Our Patient has Retinal Vascular Occlusion: What should be Done? (Retinal Vascular Occlusions)

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Abstract

Retinal vascular occlusive diseases are often associated with a variety of systemic disorders including arterial hypertension, diabetes mellitus, dyslipidaemia, systemic vasculitis, atherosclerosis related thromboembolism and thrombophilic disorders. Various types of vascular occlusions are categorised on the basis of the site of occlusion and on the type of consequent vascular damage. All present with painless diminution of vision. Clinical and fundoscopy characteristics, prognosis and, at least in part, therapeutic approach depends on both the site of vessel occlusion and the type of consequent vascular damage. Changing treatment paradigms necessitate early and appropriate diagnosis and treatment of the condition.

Introduction

Retinal vascular occlusions are not a uniform entity. Rather they reflect a whole breadth of vascular disorders. Acute retinal vascular occlusions are common blinding disorders which affect venous and arterial circulation.[1] These disorders are better understood when they are viewed as distinct individual entities. In this review, the epidemiology, pathophysiology, prognosis, clinical presentation, and management of each condition are discussed separately.

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Retinal Venous Occlusions

Retinal vein occlusion (RVO) is the most common retinal vascular disease after diabetic retinopathy. Depending on the area of retinal venous drainage effectively occluded it is broadly classified as either central retinal vein occlusion (CRVO), hemispheric retinal vein occlusion (HRVO), or branch retinal vein occlusion (BRVO). The former two can be subdivided into ischaemic and non-ischaemic CRVO or HRVO, with each having distinct clinical features and prognosis. A number of parameters can be used to assess the degree of ischaemia such as the degree of visual loss, presence of a relative afferent pupillary defect, extent of retinal capillary non-perfusion on fluorescein angiography, and electrodiagnostics showing reduced b

