NEURO-OPHTHALMOLOGIC EMERGENCIES

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Intrepid

Concussion Care Centre of Virginia, LTD.

Virginia Neuro-Optometry

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Financial Disclosures - Dr. Theis

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Tarsus – Speakers Board
PER – Speakers Board
Abbvie – Advisory Panel
Alcon – Speakers Board, Advisory panel
Dompe – Speakers Board
Zeiss – Advisory panel

All risks have been mitigated

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Goals/General Outline

- Describe the epidemiology, ocular and systemic manifestations, diagnosis and optometric management of:
  - Giant Cell Arteritis
  - Horner's Syndrome
  - Intracranial (Posterior-communicating artery) Aneurysms
  - Myasthenia Gravis
  - Intracranial Space Occupying Lesions
    - Cavernous Sinus Lesions
    - Pituitary Apoplexy

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"Neuro-ophthalmological emergencies constitute vision or life-threatening conditions if diagnosis and treatment are not promptly undertaken.

Even with immediate therapy, these clinical entities carry a high rate of morbidity."

-Lemos J, Eggenberger E. Neuro-ophthalmological emergencies. *Neurohospitalist.* 2015. 5(4): 223-233.

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Symptoms of Neuro-Ophthalmological Emergencies

- Vision Loss
- Diplopia
- Eye Pain
- Headache
- Dizziness

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Red Flags: SNOOP

S: Systemic symptoms or illness:
- Fever • Weight loss • Pregnancy • Cancer

N: Neurologic symptoms or signs:
- Clumsiness • Visual problems • Aphasia • Weakness • Confusion

O: Onset recent or sudden
- Thunderclap • Positional • Progressive

O: Onset after age 40 years:
- vascular • infection • tumor

P: Pattern Change:
- Prior headache history that is different
- Positional

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Signs of Neuro-Ophthalmological Emergencies

- Optic nerve edema or pallor
- Extraocular/intraocular abnormality
  - Multiple cranial nerve palsies
  - Pupil-involving CN III Palsy
- Anisocoria
- Ptosis

- PEARL for Concern: If you have more than one of the following
  - Pupil abnormality
  - Eyelid abnormality
  - EOM abnormality

Karmel M, Eggenberger E. Deciphering Diplopia. Eye Net. Nov/Dec 2009. PP31-34

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Patient History in a Neuro-Ophthalmological Emergency

HPI	CC: Diplopia	CC: Vision Loss
Location	Monocular or Binocular?	
Extent	Gaze dependent? -Left vs. Right, Up vs. Down, Distance vs. Near	Central or peripheral visual field? Left vs. right visual field? Quadrant/location?
Onset	When did it start? Sudden or gradual? What were you doing?	
Frequency	Is it getting better, worse or staying the same since it started?	
Duration	How long does it last? (seconds, minutes, hours or days) Intermittent or constant	
Timing	Is it worse at the beginning or end of the day?	
What makes it better?	Covering an eye? Blinking?	
Has it happened before?	History of childhood strabismus, previous eye surgery?	

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Patient History in a Neuro-Ophthalmological Emergency

- Pain
- Vision Changes (CNII)
- Headaches
- Tingling – limbs, fingers, toes
- Numbness/weakness – facial (CNV/VII), extremities
- Nausea/vomiting
- Imbalance/vertigo
- Photophobia
- Hearing loss, tinnitus
- Jaw claudication, neck stiffness, temporal artery pain
- Difficulties swallowing/breathing
- Recent Weight Loss/Gain
- Recent Fever
- Hx of (Head) Trauma
- Hx of systemic disease →Vasculopathy (HTN, DM, HyperChol), Cancer, MS, thyroid, etc
- MEDICATIONS (including topical, OTC, recently added/changed/discontinued)
- Recent Travel
- Trouble finding your words or speaking

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Examination

- Distance Visual Acuity
  - Pinhole Acuity
- Color Vision
  - Ishihara, AOHRR, Red Cap
- Pupils
  - Size in light/dark
  - Reaction to light/dark
  - Near response
  - RAPD?
- Visual Fields
  - Confrontation
  - Amsler
  - Automated
- Eyelids (MRD1/MRD2), Levator function
- Orbits (Exophthalmometry, symmetry)
- Optic Nerve Evaluation
- Fundus Evaluation
- Cranial Nerve Evaluation I-XII

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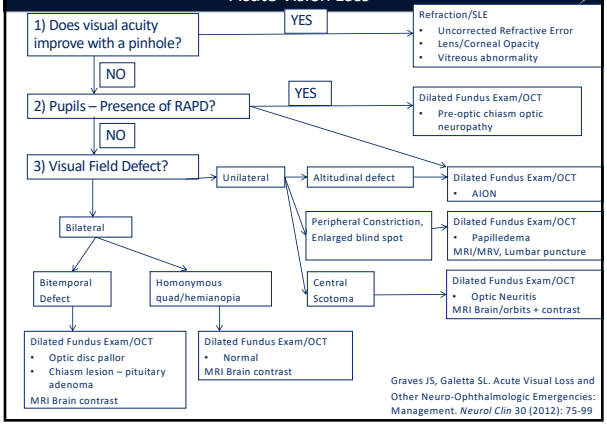
Acute Vision Loss



Graves JS, Galetta SL. Acute Visual Loss and Other Neuro-Ophthalmologic Emergencies: Management. *Neurol Clin* 30 (2012): 75-99

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Giant Cell Arteritis

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Epidemiology

GCA

- Most common systemic vasculitis affecting adults >50yo
  - Rare in people <50yo
  - Average age of onset is 74-76yo
  - For each decade after 50, incidence increases from
    - 2.0 (50-60yo)
    - 11.8 (61-70yo)
    - 31.3 (71-80yo) per 100,000 persons/year
- Women affected 2-3x more than men
- More common in whites, Nordic/Northern European ancestry, and other northern latitudes

Hoffman GS. Giant Cell Arteritis. *Ann Intern Med*. 2016;165(9):ITC65-80

AAION

- Annual incidence of AAION from GCA is 1.3 per 100,000 in patients >50yo
- Vision loss from AAION and CRAO from GCA is severe
  - 73% present with VA worse than 20/200
  - 15% of eyes have an improvement, likely from eccentric fixation

Chen JJ, Leavitt JA, Fang C, Crowson CS, Matteson EL, Warrington KJ. Evaluating the incidence of arteritic ischemic optic neuropathy and other causes of vision loss from giant cell arteritis. *Ophthalmology* 2016: 123:1999-2003

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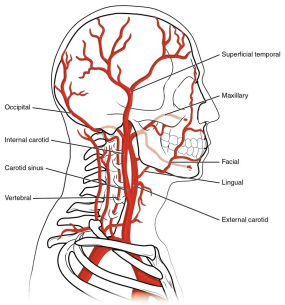
Pathogenesis



- Infectious? immune trigger in a genetically predisposed subject
- T-cell mediated granulomatous inflammation of medium- and large-vessels
  - Aorta
  - External carotid artery
    - Posterior ciliary artery → AAION
  - Temporal arteries

This Photo by Unknown Author is licensed under CC BY

Ciccia F, Rizzo A, Ferrante A, Guggino G, Croci S, Cavazza A, Salvarani C, Triolo G. New Insights into the pathogenesis of giant cell arteritis. *Autoimmunity reviews*. 2017 May. Epub ahead of print. Accessed May 21, 2017.

