# CLINICAL GRAND ROUNDS: Perspectives from an Optometrist and an Internist

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***The following conditions that we will be discussing are not the order in which we will discuss the conditions. Rather than following the notes, please follow and participate in our discussions and use the following notes as a resource with which to further solidify your understanding.***

**Giant Cell Arteritis**

- Also known as temporal arteritis
- The patient suffering from giant cell arteritis (GCA) is invariably elderly, with the mean age of 71 years at presentation.
- This condition is generally considered only after the age of 50 years. There is a 2:1 female to male ratio and a higher incidence in Caucasian patients.
- There is a multitude of systemic manifestations that can accompany and signal the presence of GCA, including malaise, weight loss and anorexia, headache about the temporal or occipital region, pulseless and indurated temporal arteries, night sweats, tongue necrosis and oral ulceration, dental abscess, scalp pain, scalp necrosis, jaw claudication when eating, head and neck swelling, anemia, depression, mental disturbance, neck pain, low grade fever, transient ischemic attack and stroke, proximal myalgia, breast masses, gynecological disorders, malignant disease, persistent flu-like illness, chronic pharyngitis, vertigo, muscle aches, cardiac arrhythmia, congestive heart failure, and myocardial infarction.
- There is a clinical entity known as occult GCA, where the patient experiences vasculogenic vision loss in the absence of systemic signs or symptoms. These patients, representing approximately 21% of patients with GCA, tend to have slightly lower erythrocyte sedimentation rates (ESR) and C-reactive protein (CRP) levels compared to symptomatic patients.
- All too often, patients with GCA are diagnosed following sudden, devastating vision loss in one or both eyes. The cause typically is arteritic anterior ischemic optic neuropathy (AAION).
- In approximately 10% of GCA cases, central retinal artery occlusion (CRAO) is the underlying etiology. Coincidentally, about 10% of CRAO is due to GCA and not emboli.
- Sudden, permanent vision loss is preceded by the ominous warning sign of bouts of amaurosis fugax in approximately 30% of cases.
    - Progression to bilateral vision loss has been known to occur with a time interval of 1-14 days between involvement of the two eyes.
- Other ocular manifestations of GCA include posterior ischemic optic neuropathy (PION), cilioretinal artery occlusion, ophthalmic artery occlusion, amaurosis fugax, diplopia and ophthalmoplegia from paresis of cranial nerves III, IV, and/or VI, tonic pupil, Horner's syndrome, ocular hypotony, chronic uveitis, episcleritis and scleritis, conjunctivitis, visual

hallucinations, posterior chiasmal field loss, cortical blindness, internuclear ophthalmoplegia, ocular ischemic syndrome and even isolated cotton wool spots.

- There are two associated similar systemic, condition known as polymyalgia rheumatica (PMR) and polyarteritis nodosa (PAN). Both involve pain and stiffness of the muscles of the proximal limbs, particularly upon waking. In fact, PMR is likely within the same spectrum GCA.

**Pathophysiologyof GCA:**

- GCA is a granulomatous inflammation of medium and large-sized arteries that have a defined internal and external elastic lamina. Cellular immunity appears to be more significant than humoral immunity in the pathogenesis of GCA. There is cellular infiltration of the muscular wall of these vessels by T lymphocytes, macrophages, histiocytes, plasma cells, and multinucleate giant cells. Histologic criteria for GCA diagnosis requires the discovery of cellular infiltrates within the vessel walls with inflammatory cells; giant cells need not be present on biopsy in order to make this diagnosis.
- As virtually any vessel within the body may be involved, GCA is a multi-system, multi-symptom disorder. The degree of ischemia tolerated varies by system, and there is often a symptomatic period of weeks to months before diagnosis is reached. In the eye, ischemia is manifested often by amaurosis fugax and intermittent diplopia and ophthalmoplegia prior to complete occlusion of the posterior ciliary, retinal, or ophthalmic arteries. When symptoms manifest ocularly, there is a much shorter time interval to severe permanent vision loss.