	Branch retinal vein occlusion (BRVO)	Central retinal vein occlusion (CRVO)	Central retinal artery occlusion (CRAO)	Branch retinal artery occlusion (BRAO)
Prevalence	0.6%-1.1%, most common form	0.1- 0.4%,	0.85/100,000.	Least common form
Most common site	Superotemporal (66%) →Inferotemporal At the arteriovenous crossing	In the region of and just posterior to lamina cribrosa		Temporal retinal arteries - occlusion after the bifurcation of the central retinal artery
Risk factors	HTN, Cardiac disease, Increased BMI at the age of 20, H/O glaucoma (DM not a significant independent risk factor)	Age>50yr, HTN, H/O glaucoma, DM, Arteriosclerotic changes, Hyperlipidaemia	Age>60yr, HTN, DM, Atherosclerosis and related Thromboembolism Carotid artery obstruction, Vasculitis (Giant cell arteritis) or Vasospasm, Structural cardiac Pathology	Age>60yr, HTN, DM, Atherosclerosis, Carotid artery obstruction, Vasculitis (Giant cell arteritis) or Vasospasm, Structural cardiac Pathology
Types	(1) Major BRVO (main branch retinal vein) (2) Macular BRVO (macular vein)	Ischemic Nonischemic.	(1) Non arteriticpermanent (2) Non-arteritic transient CRAO - analogous to TIA, has best prognosis (3) Non-arteritic CRAO with cilioretinal sparing (4) Arteritic CRAO- always due to GCA	
Clinical features:	MAJOR BRVO- asymptomatic or visual blurring MACULAR BRVO - central disturbance in vision	ISCHEMIC -sudden and severe painless monocular vision loss **worse upon awakening** NONISCHEMIC- temporary sudden obscuration of monocular vision → central blurring (macular edema) **worse upon awakening**	Sudden, painless, profound vision loss Episodes of Amaurosis fugax,	Sudden, painless and profound sectoral visual field loss which sometimes may go unnoticed.
Ocular Examination and investigations: (Diagnosis)	1.VISION- variable 2.NVI- less common 3. FUNDUS- Superficial hemorrhages, Retinal edema, Cotton wool spots, Dilated tortuous occluded vein Old vein occlusions- sheathing and venous collaterals, Chronic macular edema, Retinal neovascularization VH secondary to retinal neovascularization 4.OCT- shows quantification of macular odema 5.FFA- Peripheral and macular odema (CNP, vessel pruning) Venous filling is delayed.	Ischaemic: 1.VISION- CF or worse 2.RAPD 3. NVI- develops in about 50% eyes 4.GONIOSCOPY-NVA can develops even before NVI 5.FUNDUS- "Blood and thunder"- extensive intraretinal hemorrhages Venous tortuosity, Capillary Nonperfusion in all 4 quadrants, Typically prominent cotton wool spots, Optic disc hypperaemia and odema, Significant macular odema Optic disc collaterals-common 6.OCT- enables quantification of macular odema 7.FFA- extensive areas of CNP and vessel wall staining and leakage Nonischemic: 1.RAPD- absent or mild 2.FUNDUS: Patchy(perivenular) ischaemic retinal whitening (PIRW)-early sign in young patients Dilatation and tortuosity all the branches of central retinal vein, Dot, blot and flame shaped hemorrhages of mild to moderate extent,	1.VISION- profound visual loss 2.RAPD- within seconds of event 3.FUNDUS EXAMINATION initially may be unremarkable diffuse white-yellow appearance except for classic Cherry-red spot of foveola Early stage, within 7 days- Retinal opacity in the posterior pole Cherry-red spot (90%), Cattle trucking, Retinal arterial attenuation, Optic disc oedema (22%) and pallor At later stages- Optic atrophy, Retinal arteriolar attenuation, Cilioretinal collaterals, RPE pigmentary changes at macula 4.FFA- Fluorescein- angiography- delay in A/V transit time and not a complete lack of filling 5.OCT: highly reflective embolic plaque within the superficial optic nerve head 6.ERG Diminished b wave	1.VISION- variable 2.RAPD- often present 3.FUNDUS- Cattle trucking or box carring of vessels Ground glass retina in the area of ischemia Emboli can be seen at the bifurcation points 4.VISUAL FIELD TESTING- confirms the defect 5. FFA- delay in arterial filling and hypofluorescence of the involved segment

	Cotton wool spots, Mild optic disc odema and Macular odema Development of disc collaterals (optocilliary shunts)- markedly reduced risk of neovascularization. 3.FFA: Delayed arteriovenous transit time, masking by haemorrhages, usually good capillary retinal perfusion, some late leakage CVOS criteria- FFA-designating a surface of CNP > 10-disc diameters as ischemic and < 10 disc diameters as non-ischemic 4. OCT- particularly important in diagnosing macular oedema which is usually mild			
Pathogenesis	Venous compression at (A/V) crossing, Endothelial damage with subsequent thrombus formation, hypercoagulable disorders.	External compression of the CRV by CRA Primary CRV wall disease (degeneration or inflammation) Hemodynamic factors (hypotension and blood dyscrasias) ISCHEMIC -thrombus at or just posterior to lamina cribrosa NONISCHEMIC. - thrombus farther back from the lamina cribrosa	Three types of emboli- Glistening yellow cholesterol emboli- (Hollenhorst plaques) atherosclerotic deposits in carotid arteries Large nonglistening emboli- cholesterol, surrounded by fibrin-platelet thrombus Calcific emboli - cardiac valves	
Prognosis	Favorable 50-60% patients maintaining visual acuity 20/40 or better, even without treatment	Ischemic type - 87% final visual acuity of 20/200 or worse Nonischemic type - 80% had 20/60 or better vision	66% have a final VA of 20/400 or worse. 18% - VA of 20/40 or better in those with patent cilioretinal artery to provide for the central macula.	Fair but residual visual field deficit
Prognosis depends on	Site and extent of occlusion, Presence of ischemia, and Development of collateral circulation	Initial visual acuity is a good predictor of final visual acuity - 65%of with initial v/A of 20/40 or better remained in same range. intermediate visual acuity (from 20/50 to 20/200), 44% remained in the intermediate range, 19%improved to 20/50 or better and 37%worsened to less than 20/200. 80% of those with less than 20/200 visual acuity initially remained 20/200 or worse	Patent cilioretinal artery	Unless the foveola is completely involved in the ischemia, then BRAO has a reasonably fair prognosis.
Predictor for poor recovery	initial visual acuity of 20/200 or worse	1.Persistent macular edema, 2.Macular ischemia, 3.Neovascular glaucoma		Complete involvement of fovea
Treatment	MACULAR EDEMA - 1. argon laser photocoagulation, 2. Intravitreal	TREATMENT OF MACULAR OEDEMA-1. Intravitreal corticosteroids (effects transient) 2. Intravitreal antivascular endothelial growth factor agents	Medical therapy - (1) Dilation of the artery, (2) Increasing perfusion pressure by reduction of intraocular pressure, (3)	Same as that of CRAO but decision of aggressive treatment is based on individual basis. Review: after 3 months is warranted to reassess the