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Pathogenesis

Persistent vessel wall inflammation→ vascular damage → stenosis, occlusions, and aneurysms

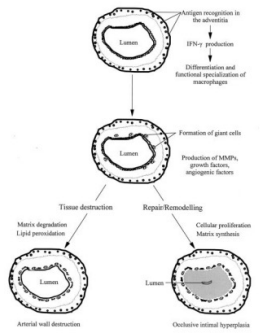

Figure 1. Schematic diagram of pathogenic pathways in giant cell arteritis. IFN-γ = interferon-γ; MMPs = matrix metalloproteinases.

Ciccia F, Rizzo A, Ferrante A, Guggino G, Croci S, Cavazza A, Salvarani C, Triolo G. New Insights into the pathogenesis of giant cell arteritis. *Autoimmunity reviews*. 2017 May. Epub ahead of print. Accessed May 21, 2017.

Image from:
Weyand CM, Goronzy JJ. Arterial wall injury in giant cell arteritis. *Arthr & Rheum*. 1999;42(5):844-853

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Why is it an emergency?

- Blindness
  - Vision loss ~10% of patients
- Stroke
- Aortic aneurysm or dissection

- The sooner GCA is diagnosed and treated, the lower the incidence of visual loss
  - However, patients presenting with poor vision have little chance of recovery despite immediate steroid treatment
- The main goal of treatment is to prevent vision loss in the fellow eye
  - Usually occurs within days in 50% of cases of untreated GCA

Hayreh SS, Podhajsky PA, Zimmerman B. Ocular manifestations of giant cell arteritis. Am J Ophthalmol. 1998;125(4):509-20

Chen JJ, Leavitt JA, Fang C, Crowson CS, Matteson EL, Warrington KJ. Evaluating the incidence of arteritic ischemic optic neuropathy and other causes of vision loss from giant cell arteritis. *Ophthalmology* 2016: 123:1999-2003

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Ocular Manifestations

Symptoms

- Sudden visual loss
  - Most frequent symptom ~50% of cases
- Transient visual loss ~30%
  - Often followed by permanent visual loss
- Diplopia ~6%
- Eye pain ~8%

Signs

- AAION (6.9%) – 1.3 per 100,000 population
  - (+) RAPD
  - Pallid ON edema
  - (+/-) retinal cotton wool spots
  - Accounts for 85% of cases of permanent vision loss
- CRAO (1.6%)
- CilioRAO (0.4%)
- Posterior ION
- Ocular Ischemic Syndrome

Hayreh SS, Podhajsky PA, Zimmerman B. Ocular manifestations of giant cell arteritis. Am J Ophthalmol. 1998;125(4):509-20

Chen JJ, Leavitt JA, Fang C, Crowson CS, Matteson EL, Warrington KJ. Evaluating the incidence of arteritic ischemic optic neuropathy and other causes of vision loss from giant cell arteritis. *Ophthalmology* 2016: 123:1999-2003

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Systemic Manifestations

- Jaw Claudication (48%)
- Neck pain (17%)
- Headache (57%)
- Scalp tenderness (20%)
- Unintended Weight loss (40%)
- Anorexia (31%)
- Myalgias (28%)
- Malaise (37%)

20% of cases with permanent vision loss from GCA may present without systemic symptoms of GCA

- Temporal artery tortuosity, prominence, and/or tenderness

Hayreh SS, Podhajsky PA, Zimmerman B. Occult giant cell arteritis: ocular manifestations. *Am J Ophthalmol*. 1998:125⑤4):521-526.

Chen JJ, Leavitt JA, Fang C, Crowson CS, Matteson EL, Warrington KJ. Evaluating the incidence of arteritic ischemic optic neuropathy and other causes of vision loss from giant cell arteritis. *Ophthalmology* 2016: 123:1999-2003

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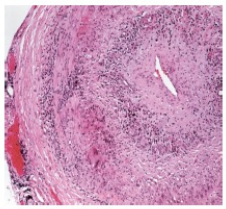
Diagnosis

- **Serological Studies**
  - Elevated ESR (85.7% sensitivity)
    - Normal in 9.2-14.3%
  - Elevated C-Reactive Protein (97.5% sensitivity)
    - Normal in 1.7%
    - ESR/CRP can also be elevated in infection and cancer
  - Abnormal CBC w/ differential (sensitivity <60%)
    - Thrombocytosis
    - Normocytic anemia
    - Leukocytosis
- **Fluorescein angiography**
  - Differentiate AAION from NAION
    - Choroidal hypoperfusion
    - Delayed choroidal filling
- **Temporal Artery Biopsy**
  - Gold Standard
    - BUT only 49-85% of patients with GCA have a (+) TAB
  - May need sequential if high clinical

Figure. **Temporal artery biopsy findings in giant cell arteritis include inflammatory infiltrates comprising lymphocytes, dendritic cells, macrophages, and multinucleated giant cells.**



The adventitia and media are the most intense sites of inflammation.

Lemos J, Eggenberger E. Neuro-Ophthalmological emergencies. *Neurohospitalist*. 2015;5(4):223-233.
Information and image from:
Hoffman GS. Giant Cell Arteritis. *Ann Intern Med*. 2016;165(9):ITC65-80

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Differential Diagnosis

- Common or migraine headache
- Atherosclerosis of large vessels
  - NA-AION
- Takayasu arteritis
- Other forms of vasculitis
- Polymyalgia rheumatica
  - 30-50% of patients with GCA also have PMR
  - PMR is 2-3x more common than GCA

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Treatment

- Steroids – IMMEDIATELY once AAION is suspected
  - Oral (60mg po) vs. IV ASAP
  - Oral taper over months to year
- Low dose Aspirin?
  - To reduce risk of ischemic events if no contraindications
- Consult PCP/internist
  - Monitor for steroid-related complications – hypertension, diabetes, osteoporosis, infection, etc.
- Smoking cessation
- Follow up – 2-4weeks

- Only 4% of patients will improve visual loss with steroids
- 4% of patients lose vision within the first 5 days, even on steroid treatment

Hayreh SS, Biousse V. Treatment of acute visual loss in giant cell arteritis: should we prescribe high-dose intravenous steroids or just oral steroids? *J Neuroophthalmol*. 2012;32(3):278-287.

Hayreh SS, Zimmerman B. Visual deterioration in giant cell arteritis patients while on high doses of corticosteroid therapy. *Ophthalmology*. 2003;110(6):1204-1215

Hayreh SS, Zimmerman B, Kardon RH. Visual improvement with corticosteroid therapy in giant cell arteritis. Report of a large study and review of literature. *Acta Ophthalmol Scand*. 2002;80(4):355-67

Jivraj I, Tamhankar M. The treatment of giant cell arteritis. *Curr Treat Options Neurol*. 2017;19(2):1-18.

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Future

- Glucocorticoids are very effective at high doses
  - Relapses occur in up to 50% of patients when doses are tapered
  - Are not ideal for chronic management
- Adjunct immunosuppressants
  - Methotrexate
    - Reduce risk of relapses
    - Positive effects may take >6 months to emerge
  - Anti-IL-6 (Tocilizumab)
    - May provide additional benefit to prednisone by inducing and maintaining remission for up to 52 weeks. Quick onset
  - Anti-TNFα (Infliximab, Adalimumab, Etanercept)
    - No additional benefit above prednisone monotherapy
    - Increased risk of infection
  - Other targeted anti-inflammatory therapies
    - Abatacept – reduced risk of relapse
    - Ustekinumab – glucocorticoid-sparing response
    - Azathioprine
    - Dapsone
    - Leflunomide
    - Anakinra

Roberts J, Clifford A. Update on the management of giant cell arteritis. *Ther Adv Chronic Disease*. 2017. 8(4-5):69-79
Jivraj I, Tamhankar M. The treatment of giant cell arteritis. *Curr Treat Options Neurol*. 2017;19(2):1-18.

