Neovascularization of the Iris as the Presenting Sign of
Complete Unilateral Intracranial Carotid Artery Occlusion

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ABSTRACT

Purpose. Ocular ischemic syndrome (OIS) is a rare condition of stenosis or occlusion of the common or internal carotid arteries leading to reduced ocular blood flow to the anterior and/or posterior segments. The purpose of this case report is to present an uncommon presentation of OIS and assist the eye care provider in accurate diagnosis, treatment, and management.

Case report. This case illustrates a rare presentation of OIS where the primary ocular finding was neovascularization of the iris and angle. Complete, unilateral, intracranial carotid artery occlusion was diagnosed via magnetic resonance angiography (MRA).

Discussion. This case further supports the theory that uveal ischemia alone in the absence of retinal ischemia may be a significant contributor for the neovascularization noted in ocular ischemic syndrome.

Conclusion. When traditional carotid duplex studies are essentially normal in the presence of iris neovascularization, the provider should consider intracranial carotid artery stenosis or occlusion as a potential cause. Early recognition of OIS is essential to prevent blindness and mortality.

Key Words: ocular ischemic syndrome, neovascular glaucoma, rubeosis iridis, carotid endarterectomy

INTRODUCTION

Ocular ischemic syndrome (OIS) is caused by a decrease of blood flow to the eye resulting in anterior and/or posterior segment ischemia.\(^1\) It is a rare condition of stenosis or occlusion of the common or internal carotid arteries primarily caused by atherosclerosis.\(^2\) Other causes include dissecting carotid artery aneurysm, giant cell arteritis, fibromuscular dysplasia, aortic arch syndrome, Takayasu arteritis, Behçet disease, trauma, carotid artery inflammation, complicated intravitreal anti-vascular endothelial growth factor injection, or post-radiotherapy for nasopharyngeal carcinoma.\(^3\)\(^-\)^\(^7\) OIS occurs primarily in the geriatric population with a mean age of 65 years; it is rarely seen prior to the age of 50.\(^3\) Men are affected twice as often as females. There is no race predilection.
Incidence is estimated at 7.5 cases per million each year; this is likely to be an underestimation as OIS is frequently misdiagnosed.\textsuperscript{4}

In 50\% of OIS cases, the affected artery is completely obstructed.\textsuperscript{5} A stenosis of 90\% or more of the common or internal carotid arteries on the same side as the affected eye is usually found.\textsuperscript{5} 20\% of cases are bilateral.\textsuperscript{4} Rarely, ophthalmic artery occlusion is responsible for OIS.\textsuperscript{5} Patients with well-developed collateral circulation between the internal and external carotid arteries or between the two internal carotid arteries can maintain adequate ocular perfusion although cases of carotid artery stenosis of only 50\% may lead to the development of OIS.\textsuperscript{3, 6}

Risk factors for OIS development include pre-existing hypertension, dyslipidemia, diabetes mellitus, and cardiovascular disease.\textsuperscript{8} Myocardial infarction and stroke are the two leading causes of death.

The most common ocular symptom is vision loss which occurs in 90\% of cases at presentation; 10\% are asymptomatic.\textsuperscript{9} Additional symptoms can include dull, aching ocular pain, transient visual loss, and prolonged photostress recovery.\textsuperscript{10} Anterior segment signs may include corneal edema or striae, elevated intraocular pressure, rubeosis iridis, cell or flare. Posterior segment findings may include retinal arterial narrowing, venous dilation, mid-peripheral hemorrhages, microaneurysms, neovascularization of the retina, neovascularization of disc, cherry-red spot, cotton wool spots, Hollenhorst plaque, and spontaneous pulsations of the retinal arteries. Chronically elevated intraocular pressure leads to optic nerve head cupping and visual field loss resulting in a secondary neovascular glaucoma. Neovascularization of the retina may lead to tractional retinal detachment or vitreous hemorrhage.

Differential diagnosis includes nonischemic central retinal vein occlusion and diabetic retinopathy; these conditions are commonly confused with OIS. Other differentials include sickle cell retinopathy, hypertensive retinopathy, and non-granulomatous uveitis.
Treatment of OIS remains difficult and controversial. In cases of rubeosis in which the anterior chamber is open, panretinal photocoagulation (PRP) may be considered but blood vessel regression may be limited. If the anterior chamber is closed with elevated intraocular pressure, cyclocryotherapy, cyclodiathermy, or filtering procedures can be considered. Panretinal photocoagulation is the primary treatment in the presence of retinal ischemia. Treatment of the underlying systemic etiology is critical. Reversing the carotid stenosis may be the most important aspect for maintaining or improving vision.