**Management:**

- Management begins with the recognition that GCA may be a potential cause of the aforementioned findings in an elderly patient. Any unexplained ocular findings, involvement of multiple vessels, or idiopathic systemic deterioration in an elderly patient should immediately raise suspicions.
- Once GCA is recognized as a potential etiopathology immediate (STAT) ESR and CRP must be ordered. ESR, a non-specific index of illness, is typically elevated in cases of GCA. However, there will be a small percentage of cases that will not manifest an elevated ESR. In these cases, supplemental confirmatory evidence provided by the CRP (a marker of inflammatory activity) is helpful. Additionally in these cases, the ophthalmic findings and systemic history become diagnostically more important. If the ESR or CRP is elevated, or if there are obvious constitutional symptoms, then a temporal artery biopsy must be performed in order to conclusively diagnose GCA.
- Systemic steroids are needed to preserve vision and reduce morbidity and mortality. However, steroids should not be withheld pending biopsy results. If history, exam findings and serology indicate GCA, then steroids must be started without delay. Biopsy results will not be immediately affected after initiation of steroid therapy.
- The therapeutic dosage of steroids is controversial. It is generally felt that patients with ophthalmic complications should receive 250 mg of IV methylprednisolone TID-QID for 3 days, followed by high doses of prednisone. Oral steroid administration may require prednisone doses up to 80 mg/day. Oral therapy should be reduced in weekly steps of 5 to 10 mg until 20 mg/day, and by 2.5 mg until 10 mg/day. Dose reduction is 1 mg/month below 10 mg, depending on symptoms and the ESR or CRP values.

- The most reliable and sensitive parameters to regulate steroid therapy are ESR and CRP levels. The suppression of systemic symptoms is not a reliable indicator. On average, time to reach the lowest maintenance dose of prednisone at which the ESR and CRP remain low and stable is nearly 49 months. Rarely will patients be able to stop steroid therapy and maintain low ESR and CRP levels
- It has been thought that systemic immunosuppressants might provide an avenue for reduction of systemic steroids and their attendant complications. However, to date, no corticosteroid-sparing benefit has been attributed to the combination of methotrexate with corticosteroid therapy.
- Recently, it has been seen that the adjunctive use of low dose aspirin (100mg/day) in steroid-treated GCA patients decreases the rate of visual loss and cerebrovascular accidents from this disease, likely by suppressing proinflammatory cytokines in the vascular lesions of GCA.

**Clinical pearls:**

- ***GCA is an ocular and systemic <u>emergency</u>!*** Untreated, progression involving the fellow eye occurs in a high number of cases ***within hours to days***. Frequently, vision loss in GCA is devastating and irreversible, and may progress despite seemingly adequate treatment.
- Headache arising de novo in elderly patients is uncommon and a reason to suspect GCA. It is not unreasonable to obtain ESR and CRP testing on elderly patients complaining of headache despite a normal ophthalmic exam.
- Temporal scalp tenderness is also occurs from herpes zoster prodrome in elderly patents.
- When suspecting GCA performing a thorough patient history is crucial. Simply asking about jaw claudication, headache, scalp tenderness, and weight loss is insufficient. As this is a multisystem disease, virtually any organ can be involved. Encourage patients to report any maladies that they are having.
- Amaurosis fugax and intermittent diplopia are extremely ominous symptoms in elderly patients and are harbingers of ensuing devastating vision loss from GCA.
- Elderly patients with unexplained cotton wool spots should be examined for GCA.

# Papilledema and Intracranial Mass Lesion

**Related Anatomy and Physiology**

- CSF is mainly produced by the choroid plexus of the lateral ventricles. It flows through the interventricular foramina into the third ventricle, then through the cerebral aqueduct into the fourth ventricle. From there, it flows into the subarachnoid space.
- CSF is absorbed passively through the arachnoid granulations that protrude into the venous sinuses and diploic veins. These veins drain into the jugular veins.
- Increased CSF pressure is transmitted to the optic nerves along their meningeal sheaths. Perineural pressure interferes with the slow component of axoplasmic flow at the level of the lamina cribrosa with resulting disc edema.

**Types of Papilledema**

1. ***Acute***--Hemorrhages and exudates are apparent In addition to hyperemia and NFL edema
2. ***Chronic***--Minimal or absent hemorrhage/edudate. Telangiectatic vessels on disc surface. Drusen-like bodies may be apparent. Optociliary shunt vessels may be present

3. ***Atrophic***--Eventually occurs if papilledema remains chronic. Optic disc pallor with nerve fiber bundle visual field defects.

