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Retinal Artery Occlusion and Neurovascular Risk

Introduction

An occlusion of the central retinal artery (CRA) or one of its branches can lead to severe acute vision loss. Patients rarely recover functional visual acuity (VA) in the affected eye, however good visual recovery can occur in transient retinal artery occlusion (RAO). Several treatment strategies have been described in the acute setting of a retinal artery occlusion (RAO). However, to date, no evidence- based treatments exist for this condition.[1] Recently, several clinical studies have emphasized the higher risk of stroke and cardiovascular events (CVE) in patients with RAOs.[2] As a result, urgent assessment of neurovascular risk factors in the context of an acute RAO is widely recommended.[2]

Definition

RAO refers to disruption of blood flow to the inner retinal layers leading to ischemia. RAO is further classified as a central retinal artery occlusion (CRAO) or a branch retinal artery occlusion (BRAO), based on the size and location of the retinal artery involved.

The definition of a stroke by the American Stroke Association is “brain, spinal cord, or retinal cell death attributable to ischemia, based on neuropathological, neuroimaging, and/or clinical evidence of permanent injury”.[3] While, retinal tissue and brain tissue are morphologically distinct, and tolerate acute ischemia differently, RAO is recognized as a type stroke by several professional bodies.[4,5]

Epidemiology and Risk Factors

The incidence of RAO is 1–2 per 100 000, and rises to 10 per 100,000 over the age of 80. Men have a slightly higher incidence than women.[5] The incidence of asymptomatic branch retinal emboli is far higher, and has been reported as 2.9% in patients aged 50 and over.[6]

RAO is associated with a myriad of vascular risk factors. There is a high prevalence of obesity, hypertension, tobacco use, hypercholesterolemia, and diabetes in CRAO patients.[5] In 30%–40% of cases, CRAO is associated with ipsilateral

internal carotid artery stenosis of greater than 70%.[7] The heart, aortic arch and great vessel can also cause emboli that block the central retinal artery or one of its branches.[5] Atrial fibrillation (AF) is more common in CRAO patients, when compared to age- and sex-matched controls. Furthermore, RAO patients with AF are more likely to have a recurrent stroke.[2] Therefore, promptly investigating RAO patients for vascular risk factors is of utmost importance.

RAO can also be due to other causes, such as an inflammatory process, an iatrogenic cause, an infectious etiology, or a hematologic disorder. While discussion of all possible etiologies of an RAO is beyond the scope of this article, giant cell arteritis (GCA)-associated CRAO should be suspected in patients over age 50, with systemic findings such as jaw claudication, polymyalgia rheumatica, diffuse posterior neck pain, scalp tenderness, new-onset headache, or elevated inflammatory markers.[5] In 1.6% of cases, CRAO was the cause of permanent visual loss in a large cohort of biopsy-proven GCA patients.[8]

Pathophysiology

The inner retina is supplied by the CRA, a branch of the ophthalmic artery, while the outer retina is supplied by the posterior ciliary circulation. Experimental studies have shown that 60 minutes of CRA blockage produces no permanent ischemic damage; however, greater than four hours of CRA blockage produces permanent irreversible ischemic retinal damage.[4] Thus, duration of CRA blockage is an important determinant of visual outcome. Up to 20%–30% of patients have a cilioretinal artery, which originates from the posterior ciliary circulation and often supplies the fovea.[5] In such cases, a CRAO patient may present with normal VA, but a severely affected visual field.

Diagnosis

RAO is associated with sudden painless monocular vision loss. Funduscopic examination will typically show retinal whitening in the area of occlusion. In a CRAO, A cherry red spot may be visible due to the preserved choroidal circulation subfoveally, surrounded by a pale ischemic retina. In an RAO, retinal emboli and segmental blood flow through attenuated retinal arteries may also be observed. Pallid optic nerve swelling accompanying an RAO should raise suspicion for an arteritic cause (GCA). Imaging modalities such as optical coherence tomography (OCT), OCT angiography and fluorescein angiography (FA) can help identify an RAO. In an acute RAO, OCT can rapidly show thickening and irregularity of the inner layers. FA can show delayed or absent retinal perfusion; however, this imaging modality is not required to establish a definitive diagnosis.[5]

Natural History

CRAO is associated with a poor visual prognosis. Over three-quarters of patients have a VA of counting fingers or worse.[5] Approximately 18% of patients spontaneously recover VA of 20/200 or better. Colour vision, visual field and stereoacuity are also severely affected in CRAO patients. BRAO has a better visual prognosis, given that a limited area of the retina is affected.