	corticosteroids AREA OF CNP - scatter argon laser photocoagulation (?vitreous hemorrhage) SHEATHOTOMY- release compression at A/V junction. Review: Cases which don't require early intervention- after 3 months Then 6 monthly intervals up to 2 years (to detect neovascularization)	3.focal grid macular photocoagulation 4. Intravitreal triamcinolone NEOVASULARISATION-PRP INVESTIGATIONAL TREATMENT-(1) Chorioretinal venous anastomosis, (2) Vitrectomy, (3) Radial optic neurotomy (4) Optic nerve sheath decompression Review: Non ischaemic: first follow up after 3 months Ischaemic: Monthly for initial 6 months to detect onset of anterior segment neovascularization. Then monitoring IOP and Gonioscopic findings for up to 2 years.	Thrombolysis, (4) Antiplatelet therapy, (5) Systemic steroids, and (6) Reducing red cell rigidity (7) Physical removal of the clot PRP- regression of iris vessels in about 65% of eyes. Review: First follow up- 3-4 weeks after presentation And at least twice at a month interval after initial follow up to assess neovascular complications if any.	fundus findings, visual field and provide an advice on prognosis.

(HTN= Hypertension, DM= Diabetes mellitus, NVI= Neovascularization of iris, NVD= Neovascularization at disc, RAPD= afferent papillary defect, FFA- Fundus fluorescein angiography, IOP-intraocular pressure, CNP- Capillary non perfusion, PRP- Pan retinal photocoagulation)

Table 1: Differences between various retinal vascular occlusions

wave amplitude, reduced b:a ratio and prolonged b-wave implicit time. BRVO can be considered a major BRVO where a quarter or more of the retina is affected or a macular BRVO where only part of the macula is affected.[2]

Presentation of RVO in general is with variable painless visual loss with any combination of fundus findings consisting of retinal vascular tortuosity, retinal haemorrhages (blot and flame shaped) and cotton wool spots, optic disc swelling and macular oedema. In a CRVO, retinal haemorrhages will be found in all four quadrants of the fundus, whilst these are restricted to either the superior or inferior fundal hemisphere in an HRVO.