**Papilledema Symptoms**

- **Headache-**nonspecific characteristics; often worsens with valsava maneuver. This is the most common symptom and is thought to occur from stretching of the meninges or cerebral veins
- **Transient Visual Obscurations-**mild blurring to complete blindness that lasts seconds. Precipitated by changes in posture and more commonly seen in chronic papilledema. It occurs from transient compression or ischemia to the optic nerve but has no bearing on visual outcome
- **Tinnitus-**Pulsatile quality reflecting flow disturbances in the cerebral venous system. Patients usually report a whooshing sound and it tends to be most prominent at night
- **Diplopia-**Typically due to abducens palsy. The abducens palsy is typically bilateral

**Visual Fields**

- Enlarged blindspot due to the increased diameter of the nerve
- Arcuate loss with nasal involvement occurs as axons die off.

# Crab Louse Infestation

- Causative organism: Crab louse family, Pediculidae, has two genera
    - Pediculus humanis (head louse)
    - Phthiriasis pubis (pubic louse)
        - Phthiriasis pubis palpebrarum (eyelash infection)
        - Predilection for pubic hair and eyelashes due to spacing between cilia.
- Organism has broad, oval abdomen with large crab-like claws
- Transmission is through hand contact with genitals or following oral-genital contact.

**Ocular Manifestations:**

- Pruritic lid margins
- Blepharoconjunctivitis
- Lid irritation and itching
- Diagnosis and Management:
- Ocular involvement is diagnosed through direct biomicroscopic observation of organism, blood tinged deposits along lid margins, reddish brown fecal matter, or oval deposits (nits) in the lashes.
- Nits represent unhatched organisms and are resistant to treatment.
- Physical removal with biomicroscope and forceps
    - Adults killed with alcohol after removal from cilia
    - Will not typically totally eradicate organism
- Bland ointment or antibiotic ointment smeared into lashes
    - Will smother adult organisms
    - Must be continued for two weeks in order to kill nits
- Physostigmine 0.25% ointment (Eserine) smeared into lashes

        - Anticholinesterases will inhibit organism respiration
        - Must extend two weeks
- Yellow mercuric oxide N.F. 1%
- Ammoniated mercury 3%
- Sodium fluorescein (concentrated as used in angiography- not diagnostic strips used in office)
- Systemic treatment to prevent reinfestation (cannot be used for ocular infestation)
        - Gamma benzene hexachloride (Kwell)
        - pyrethrin (Rid)- non-prescription
            - Toxicity prevents shampoos from being used on eyelid infestation.
            - Use with extreme care in children and pregnancy

# Central Retinal Artery Occlusion

- Clinical Picture:
    - Painless, sudden loss of monocular vision
    - Vision is markedly reduced
    - Retinal edema causing white appearance to fundus
    - Mean age is 60's
    - "Cherry red" macula due to underlying choriocapillaris perfusion
    - Optic atrophy ensues eventually
- Pathophysiology:
    - Emboli is most common cause
        - Emboli from carotid artery or heart lodging in central retinal artery at laminar constriction.
            - Cardiac emboli more common than carotid emboli in CRAO
    - Other possible etiologies:
        - Intraluminal thrombosis
        - Hemorrhage under atherosclerotic plaque
        - Vasospasm
        - Dissecting aneurysm
        - Hypertensive arteriolar necrosis
        - Circulatory collapse
        - Giant cell arteritis (10% of CRAO caused by GCA) ***
- Complications:
    - CVA
    - Myocardial infarction: main cause of death
        - Low survivorship: 9 year mortality of 56% (compared to 17% in age matched group)
    - Neovascularization rare (17% of cases and occurs within 4 weeks)
    - Ischemic ocular syndrome (a complication of carotid artery disease)
- Management:
    - When acute- immediate referral to stroke unit

- In patients over 60, CRAO may be caused by giant cell arteritis; MUST get a STAT ESR and C-reactive protein on every patient over the age of 60 years with CRAO!
- Internal medicine referral most appropriate to educe mortality
- Monitor for complications Q 3 months

