Ocular Ischemic Syndrome: a Teaching Case Report

Abstract

Ocular ischemic syndrome (OIS) is a potentially sight-threatening condition with possibly fatal underlying systemic implications. It is most commonly caused by impaired ocular perfusion from atherosclerotic disease generating obstruction of the carotid arteries. Additionally, cardiovascular morbidities often co-exist in these patients making their health status even more precarious. Ocular presentation is varied and can impact both the anterior and, more characteristically, the posterior segment. Eyecare providers have the ability to employ a multimodal approach to assess these patients and monitor hemodynamic changes throughout the course of either ocular or systemic treatment. Although OIS is rare, a provider’s ability to properly identify and diagnose it can be crucial in getting a patient the proper treatment and management in an interdisciplinary care setting.

Key Words: ocular ischemic syndrome, retinal ischemia, carotid artery stenosis

Background

While the primary focus of eyecare providers is to provide treatment and care for the structures confined within the orbital area, clinical findings that necessitate a systemic intervention often may arise. Ocular ischemic syndrome (OIS) is a prime example of a serious ocular condition that sometimes can signal severe systemic neurological damage. With the proper team in place, a patient’s overall well-being can be enhanced. We present a case report of a 65-year-old male with chronic OIS and accompanying complete stenosis of the left internal carotid artery (ICA). Furthermore, we review the epidemiology, pathogenesis, signs, symptoms, differentials, diagnostic and ancillary testing available, as well as both systemic and ocular treatment options. The intended audience is third- and fourth-year optometry students, optometry residents and current practitioners.

Case Description

A 65-year-old African American male presented to clinic for a routine eye exam with a chief complaint of blurry vision at near and some dryness symptoms. His previous ocular history was unremarkable with his last exam being two years ago. Personal eye history was void of any injuries or surgeries. His personal medical history was significant for carotid artery stenosis, dyslipidemia, essential hypertension, cerebral infarction, peripheral vascular disease, chronic periodontitis and neoplasm of the tonsils. His medications included atorvastatin, clopidogrel, metoprolol and nifedipine.

Entrance testing, including cover test, extraocular muscles, confrontations, pupils and visual field screener, were all normal. With an updated refraction, the right eye was correctable to 20/20 while the left eye was correctable to 20/25+2. Intraocular pressure (IOP) was 16 mmHg in both the right and left eye. Anterior segment findings were within normal limits in both eyes. Posterior segment findings were significant for dilated veins and extensive dot-blot hemorrhages in the mid-periphery of the left eye (Figure 1A). The right eye did not demonstrate any retinopathy. The patient was tentatively diagnosed with OIS in the left eye and referred for carotid ultrasound. He was instructed to return to the eye clinic for a fluorescein angiogram (FA).

The patient returned approximately a month later and had best-corrected visual acuity (BCVA) of 20/40 without improvement from pinhole in the right eye and 20/70 with pinhole improvement to 20/30 in the left eye. Gonioscopy was performed at this time and no neovascularization of the angle or iris was identified. IOP at this follow-up visit was 18 mmHg in the right eye and 12 mmHg in the left eye. Anterior and posterior segment findings were stable since the previous exam. Carotid ultrasound results were reviewed with findings of persistent complete occlusion of the left ICA and 50% stenosis of the right ICA (Figure 2). On FA right eye findings were inconspicuous, while the left eye showed leakage at the macula, patchy areas of ischemia in the periphery, and delayed choroidal and retinal arteriovenous filling times (Figure 1B). At this time the patient was simultaneously being evaluated by his cardiologist and vascular surgeon who decided to continue to closely monitor him instead of recommending surgical intervention for his stenosis. The patient was subsequently lost to follow-up for a couple of years before returning with BCVA in the right and left eye of 20/40. IOP at that visit was 18 mmHg in the right eye and 14 mmHg in the left eye with mid-peripheral hemorrhages still visible on fundus exam of the left eye. Other anterior and posterior findings were similar to previous findings. Throughout the years, findings in this patient have remained relatively stable with mild improvements in retinopathy of the left eye and without the development of neovascular complications. IOP has also stayed within normal range and is relatively symmetric between eyes. Surgery has continuously been deferred, and the patient is monitored annually by his vascular surgeon.
Education Guidelines

Learning objectives

1. Become familiar with the ocular manifestations of OIS
2. Become familiar with the systemic manifestations of OIS
3. Understand that ocular manifestations of OIS may be the first sign of a potentially life-threatening underlying health condition

Key concepts

1. Understand the pathophysiology of OIS
2. Become familiar with the optometrist’s role in diagnosis
3. Become familiar with how to manage patients with OIS

Discussion questions

1. What is the pathogenesis of OIS?
2. What are the symptoms of OIS?
3. What are the clinical signs of OIS?
4. What are some differential diagnoses that should be considered in cases of suspected OIS?
5. What are some ancillary tests that could be performed to aid in the diagnosis of OIS?
6. What ocular and systemic treatment is indicated for patients with OIS?

Literature review

OIS is a condition found more commonly in the elderly at a mean of 65 years of age. It is rarely seen in those younger than 50. Additionally, there is a stronger male predilection; men are affected twice as often as women. This has been associated with an increased incidence of underlying atherosclerotic disease in males. Moreover, OIS tends to be unilateral in the majority of cases. No major differences in racial incidence have been recognized.

Discussion

Teaching instructions: The authors recommend that participants read each discussion question and attempt to answer before reading the answers provided in the text. Participants may work individually or together in small groups. Learning objectives may be assessed by comparing participants’ responses to the answers provided.

What is the pathogenesis of ocular ischemic syndrome?

Atherosclerotic disease has been identified as the primary culprit in the development of OIS. Other less common causes
include Behçet’s disease, giant cell arteritis, aortic arch syndrome, Takayasu arteritis, carotid artery dissecting aneurysm and fibrovascular dysplasia.\textsuperscript{2,3} Case studies have demonstrated that OIS also may develop from complications from radiotherapy of nasopharyngeal carcinoma or after intravitreal injections of bevacizumab.\textsuperscript{4,5} Another recent case study reported OIS leading to blindness after botched facial filler injections.\textsuperscript{6} Frequently found comorbidities contributing to the patient’s poor overall cardiovascular health include hypertension and diabetes mellitus.\textsuperscript{7} Moreover, systemic vascular diseases such as ischemic heart disease, peripheral vascular disease, history of transient ischemic attacks or prior cerebrovascular accidents are commonly a part of the patient’s medical history.

Patients who develop OIS are likely to have a 90% stenosis of the ipsilateral common carotid artery or ICA leading to ocular hypoperfusion.\textsuperscript{8} In 50% of cases the artery may even be completely stenosed. Poor collateral circulation between the internal and external carotid or between both ICAs have been demonstrated to increase the risk of development of OIS.\textsuperscript{2,9} Some studies have shown that those with well-developed collateral circulation may have complete obstruction of the ICA without the development of OIS.\textsuperscript{10} Conversely, other patients with poorly developed collateral systems and as low as 50% stenosis of the ICA may go on to develop this condition.\textsuperscript{1,2,9} While the severity of occlusion may be clinically significant, OIS may be the initial manifestation of carotid stenosis in some patients. Additionally, these patients may suffer from further exacerbation of retinal ischemia when blood flow is reversed and shunted away from the eye through the ophthalmic artery (OA) into the intracranial circuit in what has been termed steal phenomena.\textsuperscript{11,12} Irrespective of the cause of the altered blood flow dynamic, the results are reduced central retinal artery pressure producing low perfusion pressure and decreased blood flow to the orbit ensuring widespread ocular hypoxia. Table 1 summarizes factors affecting the pathogenesis of OIS.

### Table 1

<table>
<thead>
<tr>
<th>Laterality of stenosis</th>
<th>Degree of stenosis</th>
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<tr>
<td>Absence or presence of collaterals</td>
<td>Chronicity of carotid artery disease</td>
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<tr>
<td>Associated systemic vascular diseases</td>
<td>Anastomotic channels created to shunt blood flow</td>
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Table 1. Click to enlarge
What are the symptoms of OIS?

Symptoms in patients with OIS can vary and may even be absent. Vision loss is a common cause for concern that often leads patients to seek care. Vision changes may arise from optic nerve (ON) damage from secondary glaucoma or from acute to chronic retinal ischemia. This can manifest as either sudden, such as an episode of amaurosis fugax, or slow changes in eyesight. A retrospective study by Brown et al. found the majority of patients noted a gradual decrease in visual acuity over the course of weeks to months, while approximately one in eight patients noticed reduced vision over a period of days or minutes. In cases of acute vision loss, embolization of the central retinal artery may be responsible. The degree of vision loss at presentation may vary with roughly one-third of patients having visual acuity of counting fingers or worse, 20/50 to 20/200, or 20/20 to 20/50. A predictive factor of visual outcomes is acuity at initial presentation, as those with poorer acuity are less likely to demonstrate improvement and likely will remain stable or deteriorate. The presence of neovascularization at the iris has also been associated with poorer visual outcomes.

Other visual complaints patients may present with include delayed visual recovery after being exposed to bright light. This may be explained by macular ischemia causing delayed photoreceptor regeneration. Additionally, patients with OIS may experience a variety of visual field defects or may have completely unaffected peripheral vision.

What are the signs of OIS?

On clinical exam the patient may present with either anterior or posterior segment involvement or both. The most potentially devastating anterior segment finding is neovascularization of the iris and/or angle. This may result in additional complications in managing the obstruction to aqueous outflow and contribute to the development of secondary glaucoma. However, due to extensive ischemia impairing ciliary body function, aqueous production could be reduced, which may cause normal to hypotonous IOP, even in the presence of neovascular glaucoma (NVG). However, hypoxia to the eye or surrounding dura mater may also be the cause, especially in the setting of normal IOP. The pain is typically described as dull with a gradual onset and may be lessened when the patient lies down.

When the entire eye is not involved, it is more common to observe posterior segment findings only (Table 2). These may include dilated retinal veins with narrowed retinal arteries, anterior and posterior ischemic optic neuropathy, cotton wool spots, retinal arterial pulsations and choriotreital atrophy. Retinal arteriovenous communications may also be identified adjacent to ischemic retinal areas. Hypoxia from lack of retrobulbar blood flow could produce ischemic damage to the ON in the context of what can present as normal-tension glaucoma. Conversely, damage to the ON secondary to the development of NVG may develop. Due to widespread ischemia and the retina’s production of vascular endothelial growth factor (VEGF), retinal neovascularization may occur with a higher incidence at the disc. Subsequently, vitreous hemorrhages may develop. Classically, retinal hemorrhages and microaneurysms are often seen in the mid-periphery. Microaneurysms may also be observed in the macula, and in combination with capillary telangiectasias can lead to macular edema. A cherry-red spot at the macula may alternatively be found when IOP exceeds the central retinal artery perfusion pressure in glaucomatous eyes or when an embolus occludes the central
What are some differential diagnoses that should be considered in cases of suspected OIS?

Common differentials that should be considered in cases of suspected OIS include diabetic retinopathy (DR) and central retinal vein occlusion (CRVO).\textsuperscript{1,2,19} Important distinctions in clinical presentation may be observed that will help elucidate the proper diagnosis. Tortuous retinal veins may support a diagnosis of CRVO as this is a feature absent in OIS. In contrast, when differentiating between DR and OIS, it has been found that intraretinal hemorrhages are generally fewer in OIS vs. diabetes. Additionally, hard exudates may point toward a diabetic etiology as this is not commonly seen in cases of OIS. However, it is important to note that OIS may sometimes co-exist with DR. In cases with discernable asymmetric or unilateral retinopathy, OIS should be considered. If funduscopic findings remain ambiguous, FA may be a beneficial test to help illuminate the true cause. Important distinguishing findings are choroidal filling defects and retinal arterial stasis that are classically found in OIS and absent in the other common differentials. Other rare but possible differentials that should be considered include autoimmune uveitis and hyperviscosity syndromes.

What are some ancillary tests that could be performed to aid in the diagnosis of OIS?

Diagnosis of OIS is achieved by imaging, particularly of the carotid arteries. Commonly, a non-invasive test such as a carotid duplex ultrasound is performed to help provide information about both flow and anatomical structure.\textsuperscript{20} Lumen diameter and velocity of blood flow are parameters indicative of the degree of stenosis. In conjunction with carotid duplex, color doppler imaging of the retrobulbar vessels, including the OA, should be considered as should computed tomography angiography and magnetic resonance angiography.\textsuperscript{21-22} Flow reversal in the OA has been demonstrated to be a highly specific indication of extensive ipsilateral stenosis or occlusion. However, it is important to note that multiple factors and possible variabilities in the vascular network can affect a patient’s propensity to develop OIS in the context of OA blood flow reversal. Additionally, Yamamoto et al. postulated that assessing flow in the central retinal and short posterior ciliary arteries could help assess risk for rubeosis iridis development.\textsuperscript{12} More invasive testing includes carotid arteriography and is usually reserved for select cases.

Aside from gonioscopy and a thorough comprehensive eye examination with dilation, ophthalmic testing that can be performed in adjunct includes FA. A prolonged arm-to-retina and arm-to-choroid circulation time is an important identifier of OIS.\textsuperscript{8,10,24} An extended choroidal filling time is considered the most specific FA sign of OIS. Meanwhile, the most sensitive sign is a prolonged retinal arteriovenous time. Staining of the major retinal vessels and branches is also commonly observed in the late stages of testing. Mid-peripheral retinal capillary non-perfusion may be an additional manifestation. Macular edema with accompanying hyperfluorescence at the optic disc from capillary leakage may sometimes be seen. While FA is more commonly done, indocyanine green angiography may also be performed. This form of imaging will confirm choroidal circulation abnormalities. Delayed arm-to-choroid and intra-choroidal circulation time should be observed.\textsuperscript{25} Vascular filling defects may also highlight areas of hypoperfusion. Associated findings may include slow filling of watershed zones. Other less commonly performed studies are electroretinography, visual-evoked potential, ocular plethysmography and ophthalmomonometry.\textsuperscript{26,27}

Recent advancements in technology have catapulted a multimodal approach to more thoroughly studying OIS. In a small study examining FA, spectral domain optical coherence tomography (SD-OCT), OCT angiography (OCT-A) and fundus autofluorescence in patients with acute retinal ischemia, a transient occurrence of a highly reflective band superior to or within the outer plexiform layer on SD-OCT was identified.\textsuperscript{28} This prominent middle limiting membrane sign was said to be a retinal ischemia marker of the junction of the retina starved for oxygen between the outer and inner vascular supply. Furthermore, OCT-A imaging outlined damaged retina by illustrating a loss of flow signal most prominent in both the deep and superficial capillary plexus of the hypoxic area. Other studies using SD-OCT have identified additional markers of poor perfusion via intravascular cross-sectional appearance, vessel reflexes, and shadowing patterns of vessels present in OIS patients.\textsuperscript{29} Enhanced depth imaging on SD-OCT has also made it possible to identify thinner subfoveal choroidal thickness in eyes with OIS and in those with symptomatic carotid artery stenosis.\textsuperscript{16-18} It was speculated that thinning may precede the classic retinal manifestations of OIS and may be correlated to vascular status of the carotid artery. This could point toward a retinal vascular insufficiency threshold that causes the signs of OIS to develop after choroidal transformations have already taken place. Also noted were smaller choroidal luminal and stromal areas with these differences noticeable when comparing the ipsilateral affected eye in those with OIS or symptomatic carotid artery stenosis to their contralateral eye.
Additionally, a positive correlation between increasing carotid artery stenosis and increased thinning of central retinal thickness, central choroidal thickness and foveal center choroidal and retinal volume was found. However, it should be noted that confounding variables make these findings on OCT not OIS-specific; therefore, it is best to use a combination of diagnostic tools.

Further advances in imaging technology have made it easier to identify retinal hemodynamic alterations with the non-invasive methods OCT-A and laser speckle flowgraphy (LSFG). OCT-A can be employed to track changes in the foveal avascular zone as well as vessel density in OIS patients before and after carotid artery stenting surgery. Therapeutic effect was observed through the increased vessel density and reduced superficial and deep avascular zones measured after surgical intervention. Meanwhile, another case study demonstrated improvement in macular perfusion via OCT-A findings after an anti-VEGF injection in OIS patients. While FA testing can give useful information, the higher resolution and detail of OCT-A can give in vivo detailed views of anatomical and topographical changes to vessel morphology throughout the course of treatments. In addition, LSFG may help illuminate the microcirculation of the ON and help gauge success of treatment efforts by giving an indication of retinochoroidal blood flow quantitatively. Possible correlations between degree of visual disturbances in patients with ICA stenosis and the decrease in choroidal blood flow have been speculated, although further studies are required. Nonetheless, with new explorations in research, LSFG may become a more useful application for assessment of hemodynamic compromise. Together, these studies demonstrate the potential for further understanding and assessment of changes in ocular blood flow dynamics in the presence of systemic medical intervention.

What ocular and systemic treatment is indicated for patients with OIS?

Urgent referrals to a team of doctors are necessary when identifying OIS patients. This includes cardiologists, vascular surgeons, neurologists and the patient’s primary care physician. Interdisciplinary care involves managing the ocular and systemic ramifications of patients’ health problems.

Treatment of patients with OIS is heavily focused on managing any potential complications that arise. While some outcomes may be irredeemable and visually devastating, such as central retinal artery occlusion or ischemic optic neuropathy, others such as neovascularization may be treated. Thus, excess production of VEGF from chronic retinal ischemia is an element that needs to be mitigated. Neovascularization of the iris, irido-corneal angle, optic disc or retina may surface and necessitates intervention, particularly to curtail the development of secondary NVG which is often poorly responsive to treatment. When this arises, it can be highly indicative of a poor visual prognosis. Risk factors for development of NVG include length of time between diagnosis of OIS and initial symptoms as well as the degree of carotid stenosis. A method commonly used to decrease oxygenation demand of the retinal tissue is ablation of the peripheral retina. Panretinal photocoagulation or anti-VEGF injections may be considered as treatment options in patients with active neovascularization, though regression is not guaranteed. In the event of poor retinal visualization, transconjunctival cryotherapy of the mid- to far retinal periphery or transscleral diode laser photocoagulation may be considered.

In the event of the development of NVG, which occurs in approximately 50% of cases, both topical and oral medications to reduce IOP may be initially employed. Topical alpha-2 agonists or beta-adrenergic blockers as well as topical or oral carbonic-anhydrase inhibitors are recommended as prostaglandins may aggravate any co-existing inflammatory response. In the event topical and oral therapeutic interventions are unsatisfactory, surgical intervention may be pursued. A trabeculectomy can be performed in patients with functional vision and more limited angle/iris neovascularization. However, outcomes are generally guarded due to a low success rate as well as possible intra- and post-operative complications. Another surgical option that could be explored is an aqueous shunt implant, especially in instances where neovascularization is advanced or trabeculectomy has failed. If the patient is experiencing pain or has a very poor visual prognosis, partial cycloablation by cryotherapy of the mid- to far retinal periphery or transscleral diode laser photocoagulation may be considered.

In the event of poor retinal visualization, transconjunctival transscleral diode laser retinopexy may be considered. Although these options may not be curative, they may surface and necessitate intervention, particularly to curtail the development of secondary NVG which is often poorly responsive to treatment. In extreme cases of refractory pain and a blind eye, enucleation or evisceration could be carried out.

When perfusion pressure to the ON is reduced in association with generalized hypoxia of the eye, even a normal IOP may begin to cause glaucomatous damage. In these instances of normal-tension glaucoma, the standard therapeutic approach to treatment can be utilized barring the presence of any inflammatory activity. If an anterior uveitis is present, the appropriate course of action would be steroidal anti-inflammatories accompanied by a cycloplegic agent to decrease the chances of a spontaneous hyphema by restricting iris movement and simultaneously stabilizing the blood-aqueous barrier. In the presence of macular edema, treatment attempts have included intravitreal injections of anti-VEGF medications and steroids. However, there is a lack of extensive research studying its efficacy in the context of OIS.

Systemic treatment of OIS may necessitate surgical intervention. A carotid artery endarterectomy (CEA) is the more
commonly performed surgery and has been shown to be effective at treating symptomatic and asymptomatic stenosis of varying degrees.40

The North American Symptomatic Carotid Endarterectomy Trial and the European Carotid Surgery Trial both recommend CEA in patients with high-grade stenosis (70-99%), but not in patients with low-grade stenosis.41-42 Patients with moderate stenosis (30-69%) may be considered for CEA.41-42 Carotid artery stenting and arterial bypass surgery are other alternatives available in select circumstances.7 If successful, carotid revascularization surgery can improve retinal perfusion. In a prospective study by Costa et al. retrobulbar blood flow was enhanced leading to alleviation of OIS-related ophthalmic findings.43 Neroev et al. also found ophthalmic improvement in acute OIS patients as well as improvement in electrophysiological parameters of the ON in some.44 Restored perfusion can improve photostress recovery, visual field defects and dark adaptation and eliminate amaurosis fugax.11,45 Once blood flow is restored to the eye, OA flow may be reversed to normal. The visual prognosis after improved hemodynamics can range from stable, to deteriorating to improved eyesight.11,44 Visual acuity improvement potential is greater if systemic surgery was performed prior to the development of iris neovascularization or secondary glaucoma as those with iris neovascularization are more likely to continue to visually decline.11,44 If bypass surgery is executed during the initial stages of NVG, a regression of neovascularization of the angle is possible as well as the impediment of further glaucomatous damage. However, an unpredictable and potentially negative side effect of surgically assisted restoration of ocular blood flow is an increase in aqueous humor that leads to increased IOP. Reperfusion of the ciliary body may lead to an increase in aqueous production that is met by fibrous tissue obstruction at the angle or iris. If this were to occur, ocular surgery may be necessary. Unfortunately, in some cases even though carotid surgery is performed, a patient’s pre-existing chronic vascular comorbidities may impair the body’s ability to adequately increase retinal perfusion.11,44

In addition to or in place of surgery, patients are often placed on systemic treatment for various comorbidities including medications to control their hypertension, diabetes, clotting, coronary heart disease, and atherosclerosis. Moreover, quitting smoking and reducing weight are recommended.44 Even with treatment, due to the frequently severe underlying systemic conditions in patients with OIS, mortality rate can be as high as 40% within five years from onset, with cardiovascular disease and stroke being the main causes.1

Conclusion

Considering that an eye examination may reveal the first signs of a potentially life-threatening underlying health condition, correctly identifying OIS could be crucial to the survival of a patient. Moreover, catching the early manifestations may help preserve sight and produce better outcomes. A multimodal approach to monitoring ocular hemodynamics may help eyecare specialists assess efficacy of systemic treatments. Eyecare providers are an integral part of the interdisciplinary team involved in a patient’s overall well-being and survival.

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