Clinical Findings and Management of Central Retinal Artery Occlusion

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Abstract
Central retinal artery occlusion (CRAO) is an ophthalmic emergency and represents the ocular equivalent of a cerebral stroke. Evidence shows that most CRAO patients suffer profound, acute vision loss, as well as an increased risk of subsequent cerebral stroke. There are no current, proven ocular treatments for CRAO. Management is targeted at evaluation and intervention of acute risk factors, preventing secondary ocular neovascular complications, and addressing underlying systemic comorbidities. This case report reviews the clinical features, etiologies, and management of CRAO.

Case Report
A 70-year-old Caucasian male presented with the subjective complaint of vision loss in the right eye which was first noted three days earlier upon awakening. He denied ocular pain, headaches, scalp tenderness, jaw claudication or any other associated neurological symptoms. He affirmed a history of previous transient ischemic attack (TIA) and stroke which was being managed with 81 mg aspirin once daily. His most recent eye examination had been performed eleven months earlier and his ocular history was remarkable for ocular hypertension, cataracts, dry eye syndrome, and presbyopia. His medical history was extensive and included diagnoses of diabetes mellitus type 2 with neuropathy, hypertension, congestive heart failure, coronary artery disease, chronic kidney disease, hyperlipidemia, venous insufficiency, cerebral infarction, cognitive impairment, ataxia, peripheral edema, esophageal reflux, pulmonary embolism, Guillain-Barre syndrome, chronic airflow obstruction, sleep apnea, seizure, and gout.

His best-corrected visual acuity was hand motion at one foot in the right eye and 20/30 in the left eye. His pupils were equal, round, and reactive to light with a 3+ afferent pupillary defect in the right eye. Extraocular muscles were unrestricted in all gazes and intraocular pressures measured 17 mmHg OD and 20 mmHg OS. Anterior segment findings were unremarkable in each eye. Dilated examination revealed nuclear sclerosis, cortical spoking, and trace posterior subcapsular opacities of the lens in both eyes. The vitreous was optically clear OU and fundus assessment revealed optic nerve cup-to-disc ratios of 0.20 in each eye. The neuro-retinal rims appeared perfused OU with slight blurring of the nerve margins on the right (Figures 1 & 2). The retinal vasculature of the right eye was narrowed with box-carring of the arteries, whereas the vasculature of the left eye revealed only slight attenuation. Diffuse retinal ischemia and whitening in all four quadrants, with cilioretinal sparing, was noted in the right eye. The fundus findings of the left eye were unremarkable. His blood pressure measured 126/71 mmHg and no carotid bruits were noted upon auscultation.

Complaints of unilateral, sudden, painless vision loss, involving the entire field of vision, in concert with the patient’s medical history, directed thoughts toward a presumptive diagnosis of central retinal artery occlusion (CRAO). Objective clinical findings of diffuse retinal whitening in all four quadrants, narrowed retinal vasculature with cilioretinal artery sparing, confirmed this suspicion. The patient was promptly transferred to the emergency room for a complete vascular work-up which revealed he had also experienced a subacute cerebrovascular accident. His daily baby aspirin regimen was subsequently replaced with clopidogrel (Plavix).

At the four-week follow-up, our patient was noted to have developed neovascular glaucoma in the right eye. Iris neovascularization (NVI) was present at the pupillary border and was present in the superior and inferior angles of the right eye. His intraocular pressure in the right eye was elevated to 28 mmHg. Fundus examination revealed right optic nerve pallor with no other vascular or retinal changes. Prompt referral was made to a local retinal specialist who addressed these proliferative findings with pan-retinal photocoagulation (PRP). Despite this intervention, the patient experienced a spike in intraocular pressure in the right eye which eventually required cyclophotocoagulation with diode laser to stabilize. He continues to be followed at regular intervals and his intraocular pressure is now successfully managed with brimonidine 0.2% BID OD.