# Central Retinal Vein Occlusion

- Thrombotic phenomenon: Properties of the blood and central retinal vein act in concert to cause thrombotic occlusion. Causes partial or complete blockage of venous return
  - Vein inflammation
  - Vascular flow and/or vessel wall abnormalities stimulate vein thrombosis
  - Hypercoagulability states, elevated viscosity, and systemic states of decreased thrombolysis promote thrombus formation. (i.e., changes in blood constituents)
  - Turbulent blood flow causing thrombus formation at lamina
  - Laminar constriction site is the nidus for occlusion. Intraluminal pressure of the vein decreases, rendering it susceptible to collapse. Compression by an arteriolosclerotic CRA further affects flow and thrombus formation. CRV and CRA share common sheath passing through lamina cribrosa.
  - External factors such as increased IOP in POAG and papilledema (causing increased pressure in the optic nerve sheath) may cause further compression and contribute to occlusion.
- Other factors that result in compression include: orbital tumor and abscesses, cavernous sinus thrombosis, and retrobulbar intranerve sheath injection.
- Systemic diseases influence thrombus formation through:
  1. External compression
  2. Primary thrombus formation (Antiphospholipid antibodies)
  3. Degenerative or inflammatory disorders of the vein itself

**Vascular occlusions and antiphospholipid antibody syndrome**

- Patients with antiphospholipid antibody syndrome (APAS) are typically female and tend to be young
- Approximately 50% of patients with antiphospholipid antibodies also have systemic lupus erythematosus (SLE) or other autoimmune diseases.
- However, in many cases, there exists APAS without associated autoimmune disease.
- The most common conditions that result from APAS which affect the eye and visual system are arterial or venous thrombosis with resultant ischemia. This manifests as central retinal vein or artery occlusion (CRVO or CRAO), papillophlebitis, anterior ischemic optic neuropathy (AION), migraine, ophthalmoparesis and diplopia, amaurosis fugax, isolated retinal hemorrhages and cotton wool spots, and retinal neovascularization.
- While these conditions typically occur in elderly patients, the patient with APAS experiences them at a younger age.
- Younger (under age 50) patients with retinal vascular occlusions should be investigated for antiphospholipid antibody syndrome

- In addition to ocular manifestations, there are often thrombi in other systems. Venous thromboses of the arm and leg, pulmonary embolism, sagital, pelvic, mesenteric, portal, and axillary have all been encountered in APAS. Transient ischemic attack (TIA) and cerebrovascular accidents are the most common occurrences from thrombosis in the arterial system. Another systemic finding that is thrombocytopenia (reduced platelet count).
- A common, and in many cases defining, event in APAS is recurrent pregnancy loss that can occur in any trimester. Preeclampsia and intrauterine growth retardation have also been found in association with APAS.
- Antiphospholipid antibodies are a group of circulating antibodies that include anticardiolipin antibody, lupus anticoagulant, and the Biologic False Positive Test for Syphilis (BFP-TS). These antibodies are directed against phosopholipid binding proteins, which prolong phospholipid-dependent coagulation assays. In this condition, phospholipids, present in cell membranes, are erroneously identified by the body as being foreign and, consequently, the body produces antibodies to the phospholipids. These antibodies appear to have an affinity for the cell membranes found in platelets, vessel endothelial cells, and clotting factors.
- Antiphospholipid antibody syndrome is an autoimmune disorder with two forms: Primary Antiphospholipid Antibody Syndrome and Secondary Antiphospholipid Antibody Syndrome. Antiphospholipid antibodies (anticardiolipin antibodies and lupus anticoagulant) are all known to commonly occur in patients with SLE.
- When these antibodies occur in the presence of SLE, it is considered a secondary syndrome. It wasn't until 1985 that Hughes identified these antibodies in seemingly normal patients experiencing thrombotic events and pregnancy loss in the absence of SLE. This primary form exists in the absence of clinically or serologically proven autoimmune disease and has been termed Primary Antiphospholipid Antibody Syndrome and occasionally referred to as Hughes' Syndrome.
- Antiphospholipid antibody syndrome is diagnosed by arterial and venous thrombosis, pregnancy loss and/or thrombocytopenia in the presence of lupus anticoagulant and anticardiolipin antibodies. The method of promoting thrombosis by the antiphospholipid antibodies is unclear. Thrombosis appears to be the cause of pregnancy loss.

