jpg?cb=13716728201939-phpapp02/95/horner-syndrome-15-638.jpg?cb=13716728201939-phpapp02/95/horner-syndrome-15-638.jpg?cb=13716728201939-phpapp02/95/horner-syndrome-15-638.jpg?cb=13716728201939-phpapp02/95/horner-syndrome-15-638.jpg?cb=13716728201939-phpapp02/95/horner-syndrome-15-638.jpg?cb=137167282019-phpapp02/95/horner-syndrome-15-638.jpg?cb=137167282019-phpapp02/95/horner-syndrome-15-6382019-phpapp02/95/horne-syndrome-15-6382019-phpapp02/95/horne

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Patient presents with anisocoria: Localize by the pupil responses

- $\bullet\,$ Asymmetry equal in light and dark
 - · Physiologic or simple anisocoria
- Asymmetry greater in dark
 - Sympathetic N.S. defect
- · Asymmetry greater in light
 - Pupil cannot constrict

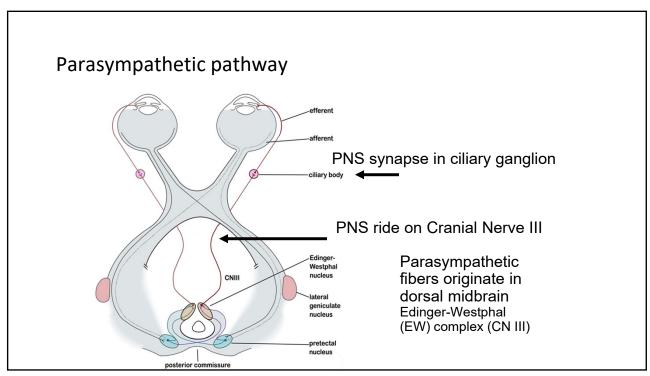
Anisocoria greater in light; Problem is the dilated pupil

- Pupil can't constrict- big pupil abnormal
 - Sphincter muscle not getting stimulated
 - Nerve defect: parasympathetic pathway
 - Iris muscle damage: slit lamp exam
- Differential diagnosis
 - Pupil involved CN III lesion
 - Adie's tonic pupil
 - Pharmacologic dilation



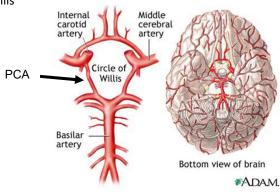
www.usba.gov/vour-visit/October12007.cfm

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PNS lesion: CN III lesion

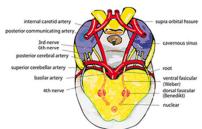
- Ride on Cranial Nerve III
 - Ride on top of third nerve
 - Nerve travels below posterior communicating artery
 - Circle of Willis



http://www.nlm.nih.gov/medlineplus/ency/imagepages/18009.htm

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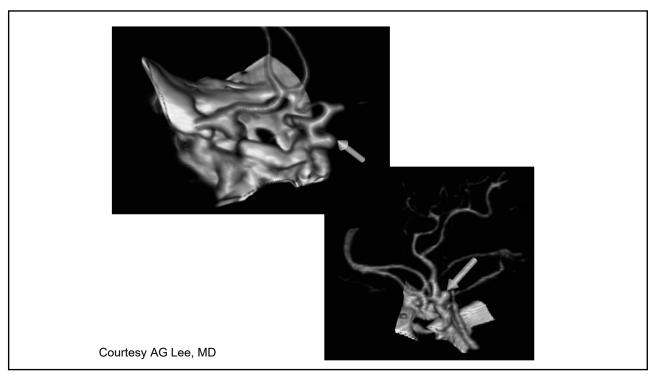
CN III "perils"

