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Capturing the occult central retinal artery occlusion using OCT

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Abstract

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Aims: To report spectral domain optical coherence tomography (OCT) findings in cases of impending or occult central retinal artery occlusion (CRAO) in which a diagnosis other than CRAO was made on initial presentation.

Methods: Retrospective, observational case series of patients diagnosed with CRAO for whom on initial presentation fundal examination and OCT findings were deemed unremarkable and/or a diagnosis other than CRAO was made. OCT images from the initial presentation were then reviewed for evidence of inner retinal ischaemia.

Results: 214 cases of CRAO were identified. 11 patients (5.14%) had been given an alternative initial diagnosis at their first presentation in casualty and were included. The age range was 20-84 years and 81% (9/11) were male. On review of initial OCT imaging performed in casualty, all cases had evidence of inner retinal ischaemia.

Conclusions: CRAO is an ophthalmic emergency which leads to vision loss which is often irreversible. Examination of the fundus may be normal early in the course of the disease and therefore a timely diagnosis may be missed. This case series reports the OCT findings of inner retinal ischaemia in patients with occult or impending CRAO which may aid in the early diagnosis and referral to stroke services.

Introduction

Central retinal artery occlusion (CRAO) is an ophthalmic emergency. Occlusion of the central retinal artery results in hypoperfusion of the inner retina, leading to rapid cellular damage and ultimately vision loss which is often enduring.[1] The diagnosis may signify a more sinister systemic condition or disease process including infectious, thromboembolic and inflammatory causes.[2] Animal models have shown that irreversible damage occurs at 105 minutes of occlusion, highlighting the importance of early detection and management.[3,4]

Macular oedema and 'cherry red spot' are the established ophthalmic signs used to diagnose CRAO, however examination of the fundus may be normal early in the course of the disease. Imaging diagnostic techniques include spectral-domain optical coherence tomography (OCT), providing real-time high-resolution retinal images which may provide objective evidence aiding diagnosis. OCT is a non-invasive imaging modality that has been pivotal in the clinical practice of ophthalmology and allows the user to obtain high-resolution cross-sectional images of the optic nerve head, retina and retinal nerve fibre layer.[5] OCT is not routinely performed in the work-up of retinal artery occlusion (RAO) and its role is still evolving.

OCT findings of impending or occult CRAO without cherry red spot have not been well described in the literature. To our knowledge, this is the first case series aiming to report on the OCT findings of impending or occult CRAOs. In this study, all patients that were initially given a diagnosis other than CRAO had their OCTs reviewed for evidence of inner retinal ischaemia. These cases may help to provide a window into the earlier detection of CRAO and therefore potential for intervention if effective treatments are developed in the future.

Methods

This was a retrospective case series review conducted at the large tertiary unit of Moorfields Eye Hospital NHS Trust, London, United Kingdom from June 2017 to June 2020. This study was registered and approved locally (MEH662) and followed the Helsinki declaration. Patients were identified from the hospital's electronic medical records system. Patients with a diagnosis of CRAO were identified who had at least one visit to the eye casualty prior to clinic diagnosis and then a subsequent follow-up in the hospital's eye clinics. All patients had a full ophthalmic work-up including exclusion of alternative diagnoses such as giant cell arteritis (GCA) on the basis of clinical examination and labs. Patients who were correctly diagnosed with CRAO on their initial casualty visit were excluded. All patients had been seen by a minimum grade of a fellow or third year senior resident ophthalmologist with the presenting fundus findings not having any features of CRAO. OCT images were captured on a DRI Triton (Topcon, Tokyo, Japan) and Heidelberg Spectralis (Heidelberg Engineering, Heidelberg, Germany).

Results

From the 214 patients identified, 11 patients (5.14%) between the ages of 20 to 84 years had been given an alternative initial diagnosis at their first presentation in casualty but then were subsequently correctly diagnosed with CRAO. Clinical characteristics and outcomes of the patients included are summarised in Table 1.

Representative patients 1, 6, 9 and 10 from Table 1 are described in the next section.

