Recognizing and managing retinal vein occlusion

Introduction

Retinal vein occlusion is the second most common retinal vascular disease after diabetic retinopathy and represents a significant cause of irreversible sight loss and disability in persons over the age of 50 years (The Branch Vein Occlusion Study Group, 1984). The prevalence of the condition is 0.7% at 49–60 years which rises to 4.6% for persons over 80 years of age (Mitchell et al, 1996). Retinal vein occlusion is an umbrella term for clinical entities arising from occlusion of the central, hemi-central or branch retinal veins. It is important to understand that retinal vein occlusion may herald underlying systemic disease. It classically presents with sudden onset painless visual loss and on fundoscopic examination the deep blood orange 'stormy sunset' retinal appearance may be seen.

Diagnosis

Retinal vein occlusion is a clinical diagnosis made after history and fundoscopic examination.

History

Patients usually report painless unilateral loss of vision over hours or days, or a reduction in vision upon awakening that may improve throughout the day (likely to be the result of nocturnal arterial hypotension).

Examination

Healthy fundoscopic appearances

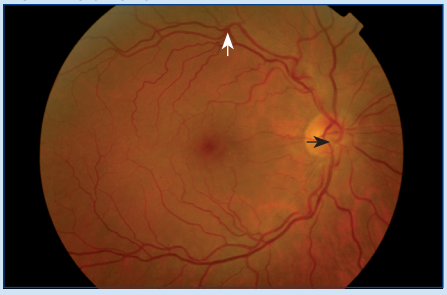
The appearance of a healthy fundus shows a flat retina with the central pigmented macula. The optic disc should have clear margins with retinal veins and arteries branching from here over the retina (*Figure 1*). Retinal veins look darker and slightly thicker than retinal arteries. The central vein divides forming the superior and inferior branches, and branches again to give rise to four tributaries draining each 'quadrant' of the retina.

Fundoscopic appearance in retinal vein occlusion

If the major outflow of the central retinal vein becomes occluded, venous pressure elevates, contributing to the formation of haemorrhages, retinal infarcts (previously known as cotton wool spots) and macular oedema (*Table 1*). The retinal appearances can look dramatic with haemorrhages in all four quadrants of the fundus, appearing darker red within the deepest retinal layers (*Figure 2*). The entire venous tree is tortuous, engorged and dilated and the disc margin is blurred.

Differential diagnoses are important to establish as retinal vein occlusion shares similar features with other retinal vascular diseases. Differentials include hypertensive retinopathy, retinopathy of blood dyscrasias, papillophlebitis and diabetic retinopathy papillitis. In the latter two conditions, swollen optic disc is the main feature, with localized retinal haemorrhages around the optic disc.

Figure 1. Right eye fundus photograph showing healthy retinal appearances on fundoscopy. Note the well-demarcated vessels and clear optic disc margins. The point at which central retinal vein occlusion occurs is shown by the black arrow, where the central retinal vein exits the eye. The site of a branch retinal vein occlusion at an arteriovenous crossing ('nipping') is indicated by the white arrow.



Causes

Two theories have been proposed to explain central retinal vein occlusion, one involving systemic factors and another related to anatomical factors. It is likely that the two interact to cause thrombus formation at sites of anatomical vulnerability.

Systemic factors

Klien and Olwin (1956) proposed three mechanisms of central retinal vein occlusion relating to different systemic disease processes which may be modifiable and treatable (*Table 2*).