In a BRVO, haemorrhages are largely localised to the area drained by the occluded branch retinal vein. Vision loss occurs secondary to macular oedema or ischaemia.[2]

Central retinal venous occlusion (CRVO)

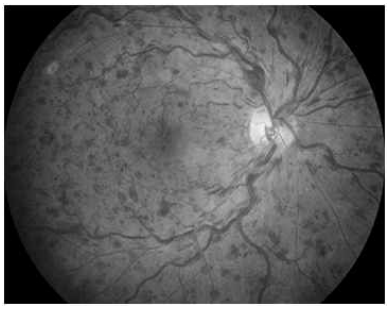

Fig 1: Right Eye of a patient with Central Retinal Vein Occlusion

Natural history of CRVO depends upon following outcomes which are considered as key aspects for counselling and management of patients and useful as guidelines for development of new therapeutic approach.[3]

(1) Change in visual acuity (VA);
(2) Development of Macular Oedema;
(3) Development of neovascular complications, including NV, VH, and NVG;

(4) Involvement of the fellow eye; and
(5) Conversion from non-ischaemic CRVO to ischaemic CRVO.

Eyes with CRVO, including non-ischaemic CRVO, generally have poor vision that declines further over time. Up to one third of eyes with non-ischaemic CRVO usually convert to ischaemic CRVO of which a quarter may develop neovascular complications over next 15 months. Ischaemic CRVO cases had poorer baseline and subsequent vision, and a high risk of neovascular glaucoma.[3]

This is the reason why prompt diagnosis and referral to the ophthalmologist, identification of associated risk factors and their proper management, counselling the patient, regular follow up for early detection of sight threatening complication are of utmost importance in the management of this condition. Here it is where the role of general practitioners and multiple disciplines becomes significant in proper referral of the patient and management of the causal factors.

Branch retinal vein occlusion (BRVO)

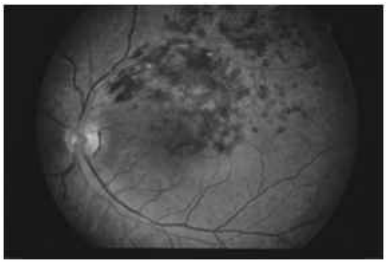

Fig 2: Left Eye of a patient with Branch Retinal Vein Occlusion

Two subtypes of BRVO have significant bearing on the outcome of their treatment. The severity of a major BRVO depends on the vessel occluded and could involve the full range of complications. In contrast, macular BRVO is usually not associated with vitreous haemorrhage and neovascular glaucoma because of the smaller area of retina affected, but often results in macular oedema and hence the vision loss.[4]

Similarly, BRVO cases where arterio-venous crossings in the nasal or peripheral retina are involved without affecting macular region, are mostly asymptomatic and do not affect visual acuity.[4]

Treatment of Retinal Venous Occlusions

The Branch Retinal Vein Occlusion Study (BRVOS) and the Central Retinal Vein Occlusion Study (CRVOS) have established a standard of care by providing both an understanding of the natural history and treatment algorithms for BRVO and CRVO in managing neovascular complications and reducing visual loss.[2] In patients with macular oedema secondary to non-ischaemic CRVO with a vision of 20/50 or worse, macular grid laser photocoagulation does not improve visual acuity although the oedema may improve. Additionally, prophylactic pan retinal photocoagulation (PRP) in ischaemic CRVO does not prevent iris or angle neovascularisation and is therefore not recommended. PRP is recommended when anterior segment, disc or retinal neovascularisation develop.[2]

CRVO causes significant ocular morbidity. While our understanding of the pathogenesis of CRVO remains limited,

there have been recent significant advances in the treatment of CRVO supported by RCTs. In the future, a combination approach will be more efficacious. Selective peripheral PRP to areas of CNP may reduce the up-regulated Vascular Endothelial Growth Factor (VEGF) load within the eye, reducing the need for repeat treatments for macular oedema. Laser-Chorioretinal anastomosis (L-CRA) could then address the raised venous hydrostatic pressure, and once this is established, then intravitreal anti-VEGF agents can be used to resolve the CME and help repair the breakdown in the blood-retinal barrier.[5]

While visual prognosis is guarded and depends on the initial status, with careful monitoring for neovascularisation and prompt PRP at the earliest sign of NVA/NVI, the complications of neovascular glaucoma should be low.[6]

Until a definitive treatment becomes available for RVO it is currently a case of using the various treatment options available to keep the macula dry (to prevent the irreversible damage caused by chronic macular oedema) and titrating this to allow a sufficient collateral circulation to develop.[2]

Retinal Arterial Occlusions

Central and branch retinal arterial occlusion is to be differentiated. Along with painless, sudden loss of central sight, visual field loss is also present. If the visual field loss is complete, CRAO is suspected and part of visual field is affected in BRAO.[7]

Central retinal artery occlusion

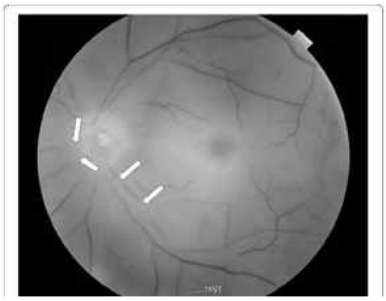

Fig 3: Left Eye of a patient with Central Retinal Artery Occlusion

It is an ophthalmic emergency. It is an ocular analogue of cerebral stroke. It indicates end organ ischaemia and gives a clue towards underlying atherosclerotic pathophysiology which might take place of possible risk factor for future cerebro-vascular accident or ischaemic heart disease.[8] Resulting ischaemia due to CRAO results in sudden profound loss.

Treatment of Retinal Arterial Occlusions

If the arterial obstruction is removed in time either spontaneously or with treatment, full visual recovery and reversal of retinal damage is possible. Treatment is beneficial only if started within 8 hours of occlusion. Few more studies have suggested that treatment is effective if started within 24 hours of onset of symptoms.[9]

Dilatation of artery: can be achieved by

- Sublingual isosorbide dinitrate;
- re-breathing of expired carbon dioxide;
- breathing in a fixed mixture of 95% oxygen and 5% carbon dioxide called as carbogen.

Physical removal of the obstruction works only when obstruction is embolus and is achieved through applying pressure

on patient's eye either with his own fingers or treating clinician's finger or lens.

Increasing perfusion pressure by reducing intraocular pressure by

- Anterior chamber paracentesis;
- Intravenous acetazolamide (a carbonic anhydrase inhibitor);
- Intravenous mannitol (an osmotic diuretic);
- Trabeculectomy

Thrombolysis

Intravenous thrombolytic agent either locally or systemically

Local Intra-arterial fibrinolysis: includes administration of fibrinolytic agent directly into ophthalmic artery

Agents used are: urokinase and recombinant tissue plasminogen activator.

Antiplatelet agents

In acute ischaemic strokes, platelets get activated and worsen the ischaemia. Hence antiplatelet agents are thought to be beneficial. Examples are aspirin, clopidogrel and intravenous tirofiban - which is non-peptide inhibitor of the platelet glycoprotein IIb/IIIa receptor.

Reducing red blood cell rigidity: as less rigid (deformable) cells are easy to pass through the vessels. Pentoxifylline has been shown to increase red blood cell deformability and has been used orally on patients with CRAO.

Systemic steroids

They treat vascular endothelial oedema leading to tissue damage which occurs following CRAO.

As the pathophysiology of CRAO and BRAO is same, their management is also same. Though CRAO is an ocular emergency causing legal blindness and an ocular analogue of cerebral stroke, no evidence based perfect treatment guidelines are available. Some important studies have shown better efficacy of local intra-arterial fibrinolysis, use of oral pentoxyphylline (in non arteritic CRAO) and enhanced external counter pulsation (EECP) combined with haemodilution in the treatment of CRAO.[9,10]

Systemic Management In Retinal Vascular Occlusions

The detection and management of systemic disease is important for reducing the risk of future vascular occlusive events both ocular and systemic. It's here, where the general practitioners can play an important role and multidisciplinary approach is required.