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Non-Arteritic CRAO, BRAO, OAO

A CRAO, BRAO, or OAO is an ophthalmologic and life-threatening emergency thatcis pathophysiologically analogous to an ischemic stroke.

Most common cause of nonarteritic CRAO = embolic occlusion of the central retinal artery at its narrowest part
- either where it enters the optic nerve sheath or
- where it enters the globe as it crosses the lamina cribrosa.

Most often the embolus originates from an
- atherosclerotic plaque in the ipsilateral carotid artery or
- from the aortic arch of the heart.

Photo Courtesy of Andrew Mick

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Stroke Risk

- Both the American Heart Association and American Stroke Association consider retinal arterial ischemia to be the equivalent of acute cerebral ischemia.
- Standard stroke workup
  - Labs: low-density lipoprotein levels, hemoglobin A1c, erythrocyte sedimentation rate, C-reactive protein level, platelet count, and troponin level,
  - Imaging studies including echocardiography, cardiac telemetry, computed tomography angiography (CTA) or magnetic resonance angiography (MRA) of the head and neck, and MRI of the brain.

•Sacco RL, Kasner SE, Broderick JP, et al. An updated definition of stroke for the 21st century: a statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2013;44(7):2064-2089.
•Lavin P, Patrylo M, Hollar M, Espaillat KP, Kirschner H, Schrag M. Stroke risk and risk factors in patients with central retinal artery occlusion. *Am J Ophthalmol*. 2018;196:96-100.

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Stroke and MI Risk

- Patients with acute CRAO had:
  - 26.7% of patients had critical carotid disease (atherosclerosis or dissection)
  - 37.3% had coincident acute stroke, usually on the ipsilateral side of the CRAO;
  - 33% had a hypertensive emergency (blood pressure >180/100); and
  - 20% had a myocardial infarction or critical structural cardiac disease.
  - Results of the cardiovascular-cerebrovascular evaluation led to a change in medication for 93% of patients and urgent surgical intervention in 25% of patients.
- Not only do patients with acute CRAO have a higher incidence of a recent prior ischemic event such as stroke or heart attack, but they also are at higher risk of having a subsequent stroke or heart attack.
- This risk is highest within the first 1 to 2 weeks after acute retinal ischemia.

•French DD, Margo CE, Greenberg PB. Ischemic stroke risk in Medicare beneficiaries with central retinal artery occlusion: a retrospective cohort study. *Ophthalmol Ther.* 2018;7(1):125-131.
• Park S, Choi N, Yang B, et al. Risk and risk periods for stroke and acute myocardial infarction in patients with central retinal artery occlusion. *Ophthalmology.* 2015;122(11):2336-2343.

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CRAO Management

Acute

- Check blood pressure
- Refer IMMEDIATELY to the nearest certified stroke center
  - Do you know where yours is?

Chronic

- The retinal opacification will usually start to resolve within a month of onset, by which time it may appear normal on clinical fundus examination.
- Approximately 3 months after the onset, the optic disc may appear atrophic with or without cilioretinal collateral vessels.
- Collateral vessels must be differentiated from neovascularization, as there are instances of anterior and posterior segment neovascularization and neovascular glaucoma developing after retinal arterial occlusions.

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Call 911 F.A.S.T.

- **F**ace Drooping
- **A**rm Weakness
- **S**peech Difficulty
- **T**ime to call 911

Other Sx

- **NUMBNESS** or weakness of face, arm, or leg, especially on one side of the body
- **CONFUSION,** trouble speaking or understanding speech
- **TROUBLE SEEING** in one or both eyes
- **TROUBLE WALKING**, dizziness, loss of balance or coordination
- **SEVERE HEADACHE** with no known cause

American Stroke Association.
A division of the American Heart Association.

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Anisocoria

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Horner's Syndrome

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Pupil Pathway Review: Sympathetic

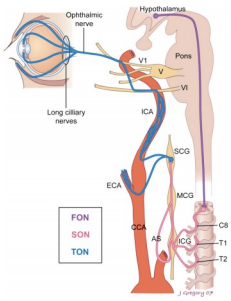

Image from:
Reede DL, Garcon E, Smoker WRK, Kardon R. Horner's syndrome: clinical and radiographic evaluation. *Neuroimaging Clin N Am.* 2008;18:369-385

- Efferent (3 neuron chain)
  1. Hypothalamus→ciliospinal center of Bulge at C8-T2 (spinal cord)
  2. Through sympathetic chain (adjacent lung apex)→ superior cervical ganglion (located at level of carotid bifurcation)
  3. Postganglionic neuron travels with the internal carotid artery until cavernous sinus, then follows CN6→CNV1→ long ciliary nerves→ iris dilator → MYDRIASIS

Abnormal: Pupil is larger in the Dark
Miotic pupil is abnormal

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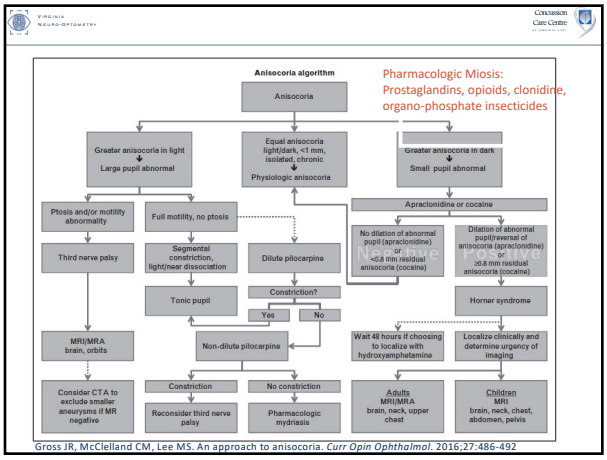

Gross JR, McClelland CM, Lee MS. An approach to anisocoria. *Curr Opin Ophthalmol*. 2016;27:486-492

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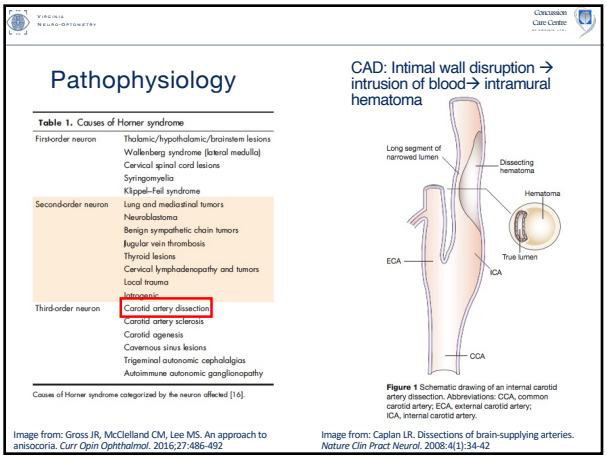