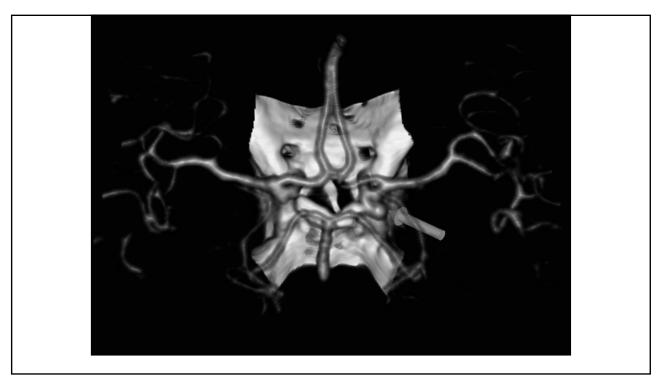


- PNS Ride on top Cranial Nerve III
 - Under posterior communicating artery (PCA)
 - Aneurysm of the PCA compresses the top of CN III and PNS
 - Enter cavernous sinus
 - Tumor, vascular, inflammatory, or infectious disease
 - Enter orbit on inferior division CN III
 - Tumor, inflammatory or infectious disease
- Synapse in ciliary ganglion in orbit
- Ride on inferior oblique division of CN III
 - Innervates pupil sphincter

http://www.cmej.org.za/index.php/cmej/article/viewFile/2686/2905/15666







Unilateral dilated pupil: Is it a CN III palsy?



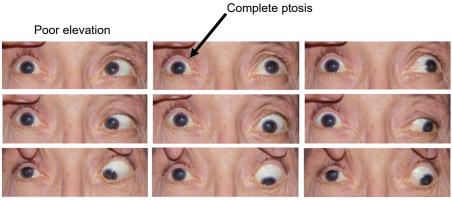
- Ptosis: Partial or complete
 - Need to lift the lid for drops?
 - Stop and reassess
- Exotropia: Partial or complete
 - Cannot adduct, elevate, depress
 - Lateral rectus (CN VI) unopposed



https://themilwaukeedrum.files.wordpress.com/2012/07/down-and-out.jpg

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Motility deficit of CN III palsy



Poor depression

Poor adduction

CN III post pharmacological dilation This patient also has CN VI palsy

So what?

- Aneurysm of PCA compresses pupil fibers
- Associated with third nerve findings
 - May be partial CN III, partial pupil
- Pupil is key to diagnosis
 - Alternative diagnosis if pupil sparing, complete CN III (ischemic)
- Expanding PCA aneurysm ruptures
 - 50% mortality
 - 50% severe neurologic damage

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Your role

- If you need to lift the lid to instill drops, Stop!
- Note pupil findings with abnormal motility
- The issue in diagnosing a dilated pupil
 - Is this a pupil involved third nerve palsy???
- Life or death encounter



Pupil involved CN III

- MRI/CTA- emergent
- Arteriogram
 - 1% risk of morbidity and mortality
- Neuroradiology/neurosurgery consult
 - Coiling/clipping of aneurysm

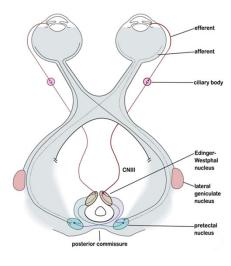


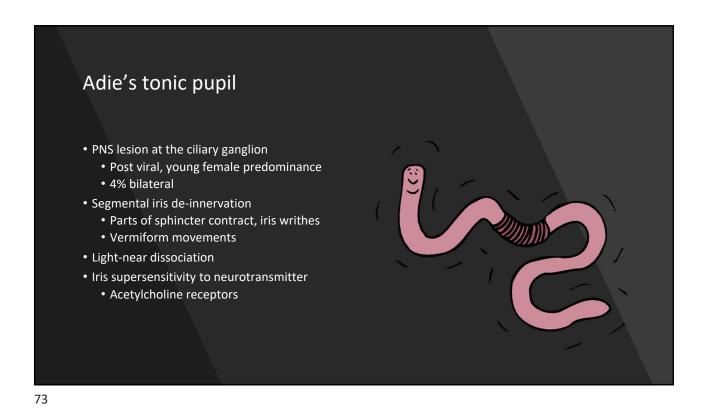
Courtesy of AG Lee, MD

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Relax: more benign causes of pupil dilation