Discussion
As the internal carotid ascends, the ophthalmic artery branch will emerge to provide arterial circulation to the eye. Multiple short posterior ciliary arteries also branch off of the ophthalmic
Central retinal artery occlusion is a relatively rare condition with an incidence of approximately 1 in 100,000 per year. Men tend to be affected more often than women, with a male to female ratio of 2:1. CRAO is most often found in older patients with a mean age of presentation in the early 60s. The incidence of CRAO tends to increase with age, and is closely associated with hypertension (67%), diabetes mellitus (33%), carotid occlusive disease (25%), and cardiac valvular disease (25%). Other common risk factors include cigarette smoking, hypercholesterolemia, and increased body mass index (BMI). An occlusion of the central retinal artery is more common than a branch retinal artery or cilioretinal artery occlusion and CRAO. In general, retinal arterial emboli are comprised of various types of material, with the majority (75%) being composed of cholesterol. Cholesterol emboli, commonly known as Hollenhorst plaques, tend to be refractile, have a yellow to orange coloration, typically lodge at a vessel bifurcation, and are most often associated with atherosclerosis of the carotid arteries or aorta. Calcium emboli (10%) are white, frequently occur on or close to the optic disc, and generally originate from cardiac valves. Platelet-fibrin emboli (15%) typically have a dull grey appearance and usually arise from atheromas within the carotid arteries. Rare cases of fat emboli from fractures and amniotic fluid have also been described.

Central retinal artery occlusion can also occur secondary to inflammatory changes within the arterial walls of large to medium-sized vessels, narrowing the vessel lumen and obstructing blood flow. The most common inflammatory disease associated with CRAO is Giant Cell Arteritis (GCA). GCA has been determined to be the underlying etiology in roughly 4.5% of CRAO cases. GCA should be suspected in patients over 55 years old who present with a CRAO, especially if accompanied by symptoms such as headaches, scalp tenderness, jaw claudication, malaise, fatigue, temporal tenderness, and fever. Other signs typically observed upon examination of a patient with giant cell arteritis include a chalky pale, swollen disc, with flame-shaped hemorrhages. Patients with giant cell arteritis should be immediately started on IV or oral steroids, and lab testing should be obtained including a complete blood count (CBC) with platelets, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) in attempt to support the clinical diagnosis.

Multiple etiologies for central retinal artery obstruction have been described including emboli, thrombus formation, vasospasm, inflammation, infection, and trauma (Table 1). The narrowest portion of the central retinal artery occurs at the point where the artery penetrates the dural sheath of the optic nerve. This represents the most likely site for an embolus to lodge, whereas thrombi most often develop posterior to the lamina cribrosa. The most common sources for emboli resulting in CRAO are atherosclerotic plaques within the carotid artery. Emboli are only visible in the retinal vasculature of 20-40% of CRAO cases. In general, retinal arterial emboli are comprised of various types of material, with the majority (75%) being composed of cholesterol. Cholesterol emboli,
painless, and profound vision loss. On occasion, patients may have a history of amaurosis fugax or brief episodes of visual loss similar to what is experienced prior to cerebrovascular accidents or transient ischemic attacks. Visual acuity is generally reduced to 20/200 or worse, and not uncommonly in the count-fingers to light-perception range. A relative afferent pupillary defect (RAPD) is to be expected in the affected eye. The classic clinical finding of CRAO is diffuse retinal whitening due to opacification of the nerve fiber layer as it becomes edematous from ischemia. CRAO also presents with retinal arteriolar constriction with segmentation of blood flow, also known as box-carring. Occasionally, an embolus may be visualized within the retinal vasculature, and there may be associated optic nerve edema or pallor. A cherry-red spot in the macula is considered another classic finding of CRAO. The cherry-red spot is due to visualization of underlying choroidal circulation through the thin foveal tissue. Because of the surrounding whitened retina, the central macula assumes this appearance. In a cilioretinal artery sparing CRAO (25% of cases) a small area of retina temporal to the optic disc may remain perfused. In 10% of CRAO cases, cilioretinal artery perfusion allows the foveola to be spared. This sparing of the foveal region results in an improvement in visual acuity of 20/50 or better in 80% of CRAO patients. It should be noted that in the setting of an ophthalmic artery obstruction, a cherry-red spot is typically not present due to ischemia of the underlying choroid, and visual acuity is typically light perception or no light perception. Over the course of several weeks following a CRAO the occluded vessel may be recanalized allowing reperfusion of retinal vessels. Unfortunately, the retinal tissue dies within hours after being deprived of oxygenated blood, so that by the time the vessel reperfusion occurs, visual recovery is not expected. At later stages in CRAO, posterior segment findings include retinal atrophy, optic atrophy, retinal arterial attenuation, cilioretinal collaterals, and macular pigment epithelial changes.