Patient 1

A 71-year old man with sudden painless loss of vision in the right eye several hours earlier presented to the eye casualty. His fundus examination was unremarkable with no RAPD and OCT on presentation was reported as normal (figure 1). His platelets, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) were not elevated. His visual acuity (VA) was 2/60 at presentation and he was asked to return the following day for visual field testing. Unfortunately, overnight his vision further deteriorated and on attending for visual field testing the vision had become perception of light (PL) in the right eye. At this point there was a clearly visible cherry red spot on fundus examination with RAPD. A repeat OCT now demonstrated marked inner retinal oedema in the right eye. He was urgently referred to the stroke team and started on the appropriate treatment. He is presently awaiting a CABG (coronary artery bypass graft) and AVR (aortic valve replacement). On review of his presenting OCT with normal fundus examination, evidence of inner retinal ischaemia is apparent (figure 1).

Patient 6

An 86 year old man presented to the eye casualty with sudden onset painless reduction in vision in the left eye. The initial VA was 6/36 and the fundus changes along with OCT was reported as suspected CNV. He was therefore referred to the emergency medical retina clinic for consideration of intravitreal injections and was seen two days after this presentation. His visual acuity had reduced further at this point to counting fingers
(CF) and fundus was pale consistent with CRAO. He was urgently referred on to the stroke team. His OCT imaging (figure 2) from presentation at the eye casualty demonstrates inner retinal oedema consistent with ischaemia and subsequent day 28 OCT shows inner retinal atrophy.

Patient 9

A 78 year old man presented to the eye casualty with sudden onset painless blurred vision in his right eye which he described as “parts missing”. His fundus examination was otherwise reported as unremarkable and OCT was determined to be normal despite having subtle patchy inner retinal hyperreflectivity consistent with ischaemia. He absconded from the eye casualty before further investigations. He then returned four days later to casualty with a further reduction in vision. His VA had decreased from 6/24 to 6/60 and OCT showed (figure 2) increased hyperreflectivity of the inner retinal layers. This was interpreted as cystoid macular oedema (CMO) and he was started on topical non-steroidal anti-inflammatory drugs (NSAIDs) with medical retina follow up in four weeks. In the medical retina clinic he was found to have had evidence of a CRAO in his right eye with vision now CF and RAPD present. He was already taking rivaroxaban so was not given aspirin but referred to the stroke team. He also developed a secondary neovascularisation of the retina and has since had two sessions of pan-retinal photocoagulation. His OCT at 2 months post insult shows inner retinal atrophy. On review of his presenting OCT with normal fundus examination evidence of inner retinal ischaemia is apparent (figure 2).

Patient 10

A 20 year old man presented to the eye casualty following painless loss of vision in his right eye whilst watching television. He described several episodes of a “black curtain” with return to normal vision, and after the third episode it remained permanent. He was otherwise fit and well with no past medical history apart from a maternal history of migraines. His fundus examination was reported as normal with RAPD present and VA of 6/60. His OCT was interpreted as normal and he was started on methylprednisolone with a referral to the neuro-ophthalmology clinic. His VA remained 6/60 and on reviewing the OCT from his initial visit, inner retinal oedema was noted consistent with a retinal artery occlusion (figure 2). He was referred to colleagues in the medical retina clinic and for vascular work-up by the stroke team on the same day. His methylprednisolone was discontinued and aspirin with clopidogrel were started acutely from the eye clinic.

Discussion

The central retinal artery branches off the ophthalmic artery; its occlusion, partial or complete, defines the disease.[4] Further classification can be applied based on the pathogenesis which includes arteritic and non-arteteric causes. The association between CRAO and vasculopathy including strokes has been well documented.[6-12] The incidence of CRAO has been shown to have similar risk factors to strokes; increases with age and more common in men.[12] Consequently, suspected cases are best managed at a stroke centre. A missed diagnosis of CRAO can have devastating consequences for a patient as referral will not be made promptly to medical physicians to initiate appropriate anti-thrombotic medication. As demonstrated in our case series, some patients were referred as late as four weeks after initial presentation in the eye casualty.