Image from: Gross JR, McClelland CM, Lee MS. An approach to anisocoria. *Curr Opin Ophthalmol*. 2016;27:486-492

Image from: Caplan LR. Dissections of brain-supplying arteries. *Nature Clin Pract Neurol*. 2008:4(1):34-42

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Epidemiology of Carotid Artery Dissection

Epidemiology
- Incidence of 2.6-5 per 100,000 population
- Peak incidence – 5th decade
- Mild male predominance
- Responsible for 25% of strokes in young adults (<45yo)

Etiology
- Traumatic
- Spontaneous
- Underlying vasculopathy
  - Fibromuscular dysplasia
  - Connective tissue disorder
    - Marfans
    - Ehler's Danlos

Robertson JJ, Koyfman A. Cervical artery dissections: a review. *J Emerg Med* 2016;52(5):508-518

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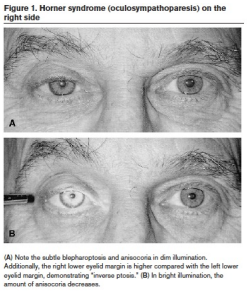
Ocular Manifestations of Horner's Syndrome in Carotid Artery Dissection

- Painful third-order Horner Syndrome ~60%
  - Ptosis ~1-2mm
    - "Inverse ptosis" – when lower lid is slightly elevated
  - Miosis (anisocoria of 1-1.5mm)
    - Dilation Lag
  - WITHOUT facial anhydrosis or partial
- Less common ocular signs of CAD
  - Transient monocular vision loss
  - NAION
  - PION
  - CRAO
  - Ocular ischemic syndrome
  - Ocular motor nerve palsies



(A) Note the subtle blepharoptosis and anisocoria in dim illumination. Additionally, the right lower eyelid margin is higher compared with the left lower eyelid margin, demonstrating "inverse ptosis." (B) In bright illumination, the amount of anisocoria decreases.

Image from: Walton KA, Buono LM. Horner syndrome. *Curr Opin Ophthalmol*. 2003;14:357-363

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Systemic Manifestations

- Ipsilateral headache ~70%
- Ipsilateral neck pain (10-30%)
- Ipsilateral ear pain (10-30%)
- Less common
  - Lower cranial nerves affected
  - Pulsatile tinnitus
  - Vertigo
  - Dysgeusia (foul taste in the mouth)
- Diseases that affect the brainstem, spinal cord, chest or neck can present with purely ocular symptoms
  - Ophthalmologic signs/symptoms can proceed ocular or cerebral infarction in 33% of patients 6-14 days

Silbert PL, Mokri B, Schievink WI. Headache and neck pain in spontaneous internal carotid and vertebral artery dissections. Neurology. 1995;45(8):1517-1522
Lemos J, Eggenberger E. Neuro-Ophthalmological Emergencies. *Neurohospitalist*. 2015. 5(4):223-233
Biousse V, Touboul PJ, D'Anglejan-Chatillon J, Levy C, Schaison M, Bousser M.Ophthalmologic Manifestations of Internal Carotid Artery Dissection. *Amer J Oph*. 1998;9304(98):565-577

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Diagnosis

Horner's Syndrome
Pharmacologic diagnosis/localization
- **Cocaine 10%**
  - (+) = Failure of pupillary dilation after one hour (ie anisocoria >1mm remains)
- **Apraclonidine 1%**
  - (+) = mydriasis of affected pupil >1mm 30-45 minutes after drop instillation
- **Hydroxyamphetamine**
  - Localizes between central (1st)/preganglionic (2nd) and postganglionic (3rd) order lesion
  - If mydriasis→ 1st/2nd order
  - (-) mydriasis (ie anisocoria>1mm remains)→ 3rd order
- Caveats
  - Cant perform cocaine and hydroxyamphetamine test on the same day (within 24-48 hours)
  - Hydroxyamphetamine test may yield a false-negative, and is not commercially available

Carotid Artery Dissection
- MRI/MRA
  - 85% sensitivity
  - 95% specificity for dissection
- CTA of head/neck or carotid doppler ultrasound
- CT of chest
- CBC with differential

Walton KA, Buono LM. Horner syndrome. *Curr Opin Ophthalmol*. 2003;14:357-363
Levy C, Laissy JP, Raveau V, et al. Carotid and vertebral artery dissections: three-dimensional time-of-flight MR angiography and MR imaging versus conventional angiography. Radiology. 1994;190(1):97-103.

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Traumatic Horner's Syndrome

Sympathetic (Adrenergic Pathway) Pupillary Dilation

- 1st order neuron
  - Stroke
  - Neck/spinal trauma
- 2nd order neuron
  - Chest cavity surgery
  - Spinal Trauma
  - Aortic damage
- 3rd order neuron
  - Damage to Carotid artery, jugular vein
  - Tumor or infection near base of skull
  - Migraines/cluster headaches

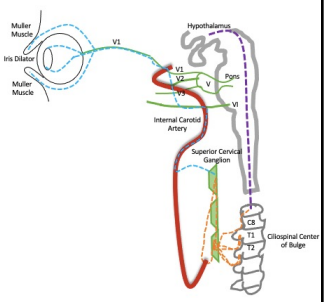

Image Source: Created by Jacqueline Theis

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Traumatic Horner's Syndrome aka Oculosympathetic Palsy

- More common in patients with injury to the neck or thorax
- Common symptoms: miosis, ptosis, anhidrosis, dilation lag
- Concerning symptoms (all of a sudden)
  - Impaired vision
  - Dizziness
  - Slurred speech
  - Difficulty walking
  - Muscle weakness/lack of muscle control
  - Severe headache/neck pain
  - →ER

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Intracranial Aneurysms

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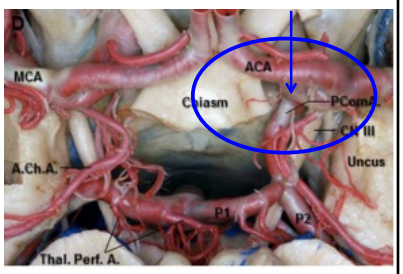
Epidemiology

- 9-36% of CNIII palsies are caused by an intracranial aneurysm
- Posterior communicating artery (PCA) aneurysms present with a CNIII palsy 30-60% of the time
- 40% of aneurysms are located at the level of the PCA, ophthalmic artery, and cavernous sinus



Lemos J, Eggenberger E. Neuro-Ophthalmological Emergencies. *Neurohospitalist*. 2015. 5(4):223-233

Image From: Park HK, Rha HK, Lee KJ, Chough CK, Joo W. Microsurgical anatomy of the oculomotor nerve. *Clin Anat*. 2017;30(1):21-31.