# Signs and symptoms of impending stroke

- Amaurosis fugax (AF)
- Transient ischemic attack (TIA)
- Visible retinal emboli

**Amaurosis Fugax**

- Painless and isolated
- Total or sectorial
- Monocular
- Disease of the carotid artery (typically)
  - Emboli are reaching the retinal arterial system and causing temporary occlusion
- Isolated or antecedent (long ago) without current symptoms are less dangerous than many current episodes of AF
- No associated neurological baggage
- Seconds to hours

    - Typically 2-5 minutes
- Resolves completely

**Uncomplicated Amaurosis Fugax**
- 85% recovery
- 10-15% get central retinal artery occlusion (CRAO)
- 2% have CVA
- 2%-4% annual risk of mortality

**Transient Ischemic Attack**
- Painless
- Total vision loss or may have no ocular involvement whatsoever
- Contralateral hemiparesis; paresthesia
    - Weakness and/or numbness of parts or all of the contralateral side with loss of motor and/or sensory system. Typically arm (most common), leg, face & arm, arm & leg. Numbness in the hand, foot, face, ½ of tongue
- Aphasia/ dysphasia
    - Inability to understand spoken words or unable to speak, depending upon which part of the brain is ischemic
- Typically lasts 15 minutes but may last for hours

**Transient Ischemic Attack (Hemispheric): Mortality**
- 25% in 1 month
- 33% in 6 months
- 60% within 7 years
- In patients over the age of 60 years with transient visual loss (TVL), either TIA or AF, you must get an erythrocyte sedimentation rate (ESR) and C-reactive protein to look for GCA. AF in an elderly patient due to transient occlusion of the ophthalmic or central retinal artery is a sign of impending, permanent, severe vision loss (often within several weeks).

**Emboli-forming conditions**
- Rheumatic heart disease
- Atherosclerosis from hypertension
- Prosthetic heart valves
- Infectious endocarditis
- Indwelling catheters
- Rhythm disturbance - Mitral valve prolapse (Barlow's syndrome).
    - 17% of females
    - Blood regurgitates back into atrium and pools where platelets can aggregate and clots can form
        - Giant Cell Arteritis (GCA)

**Emboli: Just the Facts**
- May be symptomatic (AF or TIA) or asymptomatic

- Three types of emboli/ plaques: Fischer, Hollenhorst, calcific
- Fischer- fibrin/platelet aggregate (carotid in origin, also walls of arteries and valves of heart)
  - Dull gray or white
  - Readily migrate through vascular system producing symptoms (AF)
- Hollenhorst- cholesterol (carotid in origin)
  - Refractile, glistening, yellow
  - Most common (87%) of all emboli
  - Typically do not occlude artery
  - Malleable and allows for blood to pass though the artery may appear totally blocked
  - Will readily break up and move distally, so will not be seen typically in patients complaining of AF
  - common cause of AF
- Calcific (cardiac)
  - Dull white and non-refractile
  - Usually from valvular calcification
  - Most likely to cause artery occlusion and stroke

**Visible Retinal Emboli: Mortality**

- 15% within 1 yr.
- 29% within 3 yrs
- 54% within 7 yrs
- Cardiac death more prevalent than stroke

**Management**

- Internist
- No conclusive evidence that carotid evaluation is necessary
- Majority of patients with asymptomatic visible retinal emboli do not have significant carotid disease
- Smoking is greatest modifiable risk factor for emboli. Smoking cessation is most important
- Clinical profile of patient with emboli: older Caucasian hypertensive smoking male

# Hypertensive Retinopathy

- Arteriolosclerotic vessel changes
  - Some classification schemes include vessel changes in hypertensive retinopathy and others don't
- Elschnig's spots – subtle choroidal infarcts
- CWS
- Flame shaped hemorrhages
- Macular edema (rare)
- Macular star/ ring of exudates
- Disc edema
- Arteriosclerotic changes persist
- Hypertensive changes can resolve after reduction of systemic blood pressure