Treatment

Patients with a suspected RAO should be sent to the nearest hospital Emergency Department (ER) for acute stroke work-up.[9]

Over the decades, numerous treatments have been attempted to restore perfusion and/or reverse retinal cell death in RAO patients.[1] Conservative approaches to improve VA in RAO include digital massage, topical IOP lowering drops, anterior segment paracentesis, carbogen inhalation, and hyperbaric oxygen therapy. To date, there is insufficient evidence to demonstrate that conservative treatment produces a better prognosis compared to the natural history of acute artery occlusions.[1]

More aggressive treatments for RAO include Nd:YAG laser embolysis and thrombolytic therapy. Non- controlled clinical studies have shown VA improvement after 24 hours with translumenal Nd:YAG laser embolysis to selectively fragment and dislodge the intravascular embolus.[1] However, these approaches have significant risks such as vitreous hemorrhage and subretinal hemorrhage. A meta-analysis of observational studies has shown a functional benefit from treatment with intravenous thrombolysis within a 4.5-hour window of CRAO onset.[1] However, serious adverse events such as intracranial hemorrhage have been reported in clinical trials evaluating intravenous thrombolysis within 20 hours of visual loss.[1] The impact of early (within 4.5hrs) intravenous thrombolysis in acute CRAO is currently being evaluated in a few prospective randomized clinical

trials in Europe. The results of these trials will help further clarify the role of intravenous thrombolysis in the management of an acute CRAO.[10,11] Intra-arterial thrombolysis via supraselective microcatheterization of the ophthalmic artery was evaluated in the EAGLE study within 24 hours of symptom onset. The rationale of this modality was to reduce systemic risk by delivering the thrombolytic drug closer to the site of occlusion. The study was prematurely stopped due to adverse events.[12] A 2023 Cochrane Review on interventions for acute non-arteritic CRAO determined that there is insufficient evidence to support the above-mentioned interventions.[1]

Secondary Prevention

For RAO patients, the objective is to prevent further vascular events. The evidence for stroke after ischemic retinal events has been steadily increasing over the last decade.[7] A U.S. study using 2013 National Medicare datasets found a 28-fold and 33-fold increased incidence of ischemic stroke in the first and second weeks following a CRAO respectively.[13] A population-based study from Taiwan found a 2.7 times higher rate of stroke within the first three years of a CRAO compared with matched controls, and the incidence was highest within the first month.[14] A Korean study reported a 70-fold increase in ischemic stroke within the first week after a CRAO.[15] In patients with acute RAO, urgent referral to the hospital ER expedites work-up, identifies high-risk patients, and facilitates early preventive treatment to reduce the risk of stroke and CVEs.[1]

Neuroimaging does not aid in the diagnosis of an acute RAO; however, it may reveal concomitant cerebral ischemia and help guide secondary prevention strategies. One study of a CRAO cohort from a tertiary care centre demonstrated radiologic evidence of stroke in 37.3% of patients.[16]

High-grade carotid artery stenosis should be identified promptly with computed tomography/magnetic resonance angiography or carotid ultrasound, and treated as symptomatic carotid stenosis. Treatment includes surgical revascularization or medical therapy, depending on the patient's surgical risk profile.[7] Secondary prevention in RAO often includes initiation of antiplatelet therapy.[2]

Further evaluation for a nidus of embolic disease in RAO includes echocardiography to identify a structural cardiac lesion and cardiac rhythm monitoring to identify AF.[2] If AF is discovered, oral anticoagulation is often recommended to prevent a stroke.[2]

RAO management requires a multidisciplinary approach involving neurology, ophthalmology and internal medicine, to control modifiable risk factors and monitor for complications.

Future Directions

Improving visual outcomes in acute RAO and reducing future vascular events remain important unmet needs. Given its relatively low incidence, robust randomized clinical trials at earlier time points are challenging to execute. Development of local networks between primary care physicians, optometrists, ophthalmologists and neurologists with stroke expertise should expedite care and facilitate recruitment for clinical trials evaluating potential treatments for acute RAO.

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