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Risk factors for Aneurysmal Rupture

- Increasing age (peak 6th decade)
- Female gender
- Smoking
- Hypertension
- Heavy alcohol consumption
- (+) Family history of intracranial aneurysm or subarachnoid hemorrhage
- Aneurysm size>10mm
- Genetic disorders– polycystic kidney disease
- Aneurysm location
  - PCA and basilar tip have higher rupture risk at 5 years

Etminan N, Rinkel GJ. Unruptured intracranial aneurysms: development, rupture, and prevention. *Nat Rev Neurol*. 2016;12(12):699-713,
Lemos J, Eggenberger E. Neuro-Ophthalmological Emergencies. *Neurohospitalist*. 2015. 5(4):223-233

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Ocular Manifestations

- Pain
- Mid-dilated pupil
  - Poor or absent light reaction
- Complete or partial external CNIII palsy

Image From: Ahmad K, Wright M, Lueck CJ. Ptosis. *Practical Neurology*. 2011;11:332-340

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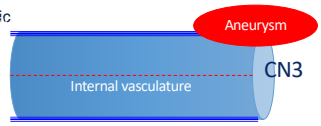
Rule of the Pupil

- Complete CN III
  - Pupil-sparing→ likely ischemic
  - Pupil-involving→ likely compressive
- Incomplete CN III
  - Pupil-sparing →???
    - 14% will have aneurysm, just present to office in an early phase before the pupillary fibers are involved
  - Pupil-Involving→ compressive



Compressive lesions:
- Most common – aneurysm
- Less common – tumor, trauma, congenital, uncal herniation, cavernous sinus mass, pituitary apoplexy, orbital disease, varicella zoster virus, ischemia, leukemia

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Topographical localization of CNIII Palsy

- Brainstem
  - Hemiparesis
  - Hemisensory loss
  - Other cranial neuropathies
- Subarachnoid space
  - Meningeal signs
  - Stiff neck
  - Severe headache
  - Other cranial neuropathies
- Cavernous sinus
  - CN – 4, 5, or 6 involvement
  - Horner syndrome
- Orbit
  - Proptosis
  - Chemosis
  - Optic neuropathy

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Diagnosis

- Digital subtraction angiography (DSA)
  - 1-2% morbidity risk
  - Gold standard
- MRA/CTA
  - Noninvasive
  - Can detect 95% of aneurysms
  - Aneurysm needs to be ≥5mm
- MRI/CT/LP
- ESR/CRP/CBC w differential

Lee AG, Hayman LA, Brazis PW. The evaluation of isolated third nerve palsy revisited. An update on the evolving role of magnetic resonance, computed tomography, and catheter angiography. *Surv Ophthalmol*. 2002;47(2):137-57

Management

- 70-100% of surviving patients make a complete or partial recovery of the oculomotor deficit
  - Usually starting with resolution of ptosis
  - Pupillary and EOM abnormalities may persist
  - Sometimes aberrant regeneration
  - Fresnel prism please ☺

Patel K, Guilfoyle MR, Bulters DO, Kirollos RW, Antoun NM, Higgins JNP, Kirkpatrick PJ, Trivedi RA. Recovery of oculomotor nerve palsy secondary to posterior communicating artery aneurysms. *Brit J Neurosurg*. 2014;28(4):483-487

45

Ocular Treatment

- Fresnel Prism
  - Serial cover test
- Patch/Occlusion (bangeter/tape)
- Eyelid Crutch
- IOP monitoring

- Things to remember
- Can take a few months for Mestinon to improve ptosis
- Prednisone is better at improving diplopia

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Myasthenia Gravis

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Epidemiology

- 2012
  - Incidence – 4-50 cases per million per year
  - Prevalence – 5-300 cases per million per year
- 2022
  - Incidence 10-29 cases per million people
  - Prevalence range 100-350 cases per million people

Punga AR, Maddison P, Heckmann JM, Guptill JT, Evoli A. Epidemiology, diagnostics, and biomarkers of autoimmune neuromuscular junction disorders. Lancet Neurol. 2022 Feb;21(2):176-188. doi: 10.1016/S1474-4422(21)00297-0. PMID: 35065040.

48

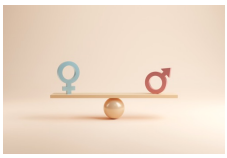
Epidemiology by Age and Gender

Age

- Juvenile MG
- Early-Onset MG (EOMG) <50yo
  - Female predominance (60-70%)
- Between 50-60yo
  - No gender difference
- Late-Onset MG (LOMG) >60yo
  - Male predominance

Gender

- Female 2x>Male from 15-64 years
- Male > Female in later onset



Vaphiades M, Bhatti M, Lesser R. Ocular Myasthenia Gravis: A Review. *Curr Opin Ophthalmol.* 2012. 23(6):537-542.
Punga AR, Maddison P, Heckmann JM, Guptill JT, Evoli A. Epidemiology, diagnostics, and biomarkers of autoimmune neuromuscular junction disorders. Lancet Neurol. 2022 Feb;21(2):176-188. doi: 10.1016/S1474-4422(21)00297-0. PMID: 35065040.

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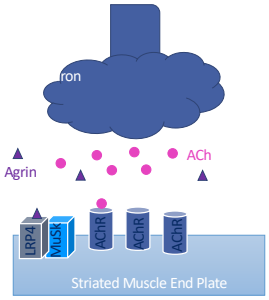
Pathophysiology

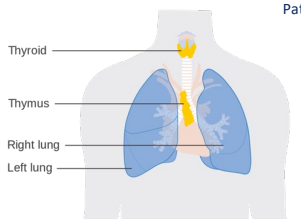


- Neuromuscular Junction
  - Presynaptic motor neuron releases acetylcholine and agrin into synaptic cleft
  - Acetylcholine binds to AChR → muscle contraction
  - Agrin binds to the complex formed by LRP4 and MuSK → AChR clustering (maintains postsynaptic structures)
- AChR – Acetylcholine Receptor
- MuSK – Muscle Specific Kinase
- LRP4 – Low-density lipoprotein receptor-related protein 4

Berrih-Aknin S, Frenkian-Cuvelier M, Eymard B. Diagnostic and clinical classification of autoimmune myasthenia gravis. *J Autoimunity. 2014;48-49:143-148*
Huijbers MG, Marx A, Plomp JJ, Le Panse R, Phillips WD. Advances in the understanding of disease mechanisms of autoimmune neuromuscular junction disorders. Lancet Neurol. 2022 Feb;21(2):163-175. doi: 10.1016/S1474-4422(21)00357-4. PMID: 35065039.

50

Autosensitization



Pathogenic/Inflammatory triggers
↓
Chronically inflamed thymus
↓
Autosensitization to AChR/MuSK/LRP4
↓
Autoreactive T-Cells
↓
Autoreactive B-Cells
↓
Auto-Antibodies

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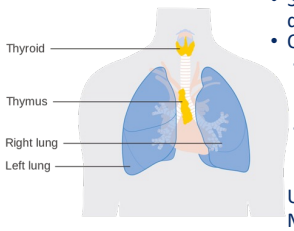
Thymus



Thymus Gland Regulates T-Cell Reactivity

- 30% of patients with thymoma develop MG
- Of patients with MG
  - 70% have thymic hyperplasia
    - AChR-Ab (+), Seronegative, EOMG
  - 10-15% have thymoma
    - LOMG

Unclear of role in MuSK/LRP4 MG

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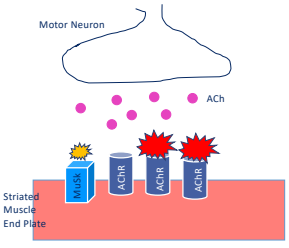
Shuey N. Ocular myasthenia gravis: a review and practical guide for clinicians. *Clin Exp Optom.* 2022;105(2):205-213.