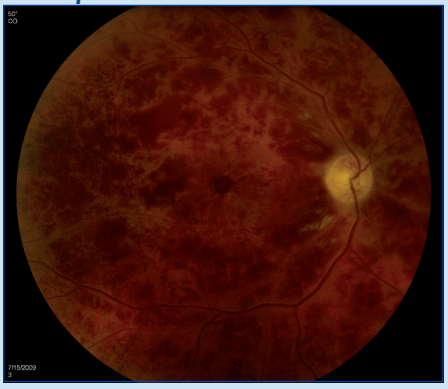
Atherosclerosis

Atherosclerosis hardens the central retinal artery into a rigid, sclerotic structure that exerts external compressive force on the neighbouring central retinal vein and

Table 1. Physical examination findings

Unilateral reduced visual acuity using Snellen or LogMAR chart	
Confrontational visual field defects are variable and often unhelpful in the acute phase	
Relative afferent pupillary defect on the affected side (indicating poor prognosis)	
Central visual distortion	
Fundoscopy	Iris looking for neovascularization
	Disc swelling
	Dilated and tortuous veins
	Retinal haemorrhages noting the distribution

Figure 2. Classical 'stormy sunset' appearances of central retinal vein occlusion with haemorrhages in all four quadrants.



Dr Meena Arunakirinathan *is FY2 in General Surgery in the Academic Surgical Unit, St. Mary's Hospital, Imperial College Healthcare NHS Trust, London W2 1NY,* **Dr Michelle AJ Ting** *is ST1 in Ophthalmology at Central Middlesex Hospital, North West London Hospitals NHS Trust, London, and* **Ms Laura Crawley** *is Consultant Ophthalmic Surgeon in Glaucoma at The Western Eye Hospital, Imperial College Healthcare NHS Trust, London*

Correspondence to: Dr M Arunakirinathan (m.arun@imperial.ac.uk)

Table 2. Systemic risk factors classified by Klein and Olwin's (1956) disease mechanism

Disease mechanism	Systemic risk factors		
Atherosclerosis of neighbouring central retinal artery	Hypertension – the commonest risk factor (in up to 64%) in patients over 50 years of age (The Eye Disease Case-Control Study Group, 1996)		
	Hypercholesterolaemia – cholesterol >6.5 mmol/litre is another common risk factor (in up to 50%) in older patients, but is of greater predominance in patients under 50 years of age (Dodson et al, 1982)		
	Diabetes mellitus – the well-documented link to retinal vein occlusion is via an increase in cardiovascular risk factors, since 70% of this group are also hypertensive (The Eye Disease Case-Control Study Group, 1996; Royal College of Ophthalmologists, 2010)		
	Smoking		
	Obesity		
Inflammation of venous wall	Behçet's disease		
	Polyarteritis nodosa		
	Sarcoidosis		
	Wegener's granulomatosis		
	Systemic lupus erythematosus		
	Goodpasture syndrome		
Hypercoagulability of blood	Primary (genetic)	Common	Factor V Leiden
			Prothrombin gene mutation
			Methyltetrahydrofolate gene mutation
		Rare	Antithrombin III deficiency
			Protein C deficiency
			Protein S deficiency
		Very rare	Fibrinolysis defects
	Secondary (acquired)	High risk for thrombosis	Antiphospholipid syndrome and hyperhomocysteinaemia – have the highest risk for retinal vein occlusion
			Multiple myeloma
			Waldenström's macroglobulinaemia
			Cancer
			Atrial fibrillation
			Myocardial infarction
			Prosthetic cardiac valves
			Tissue damage (surgery, fracture, burns)
			Disseminated intravascular coagulation
			Heparin-induced thrombocytopaenia
			Prolonged bed rest or immobilization
		Lower risk for thrombosis	Oral contraceptives – greater incidence in younger patients
			Cardiomyopathy
			Nephrotic syndrome
			Hyperoestrogenic states (pregnancy)
			Sickle cell anaemia
			Smoking

causes secondary endothelial cell proliferation. This also occurs in branch retinal vein occlusion at arteriovenous crossings (*Figure 1*).

Inflammation

Primary venous wall disease of inflammatory or degenerative aetiology predisposes to venous thrombi.

Hypercoagulability

Hypercoagulability results in haemodynamic disturbances, which lead to venous occlusion.