Ocular neovascularization (ONV) may occur following CRAO. Posterior segment ischemia causes a disruption of the homeostatic balance between pro-angiogenic factors, such as vascular endothelial growth factor (VEGF), and anti-angiogenic factors, such as pigment-epithelium derived factor. This imbalance drives the neovascularization process in the eye causing new blood vessel formation at the iris, anterior chamber angle, optic disc, or on the surface of the retina. A significant concern with occurrence of ONV is the development of neovascular glaucoma (NVG). NVG is a secondary glaucoma, often severe, attributed to development of new blood vessels over the iris and iridocorneal angle which can obstruct aqueous humor outflow and lead to significantly elevated IOP. These vessels can cause development of a fibrovascular membrane on the anterior surface of the iris and the anterior chamber angle. If left untreated, this membrane initially obstructs aqueous outflow, and later contracts to produce secondary synechial angle-closure glaucoma with high intraocular pressure. Careful examination of the iris and anterior chamber angle is essential in the follow-up care of patients who have experienced a CRAO. It is critical to look closely for iris ruberosis, which generally begins at the pupillary border, as well as for neovascularization of the angle with gonioscopy. Other signs of NVG may include mild anterior chamber reaction, corneal edema due to a spike in IOP, ciliary injection, and uveal ectropion by contraction of the fibrovascular membrane over the iris. In advanced stages, anterior iris synechiae may be noted in addition to elevated IOP.

Management of CRAO requires acute and long-term strategies. Acute, symptomatic CRAO is considered an ophthalmic emergency as permanent vision loss may result within hours if perfusion is not re-established. In general, there are no proven therapies or treatments for preventing vision loss in acute CRAO (Table 2). Although several different therapies have been supported, treatment is controversial as prognosis is grim and there is questionable benefit to treating compared to the natural course of the condition. The goal of these strategies is to restore perfusion to the retina as soon as possible, increase oxygen delivery to the retina, and limit the damage from hypoxia.

### Therapies for Management of Acute CRAO (Table 2)

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<td>Ocular massage</td>
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<td>Systemic acetazolamide</td>
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<td>Topical hypotensive medications</td>
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<td>Anterior chamber paracentesis</td>
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<td>Carbogen treatment or rebreathing of expired CO₂</td>
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<td>Nd YAG laser embolysis</td>
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Bagheri notes that there are anecdotal reports of improvement with treatment if instituted within 90 to 120 minutes of the occlusive event. In addition, an experimental study by Hayreh et al. showed no detectable retinal damage in primate models with CRAO for up to 97 minutes. However, beyond this time interval, more extensive and irreversible damage is the norm. Data suggests that CRAO lasting approximately 240 minutes results in massive, irreversible damage and treatment initiated more than four hours after the onset of vision loss, holds no expectation of restoring vision as the retina is dead at that point. None of the above therapeutic interventions have been proven effective in randomized, controlled, clinical trials, and should not be regarded as standard of care.

In the acute setting, it is imperative that clinicians be mindful that these occlusions serve as an important clinical indicator of more ominous systemic processes. Acute CRAO requires initiation of an immediate systemic medical evaluation specific to the patient, their presentation, and medical history. CRAO patients are at increased risk for stroke and require immediate referral to the nearest stroke center or emergency room for evaluation and possible acute intervention. Evidence within the last few years indicates that retinal artery occlusion is the ocular equivalent of cerebral infarction as the two conditions share the same pathogenesis. Retinal artery occlusion is caused by an acute interruption of the retinal vasculature that...
leads to retinal ischemia and visual impairment, and a cerebral infarction is caused by an acute obstruction of blood flow to the brain that results in a focal neurologic deficit. Recent studies suggest that patients with transient or permanent monocural vision loss of ischemic origin such as CRAO or BRAO may have up to 20-30% risk of concurrent cortical ischemic stroke, even when there are no other neurologic deficits. A retrospective study by Lee et al. suggested that the risk of a subsequent stroke is especially high immediately following retinal artery occlusion development. Data showed that diffusion-weighted magnetic resonance imaging within seven days of the onset of visual loss revealed acute ischemic stroke in 8 patients (24.2%) out of a total of 33 retinal artery occlusion patients. Results from the study demonstrate the importance of a systemic evaluation to prevent stroke among patients with retinal artery occlusion as soon as possible due to elevated early stroke risk. This is supported by the recommendation from the American Heart Association/American Stroke Association (AHA/ASA) that all patients with suspected brain or retinal ischemia undergo immediate brain imaging and etiological work-ups.

