

Conversations in Retinal Vascular Disease

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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:
 - 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 reduce mortality
- Monitor for complications Q 3 months

Cilioretinal Artery Occlusion:

- Local infarcted area
- Severe loss of central acuity with preservation of peripheral field
- Systemic causes similar to CRAO
- Higher incidence of GCA, especially if concurrent AION exists

Branch Retinal Artery Occlusion:

- Visible retinal emboli lodged in arteriole
 - Cholesterol
 - Calcific
 - Fibrin-platelet
 - Infectious
- Rarely caused by GCA
- Acuity 20/20 to hand motion depending upon the degree of involvement (macula)
 - Patients commonly report sudden onset of field loss
- Whitened retina in distribution of arteriole
- With resolution, retina becomes more normal in appearance (but not function)
- Neovascularization is rare
- Systemic associations same as CRAO, but lower survivorship
- Internal medicine/ Cardiology referral

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 arteriosclerotic 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, sagittal, 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 phospholipid 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.

Branch Retinal Vein Occlusion

- Occurs at arteriovenous crossing
- Most commonly superiotemporal
- Arteriosclerotic etiology: as the arteriole becomes sclerotic, it compresses the underlying venule leading to thrombus formation and leakage from the capillary beds draining into the venule. At no time in vascular occlusion does the vein or venule ever leak. All leakage is from the capillaries.
- Vein compression will lead to turbulent blood flow, which damages the endothelium and sets the stage for platelets, thrombin, and fibrin to form a thrombus.
- May present with loss of acuity and/or field, but may be asymptomatic
- There are three location classification for BRVO
 1. Hemispheric
Before the first bifurcation. Technically HRVO
 2. Intermediate
After the first bifurcation. Typical BRVO appearance
 3. Twig
Macular area only

New Insight into the Management of BRVO: BRAVO Studies

- Two phase 3 multicenter, prospective clinical trials assessing the safety, tolerability, and efficacy of intravitreal ranibizumab (Lucentis) injections (compared with sham placebo) in the treatment of macular edema secondary to BRVO.
- The BRAVO trial includes patients with BRVO or hemiretinal vein occlusion
- Secondary endpoints include evaluating the efficacy of the treatment in improving other visual acuity measures, anatomic outcomes, and patient-reported measures of visual function.
- Patients are randomized 1:1:1 to either sham injection, ranibizumab 0.3 mg, or ranibizumab 0.5 mg. They receive monthly injections for 6 months. During the second 6-month period, patients are evaluated monthly and treated on a PRN basis.
- In BRAVO, patients are eligible for rescue laser therapy, if necessary
- Data from the BRAVO study in branch-RVO showed at month six, patients who received 0.3 mg of Lucentis had a mean gain from baseline BCVA of 16.6 letters and patients who received 0.5 mg of Lucentis had a mean gain of 18.3 letters. In the CRUISE study in central-RVO, at month six, patients who received 0.3 mg of Lucentis had a mean gain from baseline BCVA of 12.7 letters and patients who received 0.5 mg of Lucentis had a mean gain of 14.9 letters. In both trials, a statistically significant mean gain in BVCA was observed as early as day seven for both doses of Lucentis compared with sham. The studies were not designed to compare the two doses of Lucentis.
- The two doses of ranibizumab used in the BRAVO study showed a statistically significant improvement in best corrected visual acuity at 6 months compared with sham injection. The safety profile of ranibizumab was consistent with previous experience, and no new adverse events were observed.

The main outcome for BRAVO was improvement in treated patients greater than that in sham-treated patients at 6 months. At 12 months, the therapeutically treated patients maintained the improvements; there were also improvements for sham-treated groups as well. While the therapeutically treated patients had statistically greater improvement than the sham-treated patients at 12 months, the differences were not as great as at 6 months.

Signs and symptoms of impending stroke

- Transient ischemic attack (TIA)
 - Amaurosis fugax (AF)- amaurosis = blindness; fugax = fleeting
 - Transient monocular blindness
- Visible retinal emboli

Clinical Pearl: TIA and AF are straws that tell which way the intracranial wind is blowing.