Local anatomical vulnerability

The central retinal artery and corresponding vein lie adjacent to each other within a common adventitial sheath, which thickens and scleroses with age or when a patient has uncontrolled glaucoma. Upon exiting the optic nerve head, the vessels enter a small window in the lamina cribrosa where their luminal diameters suddenly narrow, a point of high resistance to flow. This high resistance leads to turbulent blood flow (Green et al, 1981), which damages the endothelium and leaves the subendothelial extracellular membrane exposed, predisposing the vessel to thrombosis.

Certain ophthalmic diseases can increase local anatomical vulnerability by compromising the retinal blood supply and increasing hypercoagulability: glaucoma (open angle or angle closure), orbital trauma and optic disc vasculitis, the latter being of greater importance in patients less than 50 years of age.

Classification

The main subtypes of retinal vein occlusion are central, hemi-central and branch retinal vein occlusion (*Figure 3*). Central retinal vein occlusion encompasses two distinct pathogenic entities, ischaemic and non-ischaemic retinal vein occlusion. A summary of examination features with each sub-type is given in *Table 3*.

Ischaemic central retinal vein occlusion

Ischaemic central retinal vein occlusion is associated with greater loss of vision at time of diagnosis (<6/60), a relative afferent pupillary defect and poorer prognosis than the non-ischaemic form. Profound retinal ischaemia leads to new vessel formation in

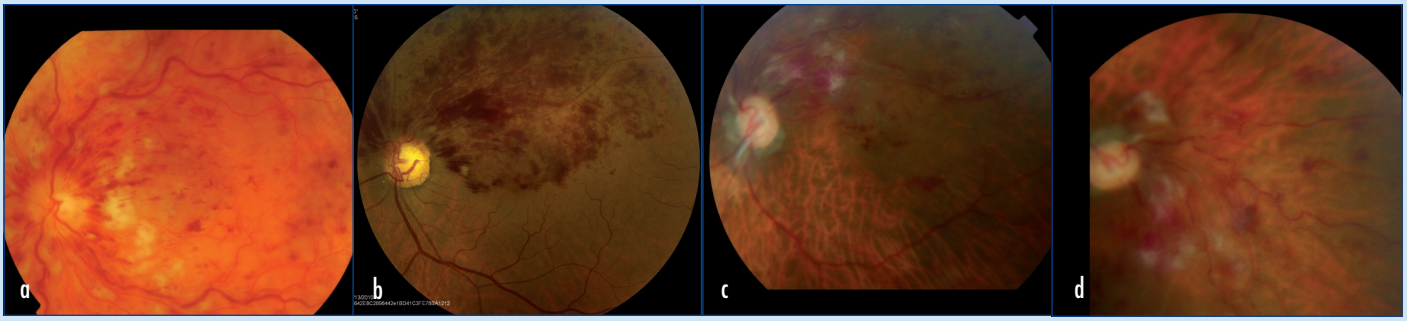


Figure 3. Fundoscopic features of retinal vein occlusion. a. Left central retinal vein occlusion. b. Left hemi-retinal vein occlusion. c. Left branch retinal vein occlusion. d. Cotton wool spots overlying the ischaemic retina.

the retina, iris and the irido-corneal drainage angle causing rubeotic glaucoma (*Figure 4*). In this situation, aqueous outflow is blocked and the intraocular pressure rises dramatically causing extreme pain and further loss of vision with poor prognosis. For this reason it is important to distinguish ischaemic from non-ischaemic central retinal vein occlusion, as prophylactic treatment in the form of pan-retinal photocoagulation laser or anti-vascular endothelial growth factor (VEGF) injections can be administered to prevent neovascularization.

Non-ischaemic central retinal vein occlusion

The main difference between ischaemic and non-ischaemic central retinal vein occlusion is the presenting level of vision and the absence of relative afferent pupillary defect. Of the two, non-ischaemic central retinal vein occlusion has a much better visual outcome, but it has a tendency to be complicated by cystoid macular oedema.