52

Pathophysiology



- Role of the Thymus?
  - Pathogenic/inflammatory triggers→ chronically inflamed thymus→ autosensitization to AChR→ autoreactive T Cells → production of autoantibodies
- Autoantibodies prevent binding of ACh and DOK7 from binding to AChR and MuSK
  - Anti-AChR
  - Anti-MuSK
- Neuromuscular junction dysfunction leads to painless, fatigable weakness of voluntary muscles

Berrih-Aknin S, Frenkian-Cuvelier M, Eymard B. Diagnostic and clinical classification of autoimmune myasthenia gravis. *J Autoimunityl. 2014;48-49:143-148*

53

Ocular Manifestations

- 15% of MG patients have ocular MG only
- Majority of patients have ocular manifestations in first year of onset
  - Required to have 2 years without further generalization of MG to be diagnosed as having purely ocular form

- Ptosis
  - variable, worse with fatigue
- Diplopia/EOM involvement/Ophthalmoplegia
  - variable, worse with fatigue
- Orbicularis weakness
- Normal pupils
- Cogan's Lid Twitch

Vaphiades M et al. Ocular Myasthenia Gravis. *Curr Opin Oph.* 2012. 23(6):537-42
Spillane E, et al. Myasthenia Gravis. *BMJ.* 2012. 8497:1-4.

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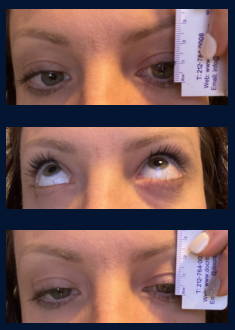
Fatigability Testing (mm)

1-2 Minutes



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Cogan's Lid Twitch

- "Twitch Response" or "Irritable Eyelid" phenomenon
- First described by David Cogan, MD in 1965
- Characteristic but not pathognomonic sign of myasthenia gravis
  - Present in 50% of MG cases, early stages
  - Rarely, seen in CN III aberrent regeneration and other edrophonium-resistant ophthalmolplegia
- Due to easy fatigability, but rapid recovery of levator palpebrae superioris muscle

Cogan D. Myasthenia Gravis: A review of the disease and a description of lid twitch as a characteristic sign. *Arch Ophthalmol* – 1965. 74:217-221

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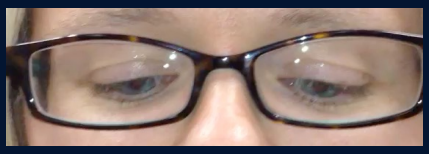
Cogan's Lid Twitch Sign



(+) Brief overshoot of the upper eyelid margin before it returns to previous ptotic position

"After 15 seconds of sustained downgaze, patient quickly returns eyes to primary position"
…or vertical saccades

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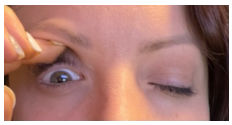
Hering's Law of Equal Innervation

Curtaining

- Examiner elevates ptotic eyelid → previously "better" side gets a ptosis

Enhanced Ptosis

- Examiner elevates the "better" eyelid→ increases the manifest ptosis



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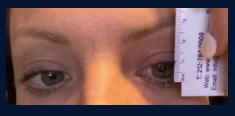
Ice Pack or Rest Test

2 Minutes

(+) = 2mm or greater improvement in ptosis



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Systemic manifestations

- 85% of MG patients
- Skeletal Muscle Fatigue
  - Facial muscles
  - Proximal limb muscles
  - Muscles for swallowing/breathing
- Other autoimmune disease
  - Thyroid disorders (Hashimoto's or Basedow diseases)
- Thymus problems
  - Thymic follicular hyperplasia ~70%
  - Thymoma (thymic epithelial cell tumor) ~10-15%

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Why is it life threatening?

- Myasthenic crisis
  - Respiratory failure due to muscle weakness
    - Severe weakness of respiratory muscles, upper airway muscles, or both
    - Usually due to poor control of generalized disease
  - Other triggers for crisis
    - Concomitant use of certain antibiotic (aminoglycosides, quinolones, antimalarials), muscle relaxants, anti-convulsants antipsychotics, botox, Beta-blockers (including topicals), and iodinated radiocontrast agents
    - Systemic infection involving respiratory tract, aspiration, and surgery
    - Emotional stress, hot environment, sudden elevation of body temperature (9)
    - Hyperthyroidism
  - Require immediate ventilatory assistance
  - Pre-immunotherapy era
    - Myasthenic crisis had significant mortality rate (up to 75%), but has fallen to <5% in recent years
    - 20-30% life-time prevalence of myasthenic crisis in patients with MG
      - Usually occurs during the course of first symptomatic presentation in the young and later in the course of disease in the elderly
      - White patients more likely to respond poorly to treatment then black patients
      - Pregnancy is known to aggravate MG

Chaudhuri A, Behan PO. Myasthenic Crisis. *Q J Med*. 2009;102:97-107
Juel VC. Myasthenia gravis: management of myasthenic crisis and perioperative care. *Semin Neurol*. 2004;24:75-81.

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Diagnostic Management

- OD Diagnostic Tests – In Office
  - Lid Twitch Sign (50-75% sensitivity/90-99% specificity)
  - Forced eyelid closure test (94% sensitivity/91% specificity)
  - Peek sign (4% sensitivity/99.6% specificity)
  - Sleep Test (99% sensitivity/91% specificity)
  - Ice Test (ptosis) (94% sensitivity/97% specificity)
  - Ice Test (diplopia) (76.9% sensitivity/98.3% specificity)
- OD/MD Diagnostic Tests (Neurologist/Neuro-Ophthalmologist)
  - Tensilon Test (Edrophonium Chloride), (92% sensitivity/97% specificity)
    - Side Effects: Bradycardia, arrhythmia, hypotension
  - Serologic Testing for Autoantibodies, Thyroid function
    - 5% of patients with myasthenia gravis also have dysthyroidism
  - CT/MRI of Thorax (rule/out Thymic abnormalities)
  - Neurophysiological Specific Tests
    - RNS – Repetitive Nerve Stimulation (29% sensitivity/94% specificity)
    - SFEMG – Single Fiber Electromyography (97% sensitivity/92% specificity)

Benetar M, Kaminski H. Evidence report: the medical treatment of ocular myasthenia (an evidence-based review). *Neurology* 2007. 68(24):2144-2149
Benatar M. A systematic review of diagnostic studies in myasthenia gravis. *Neuromusc Disord*. 2006. 16(7):459-467
Jenmaneechotchai T, Apinyawasisuk S, Jariyakosol S, Hirunwiwatkul P. Interobserver and Intra-Observer Reliability of Eyelid Tests for Ocular Myasthenia Gravis. J Neuroophthalmol. 2021 Oct 22. doi: 10.1097/WNO.0000000000001425. Epub ahead of print. PMID: 34860746.

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Serological Testing

- Generalized Myasthenia – 90-96% sensitivity, high PPV, 99% specificity
  - 87% have autoantibodies
    - 80-85% - AChR
    - 5-8% MuSK
- Ocular Myasthenia – 44% sensitivity, low NPV
  - 50-80% have autoantibodies
- (+)Autoantibody assay highly suggests MG
  - BUT (-) Autoantibody assay = inconclusive
- Seronegative – (-)AChR, (-)MuSK
  - 5-10%
  - High prevalence of cranial and bulbar muscle involvement
  - Repeated serological tests
    - 15% seroconversion rate over 1 year period
    - Patients with OMG may persistently test seronegative
  - Some (1-50%) test positive for LRP4
- Myasthenia lab order
  - AChR binding Abs (highest sensitivity)
  - AChR blocking Abs
  - AChR modulating
  - MuSK (usually better for generalized MG)
  - LRP4 (better sensitivity for OMG)

Benetar M, Kaminski H. Evidence report: the medical treatment of ocular myasthenia (an evidence-based review). *Neurology* 2007. 68(24):2144-2149
Benatar M. A systematic review of diagnostic studies in myasthenia gravis. *Neuromusc Disord*. 2006. 16(7):459-467
Shuey N. Ocular myasthenia gravis: a review and practical guide for clinicians. *Clin Exp Optom*. 2022;105(2):205-213.

