Review

Journal of INTERNATIONAL MEDICAL RESEARCH

Journal of International Medical Research
2023, Vol. 51(9) 1–12

DOI: 10.1177/03000605231198388
journals.sagepub.com/home/imr

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Progress in central retinal artery occlusion: a narrative review

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Abstract

Central retinal artery occlusion (CRAO) is a catastrophic ophthalmic emergency that severely impairs a patient's visual function, often reducing visual acuity to counting fingers or worse. Progress in CRAO research has provided new information regarding its epidemiological characteristics and led to useful assessments through various ophthalmic examinations. Additional insights about CRAO have been gained through studies of its pathophysiological mechanisms, improving intervention timing and enhancing patient prognosis. Treatment for CRAO has evolved, particularly with assistance from surgical instruments and surgical robots. Although surgical treatment is now possible, this option is not widely recognized by ophthalmologists. Conservative therapies have limited benefits compared with the natural course of disease. Recently, pars plana vitrectomy plus endovascular surgery has received considerable interest among ophthalmologists because of its potential efficacy in the treatment of CRAO. Considering the inconsistencies in rationale and efficacy of CRAO treatment modalities, it is important to distinguish between treatment effects and the natural courses of various CRAO subclasses. This narrative review explores progress in CRAO epidemiology, pathophysiology, ophthalmic examination, and treatment.

Keywords

Central retinal artery occlusion, epidemiology, pars plana vitrectomy, treatment, intra-arterial thrombosis, intravenous thrombosis

Date received: 8 May 2023; accepted: 14 August 2023

Introduction

Central retinal artery occlusion (CRAO) is an ophthalmic emergency involving acute retinal ischemia caused by the obstruction of the central retinal artery (CRA), which can result in catastrophic damage or

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complete loss of visual function.[1] This narrative review explores progress in CRAO epidemiology, pathophysiologic mechanisms, clinical assessment by various ophthalmic examinations, and novel treatments.

Search strategy

PubMed, the Cochrane Library databases, Embase, and the China National Knowledge Infrastructure (CNKI) were searched up to 30 September 2022, using the following keywords: central retinal artery occlusion, CRAO, epidemiology, pathophysiologic mechanism, ophthalmic examination, treatment, advance, and surgery.

Epidemiology and risk factors

Regional studies have revealed that the age-adjusted standardized incidences of CRAO are 2.7 per 100,000 person-years (all ages) and 93.0/100,000 person-years (people aged >80 years) in Germany,[2] 2.53/100,000 person-years (all ages) and 47.5/100,000 person-years (people aged >80 years) in Japan,[3] 2.00/100,000 person-years (all ages) and 26.01/100,000 person-years (people aged >80 years) in Korea,[4] and 1.87/100,000 person-years (all ages) in the United States.[5] Thus, the incidence increases with age. Generally, the incidence is higher in men than in women; for example, studies in Korea[6] and in Japan[3] have shown that the respective incidences in men are 1.51-fold and 1.4-fold higher than the incidences in women. CRAO seriously affects a patient's quality of life and increases the likelihood of subsequent cardio-cerebrovascular events.[7] In one study, 30% of patients with acute CRAO displayed acute cerebral ischemia on magnetic resonance imaging.[8] A nationwide study revealed that patients with CRAO were younger than patients with cerebral ischemic stroke.[9] Notably, CRAO and cerebral ischemic stroke share similar risk factors, including systemic comorbidities (critical carotid disease, hypertension, tobacco use, hyperlipidemia, cardiac valvular disease, migraine, sickle cell disease, atherosclerosis, aortic disease, aneurysm, diabetes, and carotid and coronary artery diseases).[10–12]

Pathophysiology

The CRA, a branch of the ophthalmic artery, originates from the internal carotid artery and supplies blood to inner layers of the retina and the optic disc surface; blood is supplied to outer layers of the retina by choroidal capillaries that originate from branches of the posterior ciliary artery.[12] Two studies using fundus fluorescein angiography (FFA), the gold standard for cilioretinal artery screening, revealed that at least one cilioretinal artery was present in 32.1% of 2000 eyes[13] and 825 (40.2%) of 2050 eyes.[14] The cilioretinal artery, which originates from the posterior ciliary artery, is generally responsible for maintaining central vision in patients with CRAO. However, 52.3% of eyes with a cilioretinal artery exhibit insufficient supply to the macular area because of variability in lumen diameter and the region supplied by the cilioretinal artery.[14]