- Blood pressure = internal pressure exerted on the arterial walls
  - Dependent upon:
    - Energy of the heart action
    - Elasticity of the arterial walls
    - Volume and viscosity of the blood
  - Systolic BP = arterial blood pressure during heart contraction
  - Diastolic BP = arterial blood pressure between heart contractions
- "Normal" blood pressure: ≤ 120/80 (Systolic / diastolic) **JNC 7, 2003**
  - Hypertension is defined as any elevation of blood pressure above the norm, as measured by sphygmomanometry on two separate occasions
    - Prehypertension: 120 – 139 (systolic) and/or 80 – 89 (diastolic)
    - Stage 1 hypertension: 140 – 159 (systolic) and/or 90 – 99 (diastolic)
    - Stage 2 hypertension (severe): ≥ 160 (systolic) and/or ≥ 100 (diastolic)
- Hypertensive Crises
  - Hypertensive EMERGENCY = Severe HTN + End-Organ Damage
    - End-organ damage is defined as *hypertensive encephalopathy*, *intracerebral hemorrhage*, *acute myocardial infarction*, *left ventricular failure with pulmonary edema*, *acute coronary syndrome*, *dissecting aortic aneurysm*, or *eclampsia*
    - Hypertensive **EMERGENCIES** require immediate BP reduction (not necessarily to normal ranges) to prevent or limit organ damage.

        - Patients with hypertensive emergencies are often admitted through the ER for aggressive treatment.
    - Hypertensive URGENCY = Severe HTN + NO End-Organ Damage
        - Typically identified in patients presenting for routine evaluation or with other ocular symptoms.
        - Elevated BP represents acute recognition of chronic hypertension, or – in patients already diagnosed with hypertension – nonadherence to drug therapy or inadequate treatment by the PCP.
        - Hypertensive **URGENCIES** do not warrant aggressive BP reduction, as rapid reduction of BP may be associated with significant MORBIDITY:
            - Causes a rightward shift in the pressure/flow autoregulatory curve in critical arterial beds (cerebral, coronary, renal).
            - Can result in marked reduction in perfusion, causing ischemia and infarction; BP must be reduced in a SLOW and CONTROLLED fashion.
        - Patients with hypertensive urgencies are usually treated with oral medications and followed over several days to weeks to evaluate their response to therapy.

- Pharmacologic dilation can help to identify target end-organ damage, particularly hypertensive encephalopathy (Stage 4 hypertensive retinopathy) and intracerebral hemorrhage (Terson's syndrome). Therefore, in patients with significantly elevated BP, dilated funduscopy is of PARAMOUNT importance… but ***IS THERE A SUBSTANTIAL RISK TO THE PATIENT??***

- Induction of Adverse Events secondary to Topical Phenylephrine
    - Regarding 2.5% phenylephrine (PE), numerous reports suggest there is little concern over adverse responses:
        - Jennings et al (1986) – 252 patients, ranging in age from 3 – 92 years; reported no significant changes in systolic or diastolic blood pressure in patients dilated with 2.5% PE.
        - Malhotra et al (1998) – 54 consecutive patients undergoing routine cataract extraction; found no sustained changes in blood pressure or heart rate after instillation of 2.5% PE.
        - Lam et al (2003) – 217 consecutive patients undergoing phacoemulsification; found no untoward cardiovascular effects in group dilated with 2.5% PE.
    - Approximately 41 cases involving adverse systemic reactions to **10%** phenylephrine have been reported in the peer-reviewed literature.
        - 15 patients suffered myocardial infarction after instillation of 10% PE, of which 11 resulted in fatality; these individuals had an average age of 71 years, and nine had a known history of cardiac disease.
    - Conclusions & Recommendations based on data submitted to the National Registry of Drug-Induced Ocular Side Effects:
        - 2.5% PE is recommended for routine pharmacologic dilation.

- 10% PE should be avoided in the elderly, infants, and patients with cardiac disease, idiopathic orthostatic hypotension, hypertension, aneurysms, Type 2 diabetes, and advanced arteriosclerosis.
- 10% PE should also be avoided in patients using MAO inhibitors, tricyclic antidepressants, reserpine, guanethidine, or methyldopa.