Branch retinal vein occlusion

Branch retinal vein occlusion is more common than central retinal vein occlusion and its visual prognosis is generally more favourable. Patients may be asymptomatic, or may have visual distortion with visual field defects. If the macula is involved, central vision will be affected. The Branch Vein Occlusion Study Group (1984) concluded that over half of patients diagnosed with branch retinal vein occlusion will remain stable with a visual acuity of 6/12 or better after 1 year.

Investigations

It is of paramount importance to recognize retinal vein occlusion as a marker of underlying risk for cardiovascular-associated mortality. General physicians must therefore tailor their investigations to confirm and quantify these risk factors. Mandatory tests include blood pressure measurements, electrocardiogram and blood tests as specified in *Table 4* (Yau et al, 2008).

Table 3. Key examination features and visual acuity of sub-types of retinal vein occlusion

Subtype	Key examination features	Visual acuity
Ischaemic central retinal vein occlusion	Haemorrhages in all four quadrants, relative afferent pupillary defect, large number of cotton wool spots	From 6/60 to counting fingers
Non-ischaemic central retinal vein occlusion	Haemorrhages in all four quadrants, no relative afferent pupillary defect	From 6/9 to 6/60
Hemi-retinal vein occlusion	Haemorrhages in superior or inferior fundus, giving rise to either superior or inferior hemi-central retinal vein occlusion respectively	As above depending on whether ischaemic or non-ischaemic
Branch retinal vein occlusion	Haemorrhages in one quadrant only	Not affected
	+ Supero-temporal or infero-temporal occlusion with macular oedema present	Visual acuity affected +/- altitudinal visual field defect – a unilateral filling defect above or below the horizontal meridian

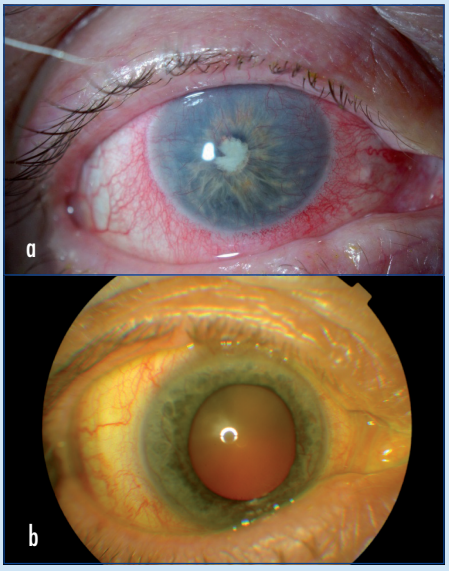
Specialist ophthalmic investigations

The Royal College of Ophthalmologists (2010) recommends referral to an ophthalmologist specializing in medical retina within 2–4 weeks of suspected presentation. This enables specialist work up with slit lamp examination, measurement of intraocular pressures, fluorescein fundus angiogram and optical coherence tomography.

Treatment

Management is aimed at maximizing visual prognosis, preventing recurrence and reducing cardiovascular mortality. It is also important to try to prevent re-occlusion of the affected vein and thrombosis in the other eye (Shahid et al, 2006; Mohamed et al, 2007). Therapeutic interventions can be broadly classified as treatments aimed at sequelae and treatments aimed at causal pathology (McAllister, 2011).

Figure 4. Rubeosis iridis. a. Hyperaemic appearances of the red eye. b. New vessels on the iris.



Treatments aimed at sequelae

Intraocular agents

Intraocular steroids can help stabilize the blood–retinal barrier and down-regulate expression of VEGF at a cost of raised intraocular pressure. For sustained release, Ozurdex dexamethasone intravitreal implant reduces the risk of vision loss with a prolonged duration of effect on cystoid macular oedema secondary to central retinal vein occlusion or branch retinal vein occlusion (Haller et al, 2010).

Recent advances in anti-VEGF monoclonal antibodies have radicalized the way cystoid macular oedema secondary to retinal vein occlusion is managed. These novel antibodies inhibit the action of VEGF which is upregulated in retinal vein occlusion, and minimize neovascularization, thus reducing the likelihood of rubeotic glaucoma. Intravitreal bevacizumab and ranibizumab have short-term beneficial effects on visual acuity and repeated injections are required to maintain the visual improvement over a long period (Zhu et al, 2013).

Table 4. Algorithm of tests in the assessment of retinal vein occlusion in clinical practice and examinations

Baseline tests	Full blood count, erythrocyte sedimentation rate, plasma viscosity
	Urea, electrolytes, creatinine
	Random and fasting serum glucose, haemoglobin A_{1c}
	Random cholesterol and fasting lipids for Framingham equation
	Plasma electrophoresis to detect myeloma and Waldenström's macroglobulinaemia in the elderly
	Electrocardiography for Framingham equation
	Thyroid function
If hypertension is present	Creatinine clearance
	Urine microscopy
	Renal ultrasound
Specialist tests if clinically indicated	Thrombophilia screen: functional protein C and protein S levels, antithrombin III levels and activated protein C resistance (factor V Leiden mutation (R506Q) polymerase chain reaction assay)
	Factor XII (Hageman factor)
	Antiphospholipid antibodies: lupus anticoagulant and anticardiolipin antibodies
	Autoantibodies: anti-DNA, antinuclear, anti-neutrophic cytoplasmic, rheumatoid factor
	C-reactive protein
	Fasting homocysteine concentration. If raised check vitamin B_{12} and folate levels also
	Serum angiotensin-converting enzyme for sarcoidosis
	Chest radiography for sarcoidosis

From Yau et al (2008)

Laser therapy

Pan-retinal photocoagulation can be administered as prophylaxis to eyes with ischaemic central retinal vein occlusion as it may reduce the neovascularization risk particularly of the iris (anterior segment). Macular grid laser is no longer recommended as it has no benefit on visual acuity (Hahn and Fekrat, 2012).

Endovascular cannulation with a microneedle

This extremely novel surgical approach flushes a thrombus out of the central retinal vein after cannulation with a microneedle. Although in its experimental stages, it may prove to be a promising option for macular oedema secondary to central retinal vein occlusion, where Ozurdex may not be appropriate, for example in a steroid non-responder (Kadonosono et al, 2013).

Treatments aimed at causal pathology

Antithrombotic agents, anticoagulants and thrombolytics

Theoretically these agents may have a role since aberrations in platelet aggregation are implicated in central retinal vein occlusion. Aspirin and ticlopidine must only be started if the risks and benefits are carefully considered, owing to their side-effects of retinal or vitreous haemorrhage. Warfarin has no role in management (Royal College of Ophthalmologists, 2010). Tissue plasminogen activator was trialled both systemically and locally into the vitreous of the eye, but was abandoned because it lead to significant extraocular haemorrhage.

Laser chorio-retinal anastomosis

This technique provides an alternative channel for obstructed venous blood to drain from the retinal venous circulation by forming an anastomosis between the obstructed retinal vein and a separate network of veins (belonging to the choroid).

Secondary prevention of systemic risk factors

Patients must be monitored and treated appropriately for hypertension, diabetes, hypercholesterolaemia, hyperviscosity and cardiovascular disease, as these are underlying causes of recurrence of retinal vein occlusion in the same or unaffected eye (*Table 5*). Lifestyle factors and pharmacological treatment prescribed by the patient's GP or internal physician where appropriate. For retinal vein occlusion secondary to hyperviscosity syndromes, haemodilution aims to lower blood viscosity to facilitate retinal microcirculatory flow. Oestrogen containing hormone replacement therapy is relatively contraindicated in women with retinal vein occlusion and oral contraceptive use is the most common underlying association so both therapies should be avoided (Royal College of Ophthalmologists, 2010).

Prognosis

Good prognostic factors for improved visual outcome include good baseline visual acuity, limited areas of retinal ischaemia, systemic normotension, younger age at diagnosis and female sex. In non-ischaemic central retinal vein occlusion, 10% of cases may resolve with normal visual acuity, but around 34% will progress to ischaemic central retinal vein occlusion by 3 years. Ischaemic central retinal vein occlusion has a poorer prognosis with progression to rubeosis iridis in 37% by 4 months, and highest risk if baseline visual acuity is less than 6/60. Branch retinal vein occlusion is associated with the best prognosis as half of all cases recover with a visual acuity of 6/12 or better.

Despite the 57% risk of macular oedema, and 20% risk of neovascularization of the retina (within the first 6–12 months), the risk of secondary glaucoma is low. By 4 years, central retinal vein occlusion and branch retinal vein occlusion may develop in the unaffected eye in 7% and 6.6% of cases respectively. Thus it is fundamental that underlying risk factors are

addressed (The Central Vein Occlusion Study Group, 1995, 1997; Royal College of Ophthalmologists, 2010).

Association of central retinal vein occlusion with myocardial infarction and stroke

Despite the well-documented association with cardiovascular risk factors there remains conflicting evidence regarding the cardiovascular and cerebrovascular-related mortality of patients with retinal vein occlusion. Pooled data from the Beaver Dam Eye Study and the Blue Mountains Eye Study showed the risk of cardiovascular mortality was double in patients under 70 years of age with retinal vein occlusion, although there was no relation to cardiovascular or cerebrovascular-related death in patients of all ages (Cugati et al, 2007). Studies from the USA and UK have shown that event rates for myocardial infarction have been similar between patients with retinal vein occlusion and controls, but there is a trend towards increased mortality from stroke in patients with retinal vein occlusion (Tsaloumas et al, 2000; Werther et al, 2011).

Conclusions

Central retinal vein occlusion is a common cause of unilateral visual loss, recognizable on examination by its striking features. This should prompt an immediate ophthalmic referral to prevent sight-threatening and irreversible sequelae of neovascularization with specialist treatment. Importantly, many of these patients have a history of cardiovascular disease, hypertension, hypercholesterolaemia or diabetes mellitus, which need to be addressed by a general physician. Younger patients presenting with retinal vein occlusion must also be worked up for thrombophilias and coagulation abnormalities. Secondary prevention is key to prevent risk to the contralateral eye as well as morbidity and mortality from stroke and myocardial infarction. BJHM

Conflict of interest: none.

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Table 5. Targeted medical management of risk factors for retinal vein occlusion

Hypertension	Target blood pressure less than 140/85 mmHg or less than 130/80 mmHg if co-existing diabetes	
Hypercholesterolaemia	Statins to maintain cholesterol under 4.8 mmol/litre	
Diabetes	Diagnosis: World Health Organization blood glucose criteria or glycated haemoglobin criteria	
	Target glycated haemoglobin: less than 7%	
Aspirin	Indications providing blood pressure control is satisfactory	Hypertension with 10-year risk of coronary heart disease >15% or
		10-year risk of total cardiovascular disease is >20%
	Contraindications: peptic ulcer, allergy, haemorrhage and during initial stages of severe haemorrhagic retinal vein occlusion	

KEY POINTS

- Dilated, tortuous veins and extensive retinal haemorrhages in affected quadrants may be seen on fundoscopy.
- Screen patients for modifiable risk factors include hypertension, diabetes, hypercholesterolaemia, smoking, physical inactivity and glaucoma.
- Specialist tests are indicated for thrombophilias or vasculitis especially in young patients.
- On examination, check for loss of visual acuity and relative afferent pupillary defect heralding ischaemia.
- Request an urgent ophthalmic referral to assess intraocular pressures and sight-threatening complications of neovascularization.