The well-established fundal findings of macular oedema and ‘cherry red spot’ are pathognomonic for CRAO. However, clinical findings differ and are based on time from event as well as type of CRAO. Signs shown to be common in the acute phase of the disease (within 7 days) include retinal opacity in the posterior pole (58%), cherry-red spot (90%), cattle trucking (19%), retinal arterial attenuation (32%), optic disk oedema (22%) and optic disk pallor (39%).[13] The avascular nature of the fovea, combined with the absence of ganglion cells, means it is not affected by retinal opacification which gives rise to the characteristic ‘cherry red spot’ sign.[13,14] Although these findings are well documented, early in the course of the disease the fundus may appear normal. Therefore clinicians ought to be careful in relying on a specific finding or a group of clinical features associated with CRAO, as these may not provide a concrete diagnosis and potentially lead to missing this sight threatening disease. In our case series, we describe eleven cases of CRAO with normal fundal examination on initial presentation. The role of OCT imaging in these cases may have been crucial and enabled timely referral to stoke team.

Previous studies have demonstrated a distinctive pattern on OCT imaging in cases of CRAO.[15-18] Acute phase changes have been described as increased reflectivity and thickness confined to the inner retina. Whereas chronic phase changes have been described as decreased reflectivity and thickness of the inner retina with corresponding increased reflectivity of the outer retina, retinal pigment epithelium and choriocapillaris layer.[15-18] Changes in both retinal thickness and reflectivity measured by OCT are seen in CRAO. Wenzel et al.[19] and Ochakowsky et al.[20] sought to establish the temporal changes in retinal thickness in acute CRAO. They demonstrated retinal thickness as a function of time. Chu et al.[21] described OCT findings of inner retinal hyper-reflectivity, as well as a prominent middle limiting membrane in the acute phase (up to 1 month) of CRAO as a pathognomonic sign for

inner retinal ischaemia. This may be a useful marker of acute CRAO particularly when retinal opacities may be subtle or resolving before the development of chronic (after 3 months) atrophic changes[22]. In addition, Chen et al.[23] postulate that optical intensity of the inner retina oedema correlates to visual prognosis.

The mechanism behind these findings are considered to be a result of retinal ischemia leading to cellular damage and retinal oedema in the acute phase, eventually progressing to atrophic changes in the chronic phase.[11] Chen and colleagues,[24] noted that cases of CRAO with a more oedematous retina had smaller cherry-red spots. They suggested the variation in size of cherry-red spots probably also could correspond to the degree of macular oedema. This would be explained by the same speculation that the more oedematous the retina was, the more ganglion cells were displaced toward the central fovea, which in turn might obscure the border of a cherry-red spot.

Patient 8 was suspected to have had a paracentral acute middle maculopathy (PAMM) lesion following uncomplicated cataract surgery. However, after review by a medical retina specialist in clinic he was diagnosed with CRAO and his day 1 post-operative OCT was correctly re-interpreted as diffuse inner retina ischaemia. Interestingly, Yusuf and colleagues,[25] have described a transient retinal artery occlusion (TRAO) phenomenon following cataract surgery in a small case series. They too describe the initial OCT imaging demonstrating inner retinal hyperreflectivity. However, all of their cases were transient in nature with excellent final visual acuity. In patient 8's case there were permanent structural changes with resultant poor vision. Furthermore, given the high degree of retinal oedema it is likely the CRAO lasted for at least 4.5 hours [19].

A recent meta-analysis looking at intra-arterial thrombolysis (IAT) concluded that IAT has great potential but further controlled trials are needed.[26] Evidence is emerging that intravenous fibrinolytic therapy (IFT) may be a more promising treatment modality when used within 4.5 hours[27-29]. Two randomized controlled trials, THEIA NCT03197194 (presently recruiting) under revision, investigating IFT in CRAO with symptom onset within 4.5 hours will evaluate this modality further [30]. Asnovel treatment strategies continue to be investigated and the use of OCT to diagnose CRAO early in its evolution may provide an additional window of opportunity for intervention. For instance, recently Hadanny and colleagues,[31] found hyperbaric oxygen therapy to be effective in CRAO before the onset of a cherry-red spot. They postulate based on their findings that cherry-red spot is a marker for irreversible anoxic retinal damage.

OCT changes in the branch retinal artery occlusion (BRAO) are also well documented [22,32,33]. This study did not aim to identify missed BRAO patients with OCT findings at presentation but careful examination of the OCT would aid diagnosis in these cases also. The OCT findings of patient 3, 4 and 11 were similar in showing inner retinal oedema which was missed at presentation but they were not included in figure 2 as the composite from other patients adequately demonstrates the range of subtle changes which may be seen.