Staging of CRAO

A systematic review[15] of experimental and clinical studies regarding CRAO by Tobalem et al. revealed several key findings. Twelve to 15 minutes of complete (i.e., total) CRAO is sufficient to cause irreversible ganglion cell death; subsequent treatment is likely to be futile. In contrast, incomplete CRAO can often be effectively treated within several hours after onset. The time until emergency treatment has substantial clinical and medicolegal implications. Accurate recognition is essential because it allows ophthalmologists to

rapidly determine whether to initiate surgical treatment and predict the efficacy of such treatment.[16,17] There are three stages of CRAO: incomplete, subtotal, and total.[16] These stages have the following clinical characteristics. Incomplete CRAO is characterized by reduced visual acuity, an inconspicuous cherry-red spot on the retina, mild retinal edema, and delayed blood flow. Subtotal CRAO is characterized by severely decreased visual acuity, a conspicuous cherry-red spot on the retina, and substantially diminished/interrupted blood flow; the artery exhibits a "cattle track" sign. Total CRAO differs from subtotal CRAO in that there is no light perception and no blood flow in the perimacular arterioles.

Features of retinal emboli

According to their contents, three main types of emboli can be identified in the retinal arterial circulation: cholesterol, platelet-fibrin, and calcified.[18] Cholesterol emboli are the most common type (much more common than the other two), whereas platelet-fibrin emboli and calcified emboli are considerably less prevalent. Cholesterol emboli are yellow or copper-colored entities with a spherical or rectangular shape; they usually originate from ulcerated atherosclerotic lesions in the carotid arteries.[19,20] Platelet-fibrin emboli are mobile, dull, grayish-white entities that originate from carotid and intracardiac thromboses.[21,22] Calcified emboli are white solid entities with an oval shape that typically originate from calcified aortic stenosis; they also occur in patients with mitral valve disease or aortic valve disease.[23,24] Periarteriolar sheathing, a post-embolic phenomenon in some patients with cholesterol or calcified CRAO, is regarded as a giant cell reaction and a type of injury-induced endothelial cell proliferation.[25] Almost all cases of CRAO with periarteriolar sheathing are caused by cholesterol embolization. With respect to the distribution of emboli in retinal arterioles, all three types of emboli tend to be located in the optic disc or temporal arterioles.[18] Periarteriolar sheathing is also much more common in the temporal circulation. In patients with CRAO, 17% of retinal emboli are visible with an ophthalmoscope, and approximately half of these are platelet-fibrin emboli.[26]

Types of CRAO

Based on its clinical manifestations and etiology, CRAO can be categorized into four clinical subclasses[1]: non-arteritic permanent, arteritic, non-arteritic with cilioretinal artery sparing, and non-arteritic transient.

Non-arteritic permanent CRAO is the most common type, present in more than two-thirds of patients with CRAO. Among patients with this type of CRAO, 93.2% present with visual acuity of counting fingers or worse; only 22% display any improvement within 1 week after onset. Typical characteristics include a cherry-red spot, grayish retinal edema, retinal artery narrowing, and minimal or no residual retinal circulation on FFA.[1]

Non-arteritic transient CRAO resembles a transient ischemic attack and is present in approximately 16% of patients with CRAO; it has the best visual prognosis among the four types. Restoration of blood flow allows symptoms to resolve, such that 82% of affected patients eventually demonstrate visual improvement and 37.9% achieve visual acuity of 20/40 or better within 7 days after onset.[1] Causative factors include (but are not limited to) a rapid decrease in perfusion pressure or rapid increase in intraocular pressure (IOP), migration of emboli, and vasospasm.[27] Ocular recurrence and cerebrovascular events are possible: 22.2% of patients treated for non-arteritic transient CRAO experience ipsilateral stroke within 5 years.[28]

Non-arteritic CRAO with cilioretinal artery sparing is present in approximately 14.3% of patients with CRAO.[1] Although this type of CRAO is permanent, supply from the cilioretinal artery may allow affected patients to exhibit good central visual acuity. Visual acuity significantly improves in 67% of affected eyes, and 20% of all eyes maintain visual acuity of 20/40 or better at 7 days after onset.[1]

Arteritic CRAO, present in 4.5% of patients with CRAO, has the worst prognosis among the four types.[1] The most common cause is giant cell arteritis (GCA), an idiopathic vasculitis that mainly affects the head and upper body in older adults; it nearly always leads to stenosis and occlusion of small to medium-sized arteries.[29] Superficial temporal artery biopsy is important for the diagnosis of GCA. Typical features include concentric intimal hyperplasia, disruption of the internal elastic lamina, and infiltration of multinucleated giant cells; notably, the absence of giant cells on biopsy does not exclude the possibility of GCA.[30] Nearly all eyes with GCA-induced CRAO also exhibit arteritic anterior ischemic optic neuropathy.[31] The diagnosis can be confirmed by an elevated C-reactive protein level; increased erythrocyte sedimentation rate; and the presence of fever, systemic headache, otalgia, and chewing pain. Because the ophthalmic artery is involved in the pathogenesis of arteritic CRAO, both the CRA and ciliary artery are blocked, hindering improvements in visual acuity unless high-dose corticosteroids are administered.[32]