Transient Ischemic Attack

- The definition of transient ischemic attack has changed from a focal, neurologic event that lasts less than 24 hours to one that typically lasts less than 1 hour and is not associated with changes on neuroimaging. A brief episode of neurologic dysfunction caused by focal brain or retinal ischemia, with clinical symptoms typically lasting less than one hour, and without evidence of acute infarction.
 - Most transient ischemic attack symptoms last less than 1 hour and typically less than 30 minutes
- Symptoms consistent with transient ischemic attack include hemiparesis, hemisensory loss, hemifacial weakness of upper motor neuron distribution, *amaurosis fugax*, and aphasia
 - 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
- The anterior circulation consists of the internal carotid arteries, the middle cerebral arteries, the anterior cerebral arteries, and their tributaries. It receives 80% of the cerebral blood flow and accounts for 80% of transient ischemic attacks and strokes. Amaurosis fugax indicates an abnormality in the ophthalmic branch of the internal carotid artery distal to the bifurcation.
- Painless
- Diplopia may occur from TIA involving posterior circulation (vertebrobasilar vascular distribution)
 - Dizziness is a common finding
- TIA may have no ocular involvement whatsoever

Amaurosis Fugax

- Transient monocular blindness/ transient monocular vision loss
- May be a manifestation (criterion) of TIA, though can occur from other causes

- Painless and isolated- Involves vision only
- Total or sectorial
 - Amaurosis fugax can manifest in a variety of ways aside from the classic “curtain-like” visual loss, including clouding, graying, or darkening of vision. A horizontal visual field defect suggests segmental embolization to the superior or inferior branch of the retinal artery
- 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 and may be the sole finding in a TIA
- Seconds to hours
 - Typically 2-5 minutes
- Resolves completely
- Other types of amaurosis fugax
 - Light-induced amaurosis fugax:
 - Patient may report loss of vision in the ipsilateral eye after exposure to bright light (e.g., looking outside on a sunny day). Indicates significant internal carotid artery stenosis or occlusion
 - Gaze-induced amaurosis fugax- when looking in a certain direction, the patient loses vision
 - Usually indicative of a retro-orbital mass lesion

Clinical Pearl: Amaurosis fugax has historically been considered as an isolated finding. Today, it is considered a manifestation of TIA. Previously, transient monocular vision loss alone was called amaurosis fugax. Now, it is called a TIA.

Clinical Pearl: Things other than emboli can cause amaurosis fugax.

Transient Ischemic Attack: Prognosis

- TIA portends the possibility of a subsequent CVA/ stroke with permanent neurologic deficits.
- TIA also indicated widespread vascular disease putting patients at risk of myocardial infarction and cardiac death
- Patients with amaurosis fugax as only manifestation of TIA are at lesser risk than pts. with hemispheric TIA
 - Risk of arterial occlusion (with permanent vision loss), CVA, and MI.
- Risk of future events for TIA dictated by cause and degree of carotid stenosis

Clinical Pearl: A patient experiencing amaurosis fugax is considered to have experienced a TIA if the cause of the AF is vascular. Patients can experience TIAs that have no visual involvement as well.

Pathophysiology of TIA and AF:

1. Hypertension leading to atherosclerosis with subsequent thromboembolism formation

**Cholesterol → fatty streak → atheroma → ulceration → thrombus → plaques
→ emboli**

2. Emboli-forming conditions (other than HTN)
 - Rheumatic heart disease
 - Prosthetic heart valves
 - Bacterial 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
3. Giant Cell Arteritis (GCA)- Thrombus formation due to vessel wall and lumen obliteration from inflammation
 - 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).
4. Vasospastic
 - Non-embolic arterial narrowing
 - Vasospastic substance (Cocaine) use
 - Migraine?
5. Hematological
 - Polycythemia (Too much hemoglobin)
 - Sickle cell (#1 hematological cause of transient vision loss)
 - Anemia (Too little hemoglobin)
 - Hypercoagulability states
 - Anti-phospholipid antibody syndrome

Emboli: Just the Facts

- May be symptomatic (AF or TIA) or asymptomatic
- The main factor associated with retinal emboli is smoking
- Three types of 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

Clinical Pearl: The patient most likely to manifest asymptomatic retinal emboli is an older hypertensive man that smokes. Smoking cessation is absolutely essential for these patients.

- **Clinical Pearl: The literature does not support carotid evaluation for patients with asymptomatic retinal emboli because the majority does not have significant carotid stenosis. There is no definitive management of these patients. It's best to refer them for an atherosclerotic evaluation and let the internist decide what to do.**