Patients who are vascular surgery candidates should be referred for consideration of carotid endarterectomy or stenting.

This case report illustrates a rare presentation of OIS in a patient with asymptomatic neovascularization of the iris and angle where systemic work-up revealed complete, unilateral intracranial carotid artery occlusion. The purpose of the report is to assist the clinician in accurately diagnosing OIS with a discussion of the signs, symptoms, work-up and treatment options.

**CASE REPORT**

An 82-year-old Caucasian female presented for a routine eye exam with the chief complaint of constant near blur without glasses in both eyes (OU) for years. Ocular history included pseudophakia OU. Medical history was positive for type II diabetes mellitus, anemia of end stage renal disease, angina pectoris, chronic diastolic congestive heart failure, chronic myocardial ischemia, essential hypertension, gout, peripheral vascular disease, and primary hypothyroidism. Family medical and ocular history was negative. Medications included allopurinol (Zyloric®, Teofarma, Pavia, Italy), atorvastatin (Lipitor®, Pfizer, New York, NY), furosemide (Lasix®, Sanofi, Bridgewater Township, NHJ), insulin (NovoLog®, Novo Nordisk, Seattle, WA), levothyroxine (Synthroid®, Abbott Laboratories, Chicago, IL), and spironolactone (Aldactone®, Pfizer, New York, NY). Allergies included fish oil and sulfonamides. She was a former
smoker and denied the use of alcohol or recreational substance abuse. She was oriented to person, place, and time; her mood was appropriate.

Best-corrected visual acuity was 20/30 right eye (OD) and 20/30 left eye (OS). Blood pressure was 161/76 right arm sitting; self-reported HbA1c was 7.2%. Pupils were normal without relative afferent pupillary defect. Confrontation visual fields were full OD, OS. Extraocular muscles showed full range of movement OU. Distance cover test was orthophoric. Biomicroscopy revealed normal lids and lashes OD, OS. The bulbar conjunctiva was normal OD, OS. The cornea showed 2+ guttata with trace endothelial edema OD, OS. The anterior chamber was deep and quiet OD, OS. Neovascularization of the iris was noted OD; negative OS. Goldmann applanation tonometry was 16 mmHg OD and 14 mmHg OS at 2:40 p.m. Gonioscopy revealed grade III trabecular meshwork 360° with neovascularization of the angle (NVA) in the nasal, inferior and temporal quadrants OD; grade IV ciliary body 360° without NVA OS. Dilated fundoscopy showed a well-centered posterior chamber intraocular lens, clear vitreous, normal macula, and flat periphery without breaks OD, OS. Optic nerves were 0.70 x 0.70 OD and 0.60 x 0.60 OS without pallor, edema, or neovascularization. Rare scattered microaneurysms were noted throughout the posterior pole OD, OS. The retinal arteries showed attenuation OD, OS. There was no evidence of mid-peripheral hemorrhages OD, OS.

Cirrus Spectral domain-optical coherence tomography (SD-OCT) of the optic nerves shown in Figure 1 demonstrated abnormal inferior thinning of the retinal nerve fiber layer OD; normal OS. Humphrey visual field 30-2 SITA-Fast presented in Figure 2 demonstrated a superior greater than inferior arcuate OD and an inferior arcuate and superior-nasal step OS. Bilateral carotid arterial duplex ultrasound demonstrated thick calcified atherosclerotic plaque at the carotid end bulbs and internal carotid arteries with less than 50% stenosis. A questionable stenotic lesion in the distal right internal carotid artery prompted an MRA of the head and neck which demonstrated 100% occlusion of the right intracranial portion of the internal carotid artery as shown in Figure 3. Complete blood cell count with
platelet differential (CBC w/ diff), Westergren erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) was normal.

**Figure 1**

Cirrus SD-OCT of the optic nerves indicating abnormal thinning of the inferior retinal nerve fiber layer OD; normal OS.
Humphrey visual field 30-2 SITA-Fast demonstrated a superior > inferior arcuate OD (B) and an inferior arcuate and superior-nasal step OS (A).

Brain MRA illustrating complete, right intracranial carotid artery occlusion (red arrows).

Ocular ischemic syndrome secondary to right intracranial carotid artery occlusion was diagnosed in addition to mild background diabetic retinopathy OU. Neovascular glaucoma secondary to ocular
ischemic syndrome OD and normal tension glaucoma suspect OS was treated with Alphagan® 0.2% ophthalmic solution (brimonidine tartrate 0.2% oph sol, Sandoz, West Princeton, NJ), 1 gtt b.i.d. OU. The patient’s primary care physician was alerted of the diagnoses and educated regarding the importance of blood pressure, glucose and cholesterol control. In the case of complete carotid artery occlusion, carotid endarterectomy was contraindicated; the primary care provider prescribed clopidogrel (Plavix®, Bristol-Meyers Squibb, Seattle, WA). Fuch’s corneal dystrophy OU was the primary cause of decreased vision; she was prescribed sodium chloride 5% ophthalmic solution (Muro-128® 5% oph sol, Bausch & Lomb, Irvine, CA) 1 gtt q.i.d. OU and sodium chloride 5% ophthalmic ointment (Muro-128® 5% oph ung, Bausch & Lomb, Irvine, CA) instill into inferior cul-de-sac at bedtime OU. She completed a Retina consultation; no panretinal photocoagulation (PRP) was advised. A two-week follow-up revealed a poor response to anti-glaucoma therapy with an IOP of 16 mmHg OD, OS. She was advised to increase brimonidine 0.2% to t.i.d. OU. Follow-up examination one week later revealed stable visual acuity and improved IOP control at 12 mmHg OD, OS without NVI or NVA progression as assessed via gonioscopy. The author transferred the patient’s care to a fellow colleague due to personal job relocation. The patient was asked to follow-up in one month for intraocular pressure check, dilated fundoscopy, pachymetry, Cirrus OCT RNFL and repeat HVF studies. She was re-educated regarding the importance of controlling blood pressure, blood sugar, cholesterol, weight loss, exercise, nutrition and tobacco avoidance.

DISCUSSION

This case illustrates a rare presentation of OIS where the primary sign of complete, unilateral, intracranial carotid artery occlusion was neovascularization of the iris and angle; this suggests that uveal ischemia alone without retinal ischemia was primarily responsible for the neovascularization seen in this case of OIS and supports previous experimental animal models. Treatment of OIS remains difficult and
controversial. This case was managed conservatively with anti-glaucoma topical therapy to improve ocular perfusion. PRP was not pursued in the absence of retinal ischemia. IOP has been documented to rise after PRP and may further compromise the ocular and optic nerve head perfusion leading to vision loss. Chronic reduction of retrobulbar blood flow may also lead to normal tension glaucoma as suspected in the left eye in this case.17

Clinicians must attain a high index of suspicion for intracranial carotid artery stenosis or occlusion in the presence of anterior segment neovascularization of unknown etiology and essentially normal Carotid Duplex ultrasonography. Atherosclerosis is the underlying systemic issue leading to OIS in the majority of patients with carotid occlusive disease.18 Patients who develop OIS show decreased blood flow in the retrobulbar vessels and reversal of ophthalmic artery blood flow.19 The ophthalmic artery steals or shunts blood flow away from the eye to the low-resistance intracranial vascular supply leading to hypoperfusion and subsequent ocular ischemia.20 The pathogenesis of OIS is related to the degree of carotid artery stenosis, presence or absence of collateral vessels, anastomotic channel variations, carotid artery disease chronicity, bilaterality, and systemic vascular disease associations.21 Reduced vision and visual field loss are commonly reported on presentation of OIS.9 Visual field patterns can vary greatly from normal to central scotoma, nasal defects, or centrocecal defects.21 Some have profound visual field loss with only the central island or temporal island of vision remaining. Ocular angina or pain is present in approximately 40% of eyes with OIS; 94% of these eyes have NVI.9 The characteristic dull, aching pain is caused by elevated intraocular pressure or ischemia. Lying down relieves or lessens the pain. Additional anterior and posterior segment signs are detailed in Tables 1 and 2, respectively.22 In cases of OIS with neovascular glaucoma, optic nerve cupping occurs.23 Chronic reduction of retrobulbar blood flow may lead to normal tension glaucoma.17

Diabetic retinopathy and central retinal vein occlusion are among the differential diagnosis for OIS. Diabetic retinopathy may co-exist with OIS; patients with marked asymmetry or unilateral
Retinopathy should be evaluated for carotid occlusive disease. Mid-peripheral microaneurysms are more common in OIS whereas diabetic retinopathy is primarily located in the posterior pole. The differential diagnosis should also include hyperviscosity syndromes like the polycythemias (polycythemia vera or primary familial and congenital polycythemia), multiple myeloma, leukemia, Waldenström macroglobulinemia, sickle cell anemia, and sepsis. Complete blood cell count with differential, serum viscosity, prothrombin time (PT), international normalized ratio (INR), partial prothrombin time (PTT), serum protein electrophoresis (SPEP), and immuneelectrophoresis may be obtained in highly suspect cases. A new onset of uveitis in a patient age 50 or greater should prompt the clinician to consider OIS. OIS is encountered rarely as a manifestation of giant cell arteritis (GCA); ESR and CRP were obtained in the patient presented here to evaluate for occult GCA. When OIS and GCA are associated, the more typical presentation includes an anterior ischemic optic neuropathy associated with corneal edema, Descemet folds, uveitis, lens opacities, and ocular hypotony. Other systemic associations with OIS include aortic arch syndrome and Takayasu arteritis. Further cardiology consult and conventional cardiac angiography may be appropriate for suspect cases.

**Table 1. Anterior Segment Signs of Ocular Ischemic Syndrome**

<table>
<thead>
<tr>
<th>Anterior synechia</th>
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<tr>
<td>Asymmetric cataract</td>
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<td>Bullous keratopathy</td>
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<tr>
<td>Conjunctival injection</td>
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<tr>
<td>Corneal edema</td>
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<td>Corneo-scleral melting</td>
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<td>Descemet folds</td>
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<tr>
<td>Episcleral injection</td>
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<tr>
<td>Fixed semi-dilated pupil with afferent pupillary defect</td>
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<tr>
<td>Iris atrophy</td>
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<tr>
<td>Neovascular glaucoma</td>
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<tr>
<td>Posterior synechia</td>
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<tr>
<td>Rubeosis iridis</td>
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<tr>
<td>Sluggish pupil response with afferent pupillary defect</td>
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<tr>
<td>Spontaneous hyphema</td>
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<tr>
<td>Uveal ectropion</td>
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<td>Uveitis</td>
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Table 2. Posterior Segment Signs of Ocular Ischemic Syndrome

<table>
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<tr>
<th>Sign</th>
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<tr>
<td>Anterior ischemic optic neuropathy</td>
</tr>
<tr>
<td>Cherry-red spot</td>
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<tr>
<td>Cholesterol emboli</td>
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<tr>
<td>Choroidal neovascular membrane</td>
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<tr>
<td>Cobblestone degeneration</td>
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<tr>
<td>Cotton wool spots</td>
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<tr>
<td>Macular capillary telangiectasia</td>
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<tr>
<td>Microaneurysms</td>
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<tr>
<td>Neovascularization elsewhere</td>
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<tr>
<td>Neovascularization of the disc</td>
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<tr>
<td>Retinal arteriovenous communications</td>
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<td>Retinal artery attenuation</td>
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<tr>
<td>Retinal hemorrhages</td>
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<tr>
<td>Retinal vein dilation</td>
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<tr>
<td>Spontaneous retinal arterial pulsations</td>
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<tr>
<td>Vitreous hemorrhage</td>
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<tr>
<td>Wedge-shaped areas of chorioretinal atrophy</td>
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Management of OIS is multidisciplinary where the aim is to treat the ocular complications and prevent further ocular damage, treat the associated vascular risk factors, and perform surgery when indicated. Suppression of ocular inflammation using long-acting cycloplegic agents and steroids is warranted in the presence of uveitis. Ocular hypotensive agents that reduce aqueous outflow such as topical beta-blockers, alpha-agonists, and topical or oral carbonic anhydrase inhibitors are helpful to lower intraocular pressure. Prostaglandins should be avoided because of their pro-inflammatory nature.

Pilocarpine and other anticholinergic agents are generally contraindicated because of the risk for increasing inflammation. IOP control can be challenging in neovascular glaucoma. Trabeculectomy with antimetabolites, aqueous shunt implants, or diode laser cyclophotocoagulation may be warranted when topical therapy is refractory. In this case, topical beta-blockers were contraindicated due to pre-existing cardiac disease; topical brimonidine 0.2% ophthalmic solution was initiated as first line therapy. The lowest dose was not sufficient to maintain IOP control; therefore, the maximum dose was prescribed.
Capillary non-perfusion indicative of retinal ischemia is typically treated with panretinal photocoagulation (PRP). If there is no evidence of retinal ischemia (as in the case presented), there is no scientific rationale to recommend PRP. Adverse effects of PRP such as pain and further visual field constriction are possible. PRP causes regression of iris neovascularization in only 36% of the treated eyes with OIS. Even with adequate PRP application, posterior segment ischemia and neovascularization may still develop or get worse. There have been attempts to treat macular edema in the course of OIS with intravitreal injections of steroids (e.g., triamcinolone acetonide) and vascular endothelial growth factor (VEGF) inhibitors; however, there is not enough data to confirm their safety and efficacy.

Referral to a primary care physician or neurologist is recommended when OIS is discovered. Given the high rate of myocardial infarction and stroke, treatment of the underlying pathology is warranted. To date, no randomized controlled clinical trials have examined the use of antiplatelet therapy or anticoagulation for atherosclerosis related to OIS; however, significant evidence in both the cardiac and stroke literature suggest that aspirin should be considered as first-line treatment. Clopidogrel or a combination of aspirin and dipyridamole have been used as alternatives.

Anticoagulation may also be considered in those with cardiac valve disease. Lifestyle modifications and pharmacological control of hypertension, diabetes mellitus, dyslipidemia, obesity, and tobacco cessation are helpful. Daily folate and vitamin B complex supplementation is appropriate for hyperhomocystenemia.

The role of carotid endarterectomy (CE) in OIS is controversial as there is no level I or II evidence for its efficacy. Two major multicenter trials, the European Carotid Surgery Trialists (ECST) study and the North American Symptomatic Carotid Endarterectomy Trial (NASCET), both showed benefit of CE in patients with cerebral ischemic events and ipsilateral severe (70-99%) carotid stenosis. A cerebral ischemic event was defined as a hemispheric or retinal transient ischemic attack or stroke. There are no class I or II studies of the effects of CE on OIS. Several small series or individual case reports have
suggested improved ocular blood flow post-CE;\textsuperscript{35-36} others have reported worse visual acuity in 60% of patients.\textsuperscript{8} Hence, it is valuable to inform OIS patients that CE may not improve visual function but rather serves to mitigate subsequent cerebral ischemia.

Before the development of central retinal artery occlusion or neovascular glaucoma, some patients with OIS caused by ipsilateral occlusion of the internal carotid artery have undergone an extracranial-to-intracranial carotid bypass procedure with limited success.\textsuperscript{37} It is rarely performed and not routinely recommended as other studies have reported no benefit.\textsuperscript{38} The use of angioplasty and stenting in patients with OIS who have severe ICA stenosis has not been fully assessed. Given the patient in this case report presented with evidence of neovascular glaucomatous damage in the right eye and complete, right intracranial carotid artery occlusion, vascular surgery consult was not advisable. She was treated medically.

Rubeosis iridis and vision loss related to tissue infarction in OIS is associated with a poor prognosis for visual recovery.\textsuperscript{39} Moreover, patients with OIS have vascular co-morbidities and a high mortality rate. The 5-year mortality rate was 40% with the leading cause of death as cardiac disease in approximately 63% of patients.\textsuperscript{40} The Framingham study noted strict control of hypertension, dyslipidemia, tobacco use, and obesity to decrease this risk.\textsuperscript{41} The visual prognosis for this patient was guarded given the concomitant pathologies of Fuch’s corneal dystrophy and glaucoma.

CONCLUSION

Early recognition of OIS is essential to prevent blindness although the long-term visual prognosis is poor. Eye care providers play an integral role in the co-management of its primary etiology which may be life-threatening. When traditional carotid duplex studies are essentially normal in the presence of NVI, the provider should consider intracranial carotid artery stenosis or occlusion as a potential cause.
General lifestyle choices focused on a healthy diet, nutrition, exercise, healthy weight, stress reduction, and tobacco avoidance may aid in preventing disease.

REFERENCES