This is the first case series to report on the OCT findings of occult CRAOs. In this study, all patients that were initially given a diagnosis other than CRAO had evidence of inner retinal ischaemia on OCT. As demonstrated by the images in this study, when careful attention is paid to the inner retinal layers comparing to the unaffected eye, it can often become apparent that subtle ischaemia is present. The recognition of inner retinal ischaemia on OCT is often

an under recognised sign in occlusive arterial aetiology. Increased awareness and education on the interpretation of OCT in CRAO may help facilitate prompt recognition facilitating earlier diagnosis and referral to stroke services and therefore potentially reduce patient morbidity and mortality.

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References

1. Farris W, Waymack JR. Central retinal artery occlusion. 2017.
2. Olsen TW, Pulido JS, Folk JC, Hyman L, Flaxel CJ, Adelman RA. Retinal and ophthalmic artery occlusions preferred practice pattern®. Ophthalmology 2017;124(2):P120-P143.
3. Hayreh SS, Kolder HE, Weingeist TA. Central Retinal Artery Occlusion and Retinal Tolerance Time. Ophthalmology 1980;87(1):75-78.
4. Hayreh SS, Zimmerman MB, Kimura A, Sanon A. Central retinal artery occlusion. EXP EYE RES 2004;78(3):723-736.
5. Adhi M, Duker JS. Optical coherence tomography–current and future applications. CURR OPIN OPHTHALMOL 2013;24(3):213.
6. Avery MB, Magal I, Kherani A, Mitha AP. Risk of Stroke in Patients With Ocular Arterial Occlusive Disorders: A Retrospective Canadian Study. J AM HEART ASSOC. 2019;8(3):e010509-e010509.
7. Callizo J, Feltgen N, Pantenburg S, Wolf A, Neubauer AS, Jurklies B, Wachter R, Schmoor C, Schumacher M, Junker B and others. Cardiovascular Risk Factors in Central Retinal Artery Occlusion. Ophthalmology 2015;122(9):1881-1888.
8. Chang Y-S, Chu C-C, Weng S-F, Chang C, Wang J-J, Jan R-L. The risk of acute coronary syndrome after retinal artery occlusion: a population-based cohort study. BR J OPHTHALMOL 2014;99(2):227-231.
9. Helenius J, Arsava EM, Goldstein JN, Cestari DM, Buonanno FS, Rosen BR, Ay H. Concurrent acute brain infarcts in patients with monocular visual loss. ANN NEUROL 2012;72(2):286-293.
10. Kernan WN, Ovbiagele B, Black HR, Bravata DM, Chimowitz MI, Ezekowitz MD, Fang MC, Fisher M, Furie KL, Heck DV and others. Guidelines for the Prevention of Stroke in Patients With Stroke and Transient Ischemic Attack. Stroke 2014;45(7):2160-2236.
11. Lee J, Kim SW, Lee SC, Kwon OW, Kim YD, Byeon SH. Co-occurrence of Acute Retinal Artery Occlusion and Acute Ischemic Stroke: Diffusion-Weighted Magnetic Resonance Imaging Study. AM J OPHTHALMOL 2014;157(6):1231-1238.
12. Park SJ, Choi N-K, Yang BR, Park KH, Lee J, Jung S-Y, Woo SJ. Risk and Risk Periods for Stroke and Acute Myocardial Infarction in Patients with Central Retinal Artery Occlusion. Ophthalmology 2015;122(11):2336-2343.e2.

13. Hayreh SS, Zimmerman MB. Central Retinal Artery Occlusion: Visual Outcome. AM J OPHTHALMOL 2005;140(3):376.e1-376.e.
14. Hayreh SS, Zimmerman MB. Fundus changes in central retinal artery occlusion. Retina 2007;27(3):276-289.
15. Cornut PL, Bieber J, Beccat S, Fortoul V, Poli M, Feldman A, Denis P, Burillon C. Aspects évolutifs de la rétine en coupe OCT spectral domain lors des oblitérations artérielles rétiniennes. J FR OPHTALMOL 2012;35(8):606-613.
16. Falkenberry SM, Ip MS, Blodi BA, Gunther JB. Optical Coherence Tomography Findings in Central Retinal Artery Occlusion. OPHTHAL SURG LAS IM 2006;37(6):502-505.
17. Furashova O, