Abstract

Carotid occlusive disease is frequently associated with ocular involvement among which ocular ischemic syndrome (OIS) is one of the most challenging. OIS is a severe form of chronic ischemia of the anterior, posterior segments of the eye, and other orbital structures supplied by the ophthalmic artery. The diagnosis of OIS may be difficult to make because of its variable presentations. In patients with known cerebrovascular or cardiovascular disease, a careful examination should be done to look for the presence of ocular involvement. Once identified, a variety of noninvasive and invasive techniques may be employed to determine the degree of stenosis, and an appropriate treatment plan can be initiated. The first signs of carotid occlusive disease may be observed in the eye before they are observed in the cerebrovascular system, and thus, the ophthalmologist has a major role in the proper diagnosis and prompt referral. Although the prognosis for OIS is poor, early recognition and treatment of patients with carotid occlusive disease may help reduce mortality. In this article, we aim to present an overview of the current knowledge on OIS based on an extensive review of recent studies.

Keywords: Atherosclerosis, carotid stenosis, chronic ocular hypoperfusion, monocular vision loss, ocular ischemic syndrome

Introduction

The ocular manifestations of carotid artery disease include transient monocular blindness (Amaurosis fugax), central or branch retinal artery occlusion, and ocular ischemic syndrome. Ophthalmic manifestations of carotid occlusive disease are sight-threatening and may be the first manifestations of this life-threatening disease. Ocular changes secondary to carotid artery stenosis have been described earlier by various names such as ischemic ocular inflammation, ischemic coagulopathy, and ischemic ophthalmopathy. This was first reported by Hedges in 1962. Ocular ischemic syndrome (OIS) refers to the constellation of ophthalmic features that result from chronic hypoperfusion of the entire arterial supply to the eye, including the central retinal, posterior ciliary, and anterior ciliary arteries. It occurs most commonly due to atherosclerosis of the carotid artery.

We review this topic to help our fellow ophthalmologists in the proper diagnosis and prompt referral of such patients so that carotid occlusive disease is identified early and thus, the more serious life-threatening complications are prevented.

Literature Search

We searched PubMed from 1962 to May 2019 with words such as OIS, carotid artery occlusion, carotid artery stenosis, amaurosis fugax, anterior segment ischemia, posterior segment ischemia, neovascularization, giant cell arteritis, Takayasu arteritis, aortic arch syndrome, ophthalmodynamometry, ocular plethysmography, carotid artery imaging, carotid arteriography, duplex carotid ultrasound, reversed ophthalmic artery (OA) blood flow, carotid endarterectomy, extracranial-intracranial artery bypass surgery, and carotid stenting. Relevant articles were also reviewed from various national and international journals. To ensure that this review is as up-to-date as possible, PubMed was regularly reviewed during the period of preparation of the manuscript.

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Epidemiology
OIS occurs around 65 years of age and is rare before 50 years. The male-to-female ratio is approximately 2:1,[2,3] reflecting the higher incidence of atherosclerotic disease in males. There is no racial predilection. Bilateral involvement may occur in up to 22% of cases.

Etiology and Pathogenesis

Etiology
1. Atherosclerosis of the carotid vascular system[2]
2. Takayasu's Disease[4,5]
3. Aortic arch syndrome[6]
4. Giant cell arteritis[7]
5. Hyperviscosity syndrome
6. Hemoglobinopathy
7. Leukemia
8. Conditions with elevations of the PCO₂: emphysema, extreme obesity, fibrocystic disease[8]
9. Carotid artery dissection[9]
10. Fibrovascular dysplasia
11. Radiotherapy of the neck with carotid occlusion
12. Dysthyroid orbitopathy[10]
13. Moyamoya disease[11,12]
14. Neurofibromatosis[11]
15. Scleroderma[13]

Pathogenesis
There is chronic hypoperfusion of the entire arterial supply to the eye, including the central retinal, posterior ciliary, and anterior ciliary arteries. It is most commonly due to atherosclerosis of the carotid artery and is thought to occur when carotid artery stenosis is >90%. Association of OIS with carotid artery stenosis ranges from 20% to 100%.[14-16] OIS develops, especially in patients with poor collateral circulation between the internal and external carotid arterial systems or between the two internal carotid arteries. In those with poor collaterals, stenosis of <50% of the internal carotid may be sufficient for the OIS to develop; however, an occlusion can vary from <50% stenosis to complete occlusion of at least one common carotid or internal carotid artery. Arterial supply of eye [Figure 1].

Patients with OIS show decreased blood flow in the retrobulbar vessels[17] and the reversal of blood flow in the OA.[18] The OA behaves as a steal artery in these patients, shunting blood away from the eye to the low-resistance intracranial circuit causing reduction of retrobulbar blood flow and thus leading to chronic hypoperfusion and subsequently ischemia of ocular tissues [Figure 2].[19] The ischemia of the optic nerve, choroid, retinal pigment epithelium, and the photoreceptors results in the visual loss.[20]

The various factors implicated in the pathogenesis include:
• The degree of stenosis
• The presence or absence of collateral vessels
• Anatomical variations in the anastomotic channels
• The chronicity and bilaterality of the carotid artery disease, and
• Other associated systemic vascular diseases.

Clinical Features

Ocular symptoms
1. Visual loss is always very severe. Visual acuity varies from 6/12 or less in 30%-40% cases and finger counting in 30%-40% of cases
2. Pain: Dull ache over eyes it can be either due to raised intraocular pressure (IOP) or due to ischemia
3. Asymptomatic in 10%
4. Duration: It can be gradual or abrupt
   a. Gradual loss can be due to chronic posterior segment ischemia/macular edema/cataract
   b. Abrupt loss can be due to sudden, severe hypoperfusion of the retinal arterial system caused by an embolus from a carotid atherosclerotic plaque that occludes the central retinal artery (CRA).
5. Visual field assessment: It may show normal field (23%), central scotoma (27%), nasal defects (23%), centrocecal defects (5%), or only a temporal island of vision (18%).[21]

Ocular Signs

Anterior segment
• Dilated conjunctival and episcleral vessels: Sign of collateral blood flow
• Corneal edema and descemet’s membrane folds
• Scleral melting may occur secondary to subtotal occlusion of the ipsilateral internal carotid
• Ischemic pseudo-iritis: Aqueous flare with few cells

Figure 1: The arterial supply of the eye
Iris atrophy and neovascularization may be seen. Neovascularization is commonly seen at the pupillary border or the iridocorneal angle, leading to peripheral anterior synechiae and angle closure.

Iris neovascularization can lead to neovascular glaucoma (NVG) associated with fixed, semi-dilated pupil that shows a sluggish reaction to light. A relative afferent pupillary defect may be present.
• Some patients may have a normal IOP or even hypotony despite fibrovascular tissue closing the angle because of ischemia of the ciliary body and consequently reduced aqueous humor production
• A cataract is seen in late stages [Figure 3].

**Posterior segment**

• Arteries are narrowed, and veins are irregularly dilated but not tortuous.[Figure 4]
• Retinal hemorrhages are usually located in the mid-peripheral retina mostly in the deeper retinal layers; thus, dot and blot are more common than flame-shaped hemorrhages
• Microaneurysms are mostly located outside the major vascular arcades in the mid-periphery but may be macular
• Diffuse macular capillary telangiectasia has been reported to be associated with bilateral common carotid artery occlusion
• Microaneurysms and macular capillary telangiectasia may cause a perifoveal leakage and macular edema, thereby decreasing the visual acuity
• A cherry-red spot usually occurs in patients with NVG when IOP increases and exceeds the perfusion pressure within the CRA, or it may follow an embolic occlusion of the CRA
• Retinal emboli, cotton-wool spots, and retinal arterial pulsations either spontaneous or induced by light digital palpation of the globe may be seen
• Wedge-shaped areas of chorioretinal atrophy: Due to choroidal ischemia
• New vessels formation may occur at the optic disc or in the retina. New vessels on the disc are more common than new vessels elsewhere. These new vessels can bleed, resulting in vitreous hemorrhage. Rarely, severe fibrovascular proliferation can occur
• Anterior and posterior ischemic optic neuropathy
• Normal-tension glaucoma: Due to chronic reduction of the ocular blood flow.

**Orbital infarction syndrome**

Rarely, ischemia of all intraorbital and intraocular structures may occur, resulting in orbital pain, ophthalmoplegia, ptosis, hypotony, and corneal hypoesthesia with anterior and posterior segment ischemia.

**Differential Diagnosis [Table 1][6]**

**Diagnosis and ancillary tests**

**Fluorescein angiography**

Prolonged choroidal filling time, although not sensitive, is the most specific angiographic sign of OIS. A highly sensitive angiographic sign is prolonged retinal arteriovenous time that is seen in up to 95% of eyes. Arterial, early and late venous circulation times are also prolonged. Staining of the retinal vessels (arteries > veins), both the major vessels and their branches, is seen in 85% of the affected eyes. A well-demarcated leading edge of fluorescein dye is a typical finding. About 15% of eyes show macular edema in the late phase. Retinal capillary nonperfusion can be seen in some eyes, mostly in the mid-peripheral retina.[3,6,22]

**Indocyanine green angiography**

The arm-to-choroid circulation time and the intrachoroidal circulation time are both prolonged. There is a slow filling of

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**Table 1: Differentiating Ocular ischaemic syndrome, central retinal vein occlusion and Diabetic retinopathy**

| FEATURES | OIS | CRVO | DR |
|----------|-----|------|----|
| POSTERIOR SEGMENT SIGNS : |     |      |    |
| Retinal veins | Dilated but not tortuous | Dilated and tortuous | Dilated and beaded |
| Haemorrhages (location) | Dot and blot (mid periphery) | Flame shaped (in all quadrants) | Dot and blot (posterior pole and mid periphery) |
| Microaneurysms (location) | Common (mid periphery) | Uncommon | Common (posterior pole) |
| Other micro vascular abnormalities | Macular telangiectasia, retinal arteriovenous communications, capillary drop out. | Opto-ciliary shunts, capillary drop out | Intra retinal micro vascular abnormalities, capillary drop out. |
| Hard exudates | No | Rare | Common |
| Optic disc | Normal | Swollen (commonly) | Diabetic papillopathy (rarely) |
| Central retinal artery perfusion pressure | Decreased | Normal | Normal |

| FLUORESCINE ANGIOGRAPHY : | | | |
|-------------------------|-----|-------|-----|
| Arterio-venous transit time | Prolonged | Prolonged | Usually normal |
| Retinal vessel staining | Arteries > Veins | Veins > Arteries | Usually absent |
| Macular edema | Rare | Common | Common |
| Choroidal filling | Delayed, patchy | Normal | Usually normal |

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Figure 4: The posterior segment features of the ocular ischemic syndrome
the watershed zones of the choroid. Areas of vascular filling defects in the posterior pole or the mid-periphery are seen.[3,6]

**Electroretinography**
Decreased amplitude of both “a”-and “b”-waves are classically seen, and it may improve with carotid artery reconstructive surgery.[6]

**Visual evoked potentials**
The normal photostress recovery time (time taken for the visual evoked potentials (VEP) to return to baseline status) ranges between 68 and 78 s. This is prolonged in patients with severe carotid artery stenosis, and it improves following carotid surgery. The VEP may elicit visual dysfunction at a very early stage when ophthalmological changes are absent or minimal.[6]

**Ophthalmodynamometry**
Ophthalmodynamometry is used to estimate the pressure in the OA, approximately at the site of origin of the CRA. IOP is increased gradually by applying pressure to the globe, and the arteries on the optic disc are observed with a direct or an indirect ophthalmoscope. At a particular pressure, they begin to pulsate. The pressure required to produce the arterial pulsations reflects OA diastolic pressure and further pressure which is required to cause cessation of the arterial pulsations reflects OA systolic pressure. In OIS, the CRA perfusion pressure is low, and hence, the pressure necessary for the pulsations to appear is reduced. Diastolic readings are considered to be more reliable than systolic readings and are decreased in OIS, which may improve after carotid artery surgery.[6]

**Ocular plethysmography**
Ocular plethysmography is a noninvasive method for detecting carotid occlusive disease. It measures the OA pressure indirectly by recording the variations in the size and volume of the eyeball or ocular pulsations.

Both ophthalmodynamometry and ocular plethysmography have been replaced by the carotid artery imaging methods in the workup of such patients.

**Imaging methods for the evaluation of carotid occlusive disease**

**Carotid duplex ultrasound**
Carotid duplex ultrasonography is the most commonly used noninvasive test which combines both B-mode ultrasound and Doppler ultrasound, thereby providing both anatomical imaging of the vessel and flow velocity information. The parameters used to classify the severity of stenosis, including peak-systolic velocity (PSV), end-diastolic velocity, and the internal carotid artery/common carotid artery (ICA/CCA) PSV ratio.[6]

**Color Doppler imaging of retrobulbar vessels**
Distal to a hemodynamically significant stenosis, the blood pressure is decreased and thus shows a diminished blood flow velocity. Studying the flow profile in the OA, CRA, and the short posterior ciliary arteries provides hemodynamic information about the carotid and retrobulbar circulations. Reversed OA flow pattern is a highly specific indicator of ipsilateral ICA stenosis or occlusion.[3,6]

Magnetic resonance angiography (MRA) and computed tomographic angiography (CTA) have gradually replaced DSA.[6]

**Carotid arteriography**
Conventional intra-arterial digital subtraction angiography was considered the gold standard for imaging the cerebrovascular system. However, it is not ideal for screening or follow-up because of the risks of cerebral infarction, systemic complications, and high cost.[3,6]

**Which investigation to do?**
Carotid duplex ultrasonography should be the first-line investigation in patients suspected to have carotid stenosis. If surgically significant stenosis or equivocal findings are seen, further imaging with either MRA or CTA is required. If the results of both tests agree, carotid arteriography may be omitted. If results are contradictory or inconclusive, conventional digital subtraction angiography should be the final arbiter.[6]

**Recent advances**
There has been a report of affected eyes with OIS showed thinner subfoveal choroidal thickness than unaffected contralateral eyes in enhanced depth imaging optical coherence tomography images.[23] One report suggested that hyperhomocysteinemia and elevated C-reactive protein (CRP) may be associated with the development of OIS and that the measurements of plasma total homocysteine and CRP in the blood may help in the diagnosis of OIS in ICA stenosis.[24]
TREATMENT OF OCULAR ISCHEMIC SYNDROME

Goals
- Treatment of anterior segment inflammation
- Ablation of the ischemic retina
- Control of raised IOP and NVG and
- Improvement of carotid circulation.

Optic nerve function, including visual fields, should be monitored. It should be noted that patients with bilateral disease might be eligible for registration as blind due to the field loss. Patients with reduced visual acuity will require low vision aids. Smoking needs to be stopped. Medical treatment includes antiplatelet medication, control of systemic illnesses such as hypertension and diabetes. A prompt referral for full medical and neurological assessment to treat associated cardiovascular disease and other systemic risk factors is necessary.

Anterior segment inflammation is treated with topical steroids and cycloplegics.

Panretinal photocoagulation
To prevent the development of NVG, the presence of hypotensive retinopathy should be assessed both clinically and with fundus fluorescein angiography (FFA) to identify retinal ischemia, and laser panretinal photocoagulation (PRP) is performed if necessary. In the acute stage, it is important to plan FFA before the development of significant corneal edema that would preclude fundus view and effective laser PRP.

Retinal ischemia triggers the production of retinal angiogenic factors that stimulate new vessel growth, and these factors diffuse into the anterior segment giving rise to iris neovascularization (NVI). By ablating ischemic retina, the production of angiogenic factors is reduced, thereby leading to regression of NVI, thus preventing NVG.

However, it has been found that PRP alone causes NVI regression in only 36% of eyes. Hence, laser PRP in OIS is thought not to be as effective in reducing the ischemic stimulus as in diabetic retinopathy. Mizener et al. found no evidence of retinal ischemia, in the form of capillary dropout on angiography in OIS patients even in those with coincidental diabetes mellitus. In animal studies, Hayreh and Baines experimentally induced NVI due to uveal ischemia in rhesus monkeys without any retinal ischemia.

Therefore, it has been suggested that uveal ischemia alone may be responsible for NVI in some cases of OIS. These observations highlight the importance of angiography in the investigation of OIS. It has been suggested that PRP in OIS should be reserved for cases of established retinal ischemia. In this context, full peripheral retinal ablation 3000-5000 burns of 200-500 µm spot size are used. Hayreh comments that there is no scientific rationale for PRP when FFA shows no retinal ischemia.

If the fundus is not visible due to media opacities or poor pupillary dilation and it is not possible to perform adequate PRP, other modalities such as 360° transconjunctival cryotherapy in the mid-peripheral and peripheral retina or transscleral diode laser retinopexy should be considered.

Intravitreal anti-vascular endothelial growth factor (VEGF) and triamcinolone have been tried in the treatment of iris neovascularization, NVG, and macular edema complicating OIS. However, further studies with longer follow-up are needed to determine the role of intravitreal steroids and anti-VEGF in such patients.

Control of intraocular pressure
Topical β antagonists, α agonists, topical, and oral carbonic anhydrase inhibitors are first-line therapy for raised IOP. Prostaglandins and pilocarpine should be avoided because they increase ocular inflammation. Moreover, pilocarpine causes miosis and also acts on the outflow pathway which is not effective in eyes with angle neovascularization. However, medical therapy is usually not effective in controlling IOP in the long term because the trabecular meshwork is physically occluded with neovascular tissue and fibrosis. Conventional filtering surgery (trabeculectomy with Mitomycin C) also carries a limited chance of success in the presence of NVI. Tube-shunt procedures (such as the Molteno tube or Ahmed valve) may be considered as a primary procedure or after failed conventional filtering surgery in a sighted eye. Cyclodestractive procedures such as cyclocryotherapy or laser cyclophotocoagulation have been shown to be effective in controlling IOP in refractory glaucomas. Until recently, the 1064 nm Nd:YAG laser had been used. More recently, however, the 810 nm semiconductor diode laser has been shown to be better absorbed by ciliary body pigment and more effective in the cycloablation. Diode laser, when compared to Nd:YAG laser, causes less inflammation, less pain, and results in a more predictable final IOP. Complications such as phthisis bulbii, hypotony, and uveitis are also considered to be less frequent. To titrate treatment with a response, these laser applications may be applied over a number of treatment sessions. There may or may not be a concomitant improvement in visual function.

Carotid surgery
The various surgeries performed are
- Carotid endarterectomy
- Percutaneous carotid artery angioplasty and stenting
- Superficial temporal artery-middle cerebral artery (STA-MCA) bypass surgery.

Carotid artery surgery may reduce ocular ischemia, improve hypotensive retinopathy as well as reduce the risk of stroke. Carotid endarterectomy has been shown to benefit patients with symptomatic cerebral ischemia when there is >70% carotid artery stenosis. It has been shown to improve ocular blood flow. It helps the regression of iris NVI and NVG. However, the IOP may raise post carotid surgery as ciliary body circulation is improved, and aqueous production is normalized.

STA-MCA bypass surgery had been advocated if lesions are unresectable by carotid endarterectomy. However, a recent randomized trial of STA-MCA bypass surgery in patients with atherosclerotic internal carotid artery occlusion failed to show any protection against cerebral ischemia with no reduction.
in stroke rate at 2 years.\cite{22} STA-MCA bypass surgery is, therefore, no longer a widely accepted alternative to carotid endarterectomy.

**Prognosis**

Prognosis is poor in most cases. The presence of iris neovascularization at presentation is associated with a poor visual outcome. Presenting visual acuity is another significant factor predicting the visual prognosis.\cite{26} OIS associated with carotid artery stenosis has a 5-year mortality rate of about 40%\cite{25,26}. Cardiovascular disease (approximately 66%) and stroke are the main causes of death.\cite{25}

**Financial support and sponsorship**

Nil.

**Conflicts of interest**

There are no conflicts of interest.

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