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Ice Pack Test

- Cooling reduces cholinesterase activity, which increases the availability of acetylcholine → increases efficiency of acetylcholine in depolarization at the motor endplate in the levator
- High Specificity (88% true negative) and sensitivity (96% true positive) in the differential diagnosis of myasthenic ptosis
  - RNS 95% specificity, 70% sensitivity
    - Other studies find sensitivity at 75-80%
  - Neostigmine 97% specificity, 83% sensitivity
  - AChR-Abs – 28% positive
    - Other studies 80-90% in generalized myasthenia, and 40-55% in ocular myasthenia

Natarajan B, Saifudheen K, Gafoor VA, Jose J. Accuracy of the ice test in the diagnosis of myasthenic ptosis. *Neurol India*. 2016;64(6):1169-1172.

64

Medical Treatment

Long-Acting Acetylcholinesterase inhibitor (Pyridostigmine)

- Improves ptosis, less effective in resolution of EOM involvement/diplopia
- Does not affect the course of the disease

Controversial
- (-) Potential long term side effects
- (-) Disease is not life-threatening
- (+) Ocular symptoms could decrease quality of life

Immunomodulatory Therapy

- Oral corticosteroids
  - Effectively controls diplopia AND ptosis symptoms
  - Lowers risk of progression from OMG→ GMG
- Other: Azathioprine, Mycophenolate Mofetil, Methotrexate, Tacrolimus, Cyclosporine, Rituximab
- Thymectomy
- IV Ig
- Plasma Exchange

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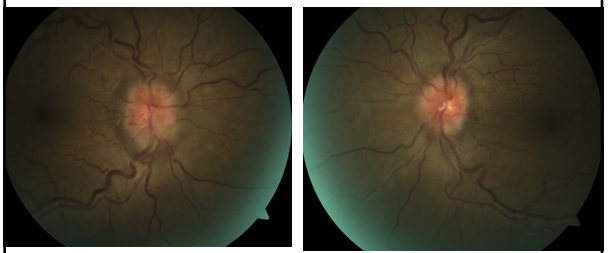
Emergency?



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Intracranial Space Occupying Lesions

- Tumor
- Inflammation
- Infection
- Ischemic infarct
- Increased intracranial pressure
  - Mass
  - Pseudotumor/IIH

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Swollen Optic Nerve(s)

Papilledema
- "Disc swelling from elevated intracranial pressure"

Until lumbar puncture – better to diagnose "optic nerve head edema"

Differential Diagnosis
- Congenital Anomaly
  - Optic disc drusen
- Infection
- Inflammation
- Ischemia

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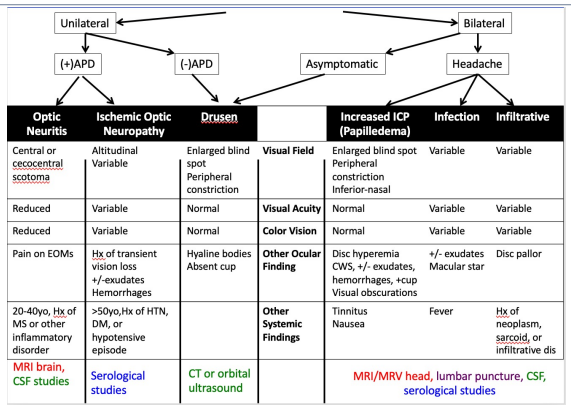
Blurred Disc Margins



Optic Neuritis	Ischemic Optic Neuropathy	Drusen		Increased ICP (Papilledema)	Infection	Infiltrative
Central or cecocentral scotoma	Altitudinal Variable	Enlarged blind spot Peripheral constriction	**Visual Field**	Enlarged blind spot Peripheral constriction Inferior-nasal	Variable	Variable
Reduced	Variable	Normal	**Visual Acuity**	Normal	Variable	Variable
Reduced	Variable	Normal	**Color Vision**	Normal	Variable	Variable
Pain on EOMs	Hx of transient vision loss +/-exudates Hemorrhages	Hyaline bodies Absent cup	**Other Ocular Finding**	Disc hyperemia CWS, +/- exudates, hemorrhages, +cup Visual obscurations	+/- exudates Macular star	Disc pallor
20-40yo, Hx of MS or other inflammatory disorder	>50yo,Hx of HTN, DM, or hypotensive episode		**Other Systemic Findings**	Tinnitus Nausea	Fever	Hx of neoplasm, sarcoid, or infiltrative dis
MRI brain, CSF studies	Serological studies	CT or orbital ultrasound		MRI/MRV head, lumbar puncture, CSF, serological studies		

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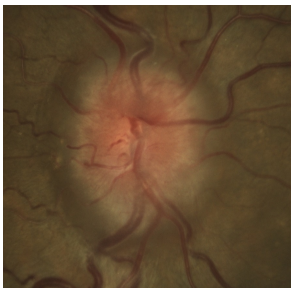
Papilledema

Symptoms
- Headache
- Nausea
- Tinnitus
- Transient visual obscurations
- Double vision
- Other neurological deficits



Graves JS, Galetta SL. Acute Visual Loss and Other Neuro-Ophthalmologic Emergencies: Management. *Neurol Clin* 30 (2012): 75-99

70

Papilledema

Signs
- Bilateral disc edema
  - Initially superior-inferior swelling
- Disc Hyperemia (its pink!)
- (+) Obscuration of retinal vessels over disc margin
- Cup is preserved
- (+) CWS/hemorrhages over time
- (-) Spontaneous Venous Pulsation
- Normal VA
- Normal Color Vision
- (+) Visual field defect
  - Enlarged blindspot
  - Peripheral field constriction

Graves JS, Galetta SL. Acute Visual Loss and Other Neuro-Ophthalmologic Emergencies: Management. *Neurol Clin* 30 (2012): 75-99

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Papilledema

Diagnosis
- Immediate Neuroimaging
- Lumbar puncture
  - Elevated intracranial (CSF) pressure

Etiology
- Mass lesion
- Severe cerebral edema
- Venous thrombosis
- Hydrocephalus
- Pseudo-tumor Cerebri

Graves JS, Galetta SL. Acute Visual Loss and Other Neuro-Ophthalmologic Emergencies: Management. *Neurol Clin* 30 (2012): 75-99

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Pseudo-Tumor Cerebri Idiopathic Intracranial Hypertension

- Normal neuroimaging
  - MRI/MRV brain
- Normal CSF examination
- Elevated opening CSF pressure

Associations/Risk Factors

- Obesity
  - Recent weight gain
  - Obstructive sleep apnea
- Anemia
- h/o medication use:
  - Glucocorticoids
  - Vitamin A products
  - Tetrocycline derivatives
  - Synthetic growth hormones
- Female predilection

Graves JS, Galetta SL. Acute Visual Loss and Other Neuro-Ophthalmologic Emergencies: Management. *Neurol Clin* 30 (2012): 75-99

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IIH - Management

- Acetazolamide
  - May improve papilledema, visual complaints, headache
  - OR other diuretics/CAIs
- Weight loss
- Baseline automated VFs after treatment initiated
  - Progressive or severe vision loss may need more aggressive therapy
    - Ventriculoperitoneal shunt
    - Optic nerve fenestration

Banta JT, Farris BK. Pseudotumor cerebri and optic nerve sheath decompression. *Ophthalmology* 2000;107:1907–12.
Liu GT, Glaser JS, Schatz NJ. High-dose methylprednisolone and acetazolamide for visual loss in pseudotumor cerebri. *Am J Ophthalmol* 1994;118:88–96

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Cavernous Sinus Lesions

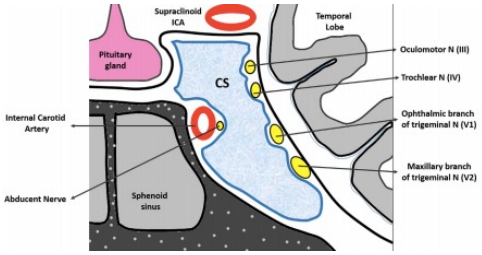

Image from: Nadarajah J, Madhusudhan KS, Yadav AK, Chandrashekhara SH, Kumar A, Gupta AK. MR imaging of cavernous sinus lesions: pictorial review. *J Neuroradiol*. 2015;42(6):305-319.

75

Cavernous Sinus Syndromes

Complete

- Ophthalmoplegia (Diplopia)
- Ptosis
- Mydriasis
- Hypesthesia of V1/V2 (facial numbness)
- Orbital Pain

Partial

- Depends on the location of the lesion

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Etiology

- Chronic Causes
  - Meningiomas
  - Metastases of head and neck cancers
  - Slow-growing carotid aneurysm
- Acute Causes
  - Cavernous sinus thrombosis
    - Extension of facial/sinus infection
  - Carotid cavernous fistula
    - Painful red eye + chemosis + pulsatile exophthalmos
  - Inflammatory reaction (Tolosa-Hunt syndrome)
  - Pituitary apoplexy

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Cavernous Sinus Thrombosis

Ocular Manifestations

- Most common 80-100% presentation
  - Proptosis
  - Chemosis
  - Ptosis
  - CN III, IV, and/or VI palsies
- Less common 50-80% presentation
  - Periorbital edema
  - Optic disc edema
  - Venous engorgement
- Least common <50%
  - Decreased visual acuity (due to ION, CRAO, CRVO, or corneal ulceration)
  - Sluggish/dilated pupils
  - Periorbital and corneal sensory loss (CNV)

Systemic Manifestations

- Most common 80-100% presentation
  - Acute onset fever
- Less common 50-80% presentation
  - Headache
  - Lethargy
  - Altered sensorium
- Least common <50%
  - Meningismus
  - Seizures
  - Hemiparesis

Lemos J, Eggenberger E. Neuro-ophthalmological emergencies. *Neurohospitalist*. 2015. 5(4): 223-233.

78

Differential Diagnosis

Orbital Cellulitis
- Painful ophthalmoplegia
- Proptosis
- Chemosis
- Fever
- Decreased vision
- UNILATERAL

Direct High-Flow Carotid Cavernous Fistula
- Periorbital edema
- Ophthalmoplegia
- Increased IOP
- Decreased vision
- (+) supraorbital bruit
- Arterialized conjunctival vessels

Lemos J, Eggenberger E. Neuro-ophthalmological emergencies. *Neurohospitalist*. 2015. 5(4): 223-233.

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Pituitary Apoplexy

80

Epidemiology

- Between 2-12% of patients with adenoma experience apoplexy
- Diagnosis of pituitary tumor unknown at time of apoplexy in ¾ of cases
- Presentation for 0.6-9.0% of surgically managed pituitary adenomas
- Male predominance ~60%
- Peak incidence in 5th decade

Briet C, Salenave S, Bonneville JF, Laws ER, Chanson P. Pituitary Apoplexy. *Endocrine Reviews*. 2015;36(6):622-645
Glezer A, Bronstein MD. Pituitary apoplexy: pathophysiology, diagnosis, and management. *Arch Endocrinol Metab*. 2015;59(3):259-64.

81

Pathophysiology

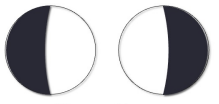
- Hemorrhage or infarction of a pituitary tumor causes a sudden enlargement of the gland due to ischemia and/or necrosis
- 2/3 are spontaneous
- 1/3 precipitating factor:
  - Hypotension
    - Surgery
  - Malignant hypertension
  - Anticoagulant treatment
  - Dopaminergic agonist treatment

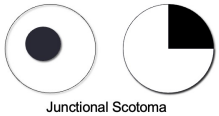
Biousse V, Newman NJ, Oyesiku NM. Precipitating factors in pituitary apoplexy. J Neurol Neurosurg Psychiatry. 2001; 71(4):542-545
Glezer A, Bronstein MD. Pituitary apoplexy: pathophysiology, diagnosis, and management. *Arch Endocrinol Metab*. 2015;59(3):259-64.
Semple PL, Webb MK, de Villiers JC, Laws ER. Pituitary apoplexy. *Neurosurgery*. 2005;56(1):65-72. discussion 3.

82

Ocular Manifestations

- Visual Field Loss
  - Bitemporal
  - Junctional scotoma
- Unilateral and/or bilateral ophthalmolplegia ~50%
  - CNIII>CNVI>CNIV


Bitemporal Loss


Junctional Scotoma

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Systemic manifestations

- Sudden severe headache ~80%
  - Retroorbital
  - Bifrontal
  - Diffuse
  - Assoc with vomiting/nausea
- Neck stiffness
- Brain stem/hypothalamus compression
  - Reduced consciousness
  - Thermoregulatory dysfunction
  - Cardiorespiratory dysfunction

- Pituitary dysfunction
  - Thyrotropic deficiency
    - Hypothyroidism
  - Corticotropic deficiency
    - Hyponatremia
    - Hypotension
  - Hypercortisolism

Symptoms evolve from hours to 2 days after onset of apoplexy

Briet C, Salenave S, Bonneville JF, Laws ER, Chanson P. Pituitary Apoplexy. *Endocrine Reviews*. 2015;36(6):622-645
Glezer A, Bronstein MD. Pituitary apoplexy: pathophysiology, diagnosis, and management. *Arch Endocrinol Metab*. 2015;59(3):259-64.

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Diagnosis and Management

- Diagnosis
  - CT Scan – 46% Sensitivity
  - MRI – modality of choice
- Acute Management - controversial
  - High-dose corticosteroid replacement – IV
  - Transphenoidal surgical decompression of the sella (ideally within 1 week)
    - 76% visual acuity improves
    - 79% visual fields improve

Glezer A, Bronstein MD. Pituitary apoplexy: pathophysiology, diagnosis, and management. *Arch Endocrinol Metab.* 2015;59(3):259-64.
Semple PL, Webb MK, de Villiers JC, Laws ER. Pituitary apoplexy. *Neurosurgery.* 2005;56(1):65-72. discussion 3.

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Summary

- Neuro-ophthalmological emergencies can present to primary care optometry
- The best way to prepare is to have a systematic process for examination and workflow
- Sometimes as an optometrist you get to save a life

Thank You!

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