Ophthalmic examination

FFA

Eyes with CRAO display longer CRA perfusion time, compared with normal eyes, as well as incomplete retinal perfusion.[33] One study identified three types of FFA findings in 63 patients with CRAO: exudation, poor perfusion, and mixed.[34] The exudation type is characterized by normal circulation time and prominent fluorescein leakage. The poor perfusion type is characterized by an arm to retina time >23 s and normal (or slightly stained) vessel walls. The mixed type has both prominent leakage and arm to retina time >23 s. Patients with the poor perfusion type are more likely to experience visual impairment, compared with patients who exhibit the exudation type.[34]

Indocyanine green angiography (ICGA)

In the late phase of ICGA, rouleaux-like hyper-cyanescent spots can occur because of red blood cell aggregation in the retinal circulation.[35] Additionally, delayed choroidal indocyanine green fluorescence perfusion is visible in the acute phase of CRAO.[35–37] Ultra-widefield ICGA is superior to FFA in terms of identifying choroidal hypoperfusion among patients with GCA-induced CRAO.[37] Therefore, ICGA is a useful clinical investigation in cases of suspected GCA.

Enhanced depth imaging-assisted optical coherence tomography (EDI-OCT)

As a non-invasive imaging system, EDI-OCT is an essential tool for detecting morphological changes in the retina and choroid; it allows accurate documentation and staging of CRAO severity, along with a general assessment of the visual outcome.[38] The degrees of inner and outer retinal edema in the acute phase, as well as subsequent thinning of the retina and choroid, can be clearly detected by EDI-OCT. Features of incomplete CRAO include mild or no inner retinal thickening and increased reflectivity. Subtotal and total CRAO commonly display photoreceptor defects and outer retinal thinning. Choroidal hypoperfusion is a distinct sign of total CRAO,[16]

consistent with the reduction of subfoveal choroidal thickness in most patients with this type of CRAO.

Optical coherence tomography angiography (OCTA)

OCTA, a non-invasive technique based on OCT, uses en face vascular maps to quantify residual perfusion of the superficial and deep capillary beds in patients with CRAO.[39] Extensive disruption of the superficial and deep capillary plexus is visible, but disruption is greater in the superficial capillary plexus.[40] OCTA monitoring may permit early non-invasive detection of capillary reperfusion after CRAO therapy, facilitating estimation of treatment efficacy.[40–42]

Treatments for CRAO

Thus far, there is no gold standard treatment for CRAO. A guideline for various types of retinal artery occlusion reported several non-surgical treatment approaches for this disease, but there is a lack of high-quality evidence-based clinical trials to support specific treatments.[43] Clinical management currently includes conservative treatments such as digital massage, topical IOP-lowering therapies, carbogen inhalation, vasodilation, anterior chamber paracentesis, and hyperbaric oxygen chamber therapy; relatively aggressive treatments are also available, such as thrombolytic therapy and neodymium-doped yttrium aluminum garnet (Nd:YAG) laser embolysis.[16,44] No large-scale randomized controlled trials have demonstrated that conservative treatment produces a better prognosis compared with the natural course of disease.[43]

Vasodilation

The main principle of vasodilation involves improving tissue ischemia via retinal artery dilation, which briefly increases the retinal supply of oxygenated blood.[44]

IOP-lowering treatment

The main principle of IOP-lowering treatment involves improving the perfusion of blocked vessels by lowering the patient's IOP and increasing overall retinal perfusion, leading to distal movement of the emboli. However, a study in 2010 revealed no difference in visual prognosis after IOP-lowering treatment, compared with the natural course of disease.[45]

Hyperbaric oxygen chamber therapy

Hyperbaric oxygen chamber therapy aims to maintain retinal function and restore vision by providing hyperbaric oxygen to facilitate adequate oxygen diffusion from the outer layer of the retina (supplied by the choroidal circulation) to the inner layers of the retina (supplied by the CRA).[46] In a case series of 45 patients, Sunny et al. found that the mean best corrected visual acuity improved from 1.87 ± 0.25 logarithm of the minimum angle of resolution (logMAR) to 1.41 ± 0.63 logMAR after treatment. Middle ear barotrauma and hypoglycemia are known complications of this treatment approach.[47]

Thrombolytic therapy

Thrombolytic therapy has been controversial because of its potential efficacy and concomitant complications. Thrombolytic therapy was originally performed in patients with acute stroke, which shares some characteristics with CRAO; it has since been successfully used in the treatment of CRAO.