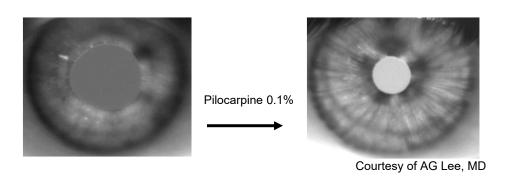
- Adie's tonic pupil
 - Ciliary body
- Pharmacologic dilation
- Iris muscle damage



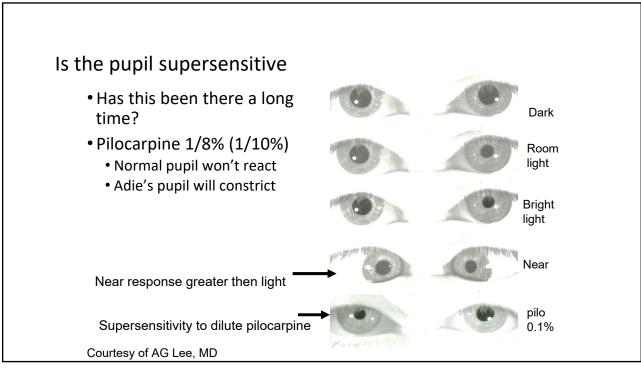


Look for vermiform movements

• Infared pupilometry: segmental transillumination defects of the pupil sphincter



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Other causes: Isolated dilated pupil

- Pharmacologic
 - Inadvertent contamination
 - Scopolamine patch
 - Naturally occurring alkaloids
 - Jimson weed
 - Angels trumpet
 - Contralateral alpha agonist for glaucoma (Alphagan, Iopidine)
 - Intentional dilation
 - Non-organic disease



Is the pupil pharmacologically dilated (had no response to pilo 1/8%)

- Pilocarpine 1%
 - Normal pupil constricts
 - Pharmacologically dilated pupil will not
- Clue:extreme dilation, suspect pharmacologic





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Iris causes

- Trauma
 - Sphincter rupture- pupil irregular
 - Acute post-traumatic mydriasis
 - Surgical: retinal laser, post cataract surgery
- Inflammation
 - Posterior synechiae
 - Iris atrophy
 - Herpetic eye disease
 - Simplex
 - Zoster



Traumatic mydriasis OS

Afferent summary

- Afferent disease: APD
 - Impulse blocked from retina to midbrain
 - May have vision loss
 - Ipsilateral loss: large retinal lesion, optic nerve
 - Homonymous hemianopsia: optic tracts- LGN
 - May have good vision
 - Even with lesions listed above
 - Lesions posterior to LGN
 - Not covered in PERRLA!
 - Must test for afferent pupillary defect (APD)

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Efferent summary: anisocoria

- Physiologic anisocoria
 - Pupil asymmetry equal in light and dark
- Sympathetic lesion (Horner syndrome)
 - Asymmetry greater in dark
 - Anisocoria > 1 mm after cocaine 10%
 - 3rd order neuron (postganglionic) damage
 - No dilation with hydroxyamphetamine 1%
 - Beware with trauma, vasculopathic, or smokers
 - Congenital- evaluate for neuroblastoma

Parasympathetic summary

- Ptosis: Stop!
 - No drops or tonometry
 - If you must lift lid- reassess
- Third nerve palsy
 - Look carefully for partial palsy
 - Dilating aneurysms are at risk for rupture



It might be an aneurysm...