Interdisciplinary work-up (What the general practitioners can do)

In arterial occlusion, embolic phenomena and Horton´s arteritis should be excluded, in addition to local ophthalmological investigations. In retinal venous occlusion, optimal treatment of arterial hypertension is universally useful, while investigations for thrombophilia are useful in patients under 50 years of age.

Assessment[11]:

In all the patients:

History and Clinical examination: including blood pressure, pulse and cardiac auscultation for murmurs is must. In suspected cases of arteritic CRAO, symptoms and signs of giant cell arteritis (leading to 1-2% cases of CRAO) like headache, scalp tenderness, jaw claudication must be ruled out.

Following investigations should be

carried out in patients with retinal vascular occlusions.

1. Blood pressure
2. Erythrocyte sedimentation rate
3. Complete blood count
4. Blood sugar levels (fasting and post prandial)
5. Lipid profile
6. Plasma protein electrophoresis
7. Serum urea, creatinine, electrolytes
8. Thyroid function tests
9. ECG

In younger patients,

Age < 50 years, bilateral cases, cases with family or previous history of thrombosis and patients with the negative results for above common investigations:

1. Chest X-ray (Sarcoidosis, tuberculosis, left ventricular hypertrophy)
2. C reactive protein (Inflammation)
3. Plasma homocysteine level (hyperhomocysteinaemia)
4. Thrombophilia screen (heritable thrombophilia)
5. Autoantibodies (rheumatoid factor, ANA, c- ANCA, Anti ds-DNA)
6. Serum angiotensin converting enzyme
7. Carotid duplex scanning (To exclude mimicking ocular ischaemic syndromes)
8. Plasma protein electrophoresis
9. 24-hour ECG (to exclude intermittent arrhythmias)

Take Home Message

Retinal vascular occlusion syndromes encompass distinct clinical entities with various pathophysiology, clinical presentation, management, and treatment. Although much progress has been made in their understanding, more is still required to prevent the devastating sequelae of these blinding disorders so as to obtain the exact and evidence-based treatment guidelines.

A particular trait of venous occlusions of the retina is their association with atherosclerosis. This signifies the particular importance of inter-disciplinary workup and treatment. General risk factors of atherosclerosis - such as arterial hypertension, diabetes mellitus, or hyperlipidaemia should be assessed in all patients. Long term blood pressure measurement, electrocardiography, and lipid status assessment are the standard investigations.[7]

Mostly being of systemic aetiology, diagnosis and treatment of retinal vascular occlusive disorders not only affect ophthalmological course of the disease but the prognosis quo ad vitam. While local diagnostic and therapeutic measures are performed by ophthalmologists, there is an important role for interdisciplinary co-operation in the investigation and systemic treatment of these events.[7]

Proper and prompt referral by primary care physicians to the Ophthalmologist play very important role in the management and visual prognosis of these ocular emergencies.

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On-Demand versus Maintenance Inhaled Treatment in Mild Asthma

The premise of most alternative approaches is that therapy with inhaled glucocorticoids might be necessary only when symptoms flare and exacerbation is potentially imminent, so treatment could be taken only in response to symptoms.

These two trials show persuasively that treatment with budesonide-formoterol on an as-needed basis prevented the most serious outcomes of poorly controlled asthma - exacerbations and loss of lung function - but was less effective at mitigating symptoms. The effects observed with budesonide-formoterol used as needed occurred at a median daily dose of inhaled glucocorticoid that was only 17 to 25% of that in the regular maintenance group. Not only does this reduce the potential for glucocorticoid side effects and improve the acceptability of the treatment regimen to glucocorticoid-averse patients, but it also has the potential to reduce costs dramatically. Assuming that approximately 18.4 million adults in the United States have asthma, that 65% of these have persistent asthma and 50 to 75% of those cases are mild, and that the average cost of a glucocorticoid inhaler is $218 per month, the savings in drug costs in the United States alone would be close to $1 billion per year.

Stephen C. Lazarus, The NEJM, 2018, Vol 378, 1940-1941