Intravenous thrombosis. Chen et al.[48] performed a randomized controlled trial in which, within 24 hours of symptom onset, intravenous recombinant tissue plasminogen activator (tPA) or intravenous saline

was administered to patients with clinically defined CRAO. After a total dose of 0.9 mg/kg tPA, 25% of the tPA group displayed $\geq$3 lines of improvement in visual acuity, compared with no significant improvement in the placebo group. One of eight patients in the tPA cohort experienced intracranial hemorrhage and ultimately survived with residual pyramidal deficits. In a case series, Hattenbach et al.[49] assessed visual acuity among patients with CRAO who had received 50 mg tPA and concomitant intravenous heparinization. Only nine of 28 eyes (32%) in 28 patients displayed $\geq$3 lines of improvement in visual acuity. In a patient-level meta-analysis, Schrag et al.[50] showed that visual acuity improved within 4.5 hours in 50% of patients with CRAO who received intravenous thrombolytic treatment; similar findings were strongly confirmed in an updated meta-analysis[51] and three other cohorts in the past decade.[52–54] According to a statement endorsed by the North American Neuro-Ophthalmology Society, tPA may be an option for the treatment of CRAO; however, a thorough discussion between the patient and treating physician is warranted (including an acknowledgement of the procedural limitations), considering the 30% incidence of concomitant cerebral ischemic stroke.[55]

Intra-Arterial Thrombolysis (IAT). The delivery of tPA into the ophthalmic circulation via super-selective microcatheter insertion, also known as IAT, is expected to reduce the risks of systemic and intracranial hemorrhage while increasing the direct thrombolytic effect on the thrombus.[56] In a case series of 249 IAT-treated patients with CRAO, Biousse et al. reported that 87 patients (34.9%) exhibited four Snellen lines of improvement in visual acuity.[57] The results of another non-randomized study[58] suggested that IAT may be effective in terms of improving visual acuity, but there was obvious heterogeneity in the duration of treatment (3.4 ± 2 hours in the IAT group and 25.8 ± 20 hours in the conservative treatment group). Schumacher et al.[59] performed the only prospective randomized trial thus far concerning the efficacy of IAT compared with conservative therapy. The study was terminated early because of patient safety concerns and the lack of a statistical difference in visual acuity. Notably, one patient in the IAT group developed cerebral hemorrhage; another patient in that group developed cerebellar hemorrhage. Temporary microcatheterization of the ophthalmic artery is generally not recommended because of the increased risk of arterial dissection and limited likelihood of visual benefit.

Nd:YAG laser embolysis

Nd:YAG laser embolysis uses infrared laser energy to non-invasively fragment emboli under a fundus contact lens. Man et al. conducted a meta-analysis of 61 patients with various types of retinal artery occlusion who had been treated with Nd:YAG laser embolysis, including 14 patients with CRAO; they found that 87% of the patients experienced some degree of visual improvement.[60] These findings suggest that Nd:YAG laser embolysis has the potential to improve visual acuity in patients with CRAO; however, the patients also had complications such as retinal and vitreous hemorrhage. Visible emboli, which represent only 17% of all emboli, are the main focus of Nd:YAG laser embolysis; this proportion is sufficiently low that Nd:YAG laser embolysis cannot be regarded as routine therapy.

Pars plana vitrectomy (PPV) plus endovascular surgery

The new approach of PPV plus endovascular surgery has received interest from an

increasing number of vitreoretinal surgeons.[61] Despite the inherent challenges, these new technologies have contributed to robust progress in CRAO management. Surgeons can perform more stable and accurate cannulation using digitally assisted robotic devices and three-dimensional visualization systems.[62–64] Notably, three-dimensional vitrectomy offers higher resolution and enhanced depth of field throughout the procedure, during which micropipette or microneedle placement must be stable for several minutes.

Takata et al. reported significant visual improvement in two patients with CRAO who underwent PPV plus endovascular surgery more than 8 hours after onset.[65] After the PPV procedure, a custom-designed microneedle was inserted into the retinal artery at the optic disc, and 0.1 to 0.2 mL of tPA was injected into the artery. This approach is distinct from IAT because the simultaneous presence of white arteries and veins was regarded as a successful injection, leading to greater pressure in the artery wall compared with IAT. This increased pressure promotes thrombolysis and helps to dislodge the emboli.

Kadonosono et al. conducted a similar study.[17] To minimize intraoperative bleeding, they performed surgery under local anesthesia with systolic pressure below 120 mmHg. After PPV procedures, 0.4 mL of tPA was injected into the CRA with an approximately 47-gauge microneedle at a pressure of 30 pounds per square inch. Visual acuity improved in all patients with incomplete and subtotal CRAO (mean onset time of 37.8 [range, 26–48] hours); only patients with total CRAO experienced no improvement. These findings are consistent with the theory established by Tobalem et al.[15]

It is important to note that the approach of PPV plus endovascular surgery should be performed by experienced PPV ophthalmologists; both Takata et al. and Kadonosono et al. reported postoperative vitreous hemorrhage and a need for additional surgeries.

PPV plus intraoperative IOP management

Methods to lower IOP lead to increased perfusion pressure within the CRA, thereby dislodging emboli. Using different approaches for PPV plus intraoperative IOP management, two recent studies[66,67] demonstrated improvements in visual acuity; notably, one patient recovered from no light perception to 20/20 within 1 month after surgery.

Okonkwo et al. performed PPV surgery under general anesthesia, with IOP controlled by a compensatory infusion system.[67] After PPV procedures, IOP was set to <3 mmHg for 3 minutes; the infusion system was completely stopped for an additional 6 minutes. During this stage of treatment, the authors gradually raised the patient's blood pressure to a maximum of 165/100 mmHg for 6 minutes. Reperfusion of the CRA and central retinal vein was observed when IOP was set to <3 mmHg, and perfusion considerably increased as blood pressure rose. One patient underwent surgery at 9 days after CRAO onset; their vison improved from counting fingers to 6/60 within 6 months postoperatively. Another patient underwent treatment 15 hours after initial presentation; their visual acuity increased from counting fingers to 6/36 + 1 within 2 months postoperatively.

Altun described an alternative approach to control IOP during surgery.[66] After conventional vitrectomy, cyclical changes in IOP were induced at a location near the optic nerve head. The active suction pressure was set to 35 mmHg for 5 s, and the continuing infusion pressure was set to 15 mmHg for 15 s. After 11 cycles, CRA reperfusion was achieved. The patient had undergone surgery 2 hours after CRAO onset; that patient's visual acuity progressed from no light perception to 20/100

on the first day, 20/40 within the first week, and 20/20 within the first month postoperatively.

PPV plus intraoperative IOP management appears to have relatively few complications; neither Okonkwo et al. or Altun reported any complications during or after surgery, perhaps because of the limited number of cases involved or the lack of arterial wall penetration.

Management of arteritic CRAO

Prompt and urgent action is needed when arteritic CRAO is confirmed or suspected to preserve the affected and fellow eyes.[68] Routine therapy should consist of high-dose (500–1000 mg) methylprednisolone over 3 days, followed by high-dose prednisone.[69] The British Society of Rheumatology recommends 75 mg of oral aspirin daily.[70]

Secondary prevention

In addition to treatment for acute CRAO, there is a need to emphasize screening for cerebrovascular risk factors. Substantial evidence suggests that CRAO is the result of secondary cerebrovascular events; a prompt and comprehensive diagnostic work-up is needed after CRAO onset, even in the absence of neurological symptoms.[71] One study showed that, within 7 days after onset, 24% to 24.2% of patients with CRAO had a concomitant acute ischemic stroke visible on magnetic resonance imaging.[71,72] At 3 years after CRAO onset, affected patients have a 2.7-fold increased risk of stroke compared with controls, and a 3.34-fold increased risk among individuals aged <60 years.[7] The relative incidence rate ratios of stroke or acute myocardial infarction significantly increased within 1 month after CRAO (14.0; 95% confidence interval, 8.90–22.00); they were highest during the first week after CRAO (44.51; 95% confidence interval, 27.07–73.20).[73] Therefore, close multidisciplinary collaboration between ophthalmologists and neurologists is needed to prevent secondary impairments.

Conclusions

As an ophthalmic emergency, CRAO poses a challenge for clinical management. However, progress in technologies and diagnostic modalities, particularly the introduction of PPV surgery, has enhanced possible treatments for CRAO. Large-scale, multicenter randomized controlled trials are needed to evaluate current treatment options and improve CRAO management.

Author contributions

Conceptualization, W.L. and D.B.; methodology, W.L. and D.B.; validation, L.K.; writing—original draft preparation, W.L. and D.B.; writing—review and editing, W.L. and L.K.; supervision: L.K. All authors have read and agreed to the published version of the manuscript.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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