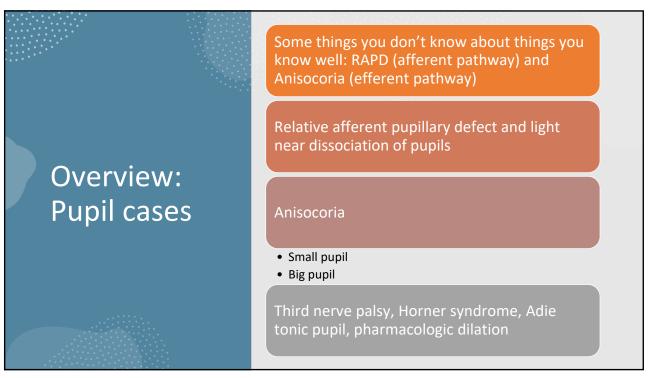
81

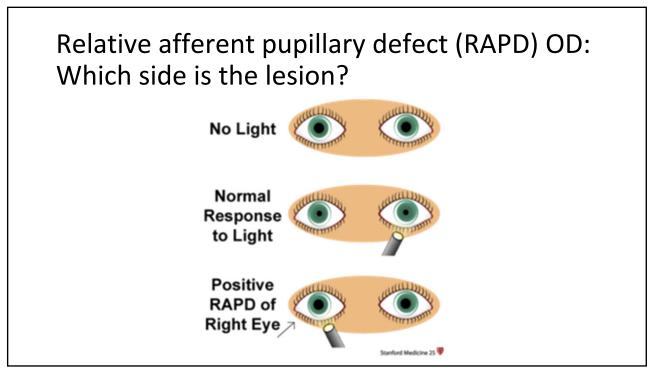
Parasympathetics, continued

- Adie's tonic pupil
 - Young women, post viral
 - Vermiform movements
 - 1/8 % pilocarpine supersensitivity
- Parasympathetic mimics
 - Pupil damage: trauma, surgery, inflammation
 - Pharmacologic (prove with pilocarpine 1%)
 - Accidental
 - Intentional

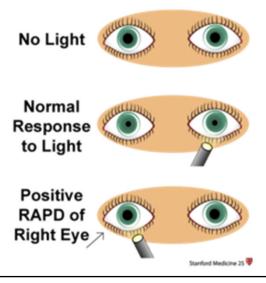








Relative afferent pupillary defect (RAPD) OD: Which pupil dilates with an RAPD OD?



85

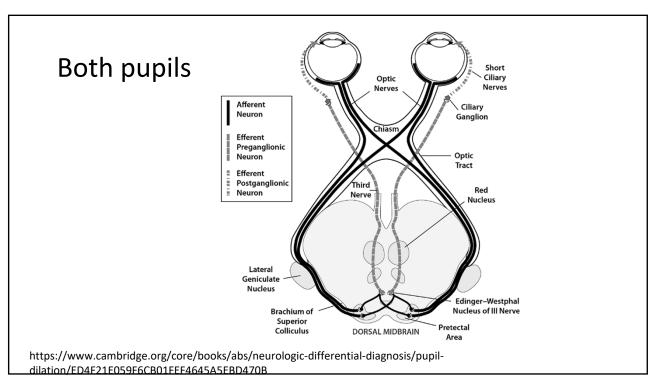
How do we check RAPD in an ipsilateral pupil involved third nerve palsy?



https://www.atlasophthalmology.net/photo.jsf?node=5830&locale=en

- What would you ask?
- What would you do on exam?
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- What would make you admit?
- What is the treatment and prognosis?

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Bilateral light near dissociation

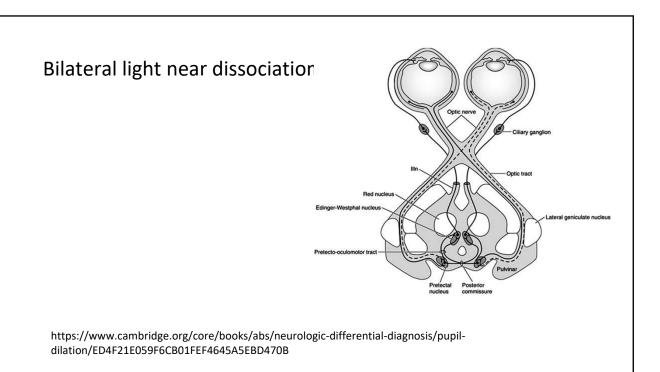




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Panel questions

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"PERRLA" ≠ NORMAL

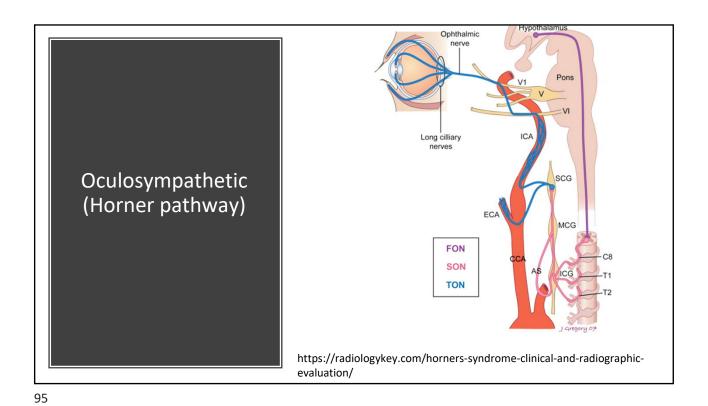


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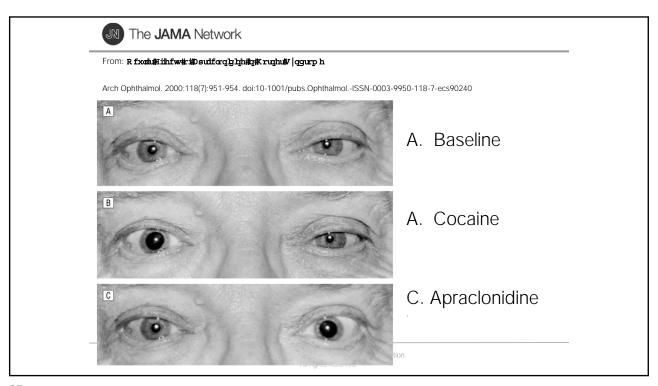
93



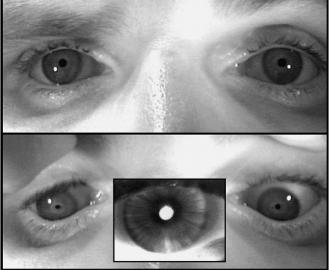
Apraclonidine test (inferior image) confirmed suspected diagnosis of Horner syndrome. *González Martín-Moro et al. Horner Syndrome, a New Complication. J Oral Maxillofac Surg 2009.*



The **JAMA** Network Sent for levator dehiscence OS



Bilateral small to pinpoint without tonic near OU



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Pilocarpine 1/10% and pilocarpine 1% do not constrict pupil

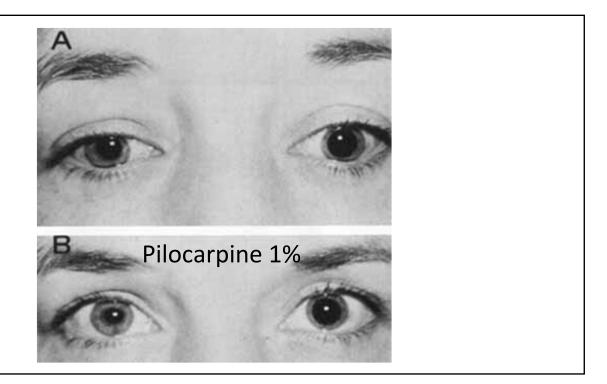




http://mmcneuro.wordpress.com/2013/02/

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What if....



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Panel questions

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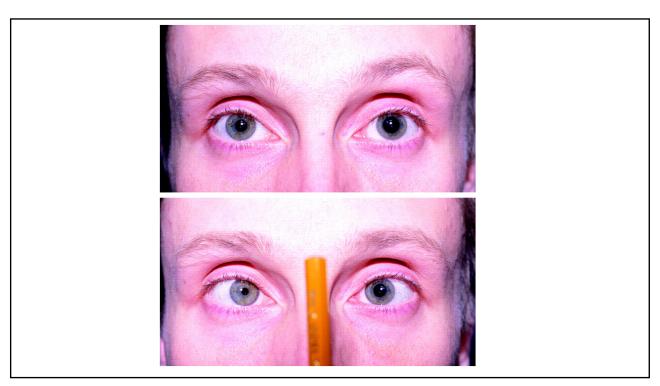
What if....