Long-term management of CRAO is directed at preventing secondary neovascular complications to the eye, particularly with concern for development of neovascular glaucoma. The reported prevalence of ocular neovascularization following CRAO ranges from 3 to 18.8% in studies conducted in the past 35 years. Mason III et al., performed a retrospective study of the development rate of ONV in eyes with a CRAO or BRAO. In the case series, 286 total eyes were evaluated, 83 of which were diagnosed with CRAO and 203 with BRAO. The average time for ONV development secondary to CRAO was 30.7 days, ranging from the date of presentation to 137 days. Results of the study demonstrated that 12 (14.5%) of 83 eyes with a CRAO diagnosis developed ONV. Eleven (91.7%) of 12 eyes with ONV had NVD, ten (83.3%) of 12 eyes had NVG, and two (16.7%) of 12 eyes had NVD. Ten of the 12 patients with ONV had multiple vascular comorbidities. The study found that type 2 diabetes mellitus is a risk factor for ONV development in eyes with a CRAO and that there is a strong association between the two, even if the patient does not have proliferative diabetic retinopathy. The average time range of development of ONV in eyes with a CRAO was from the date of presentation to approximately 5 months after the diagnosis of CRAO. Therefore, it was suggested that patients with CRAO should be closely monitored for at least the first 6 months for signs of neovascularization, especially those with type 2 diabetes.

If ocular neovascularization is detected, prompt referral for pan-retinal photocoagulation (PRP) is indicated, as this remains the benchmark in controlling the neovascular drive in cases of retinal ischemia. Off-label use of intravitreal anti-VEGF agents, such as bevacizumab, to facilitate regression of neovascularization along with PRP is also being implemented. The basis of treatment of NVG is to reduce the underlying cause, which is posterior segment ischemia. However, increased IOP and inflammation must be controlled concurrently to prevent further visual loss as well as pain and discomfort associated with NVG. Topical beta-blockers, alpha-2 agonists, and topical and/or systemic carbonic anhydrase inhibitors (CAI) are typically used in this setting. Prostaglandins should be avoided in the presence of inflammation. A topical steroid (e.g., prednisolone acetate 1% q1-6h) and cycloplegic (e.g., atropine 1% t.i.d.) should be used in the setting of inflammation and pain. Many cases of NVG, despite being treated with PRP, are unmanageable with pharmacologic treatment alone and may require additional surgical intervention by a glaucoma specialist. If IOP remains elevated despite medical therapy, the patient may require a filtration surgery, an aqueous drainage implant, or a cyclodestructive procedure. Long-term management of CRAO should address risk factors and underlying systemic conditions in order to prevent other vascular ischemic events to the fellow eye or other organs. Many patients with CRAO will lose substantial vision in the affected eye despite various treatment options and referral for counseling or vision rehabilitation should be considered.

**Conclusion**

Central Retinal Artery Occlusion should be considered an ophthalmic and systemic emergency. The causes of and risk factors for CRAO are analogous to those of cerebrovascular events and should be pointedly and urgently addressed in patients with CRAO to reduce the probability of secondary ischemic occurrences. Ocular management of CRAO should be directed to acute re-perfusion of the central retinal artery if within four hours of symptom onset, and prevention of later ocular complications, such as neovascular glaucoma. Based on recommendation from the American Heart Association/American Stroke Association, eye care providers should refer patients with a retinal artery occlusion for immediate neuroimaging and etiological work-up, as this finding is analogous to a stroke.

**References**