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Panel questions

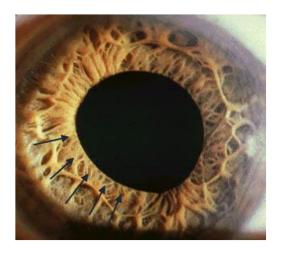
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Panel questions

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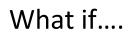
What if....

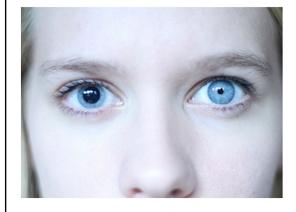


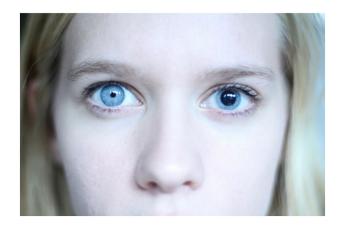
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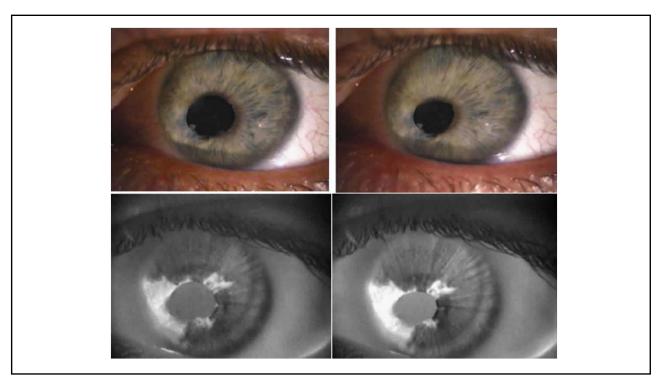
Panel questions

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What if...



- What would you ask?
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Different days



- What would you ask?
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What if....



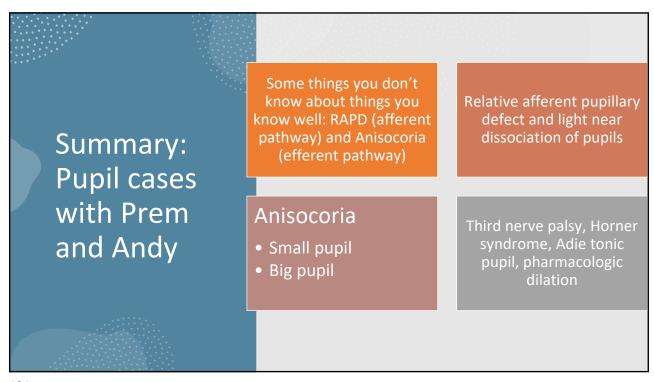
What if it was non-traumatic and there was a family history of scalloped pupil and amyloid?

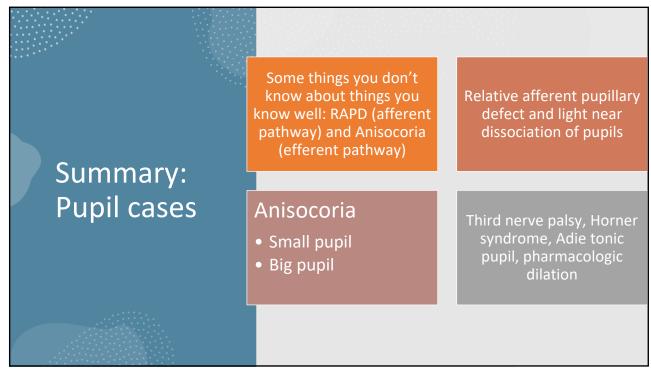


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Panel questions

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Thanks for your time & attention













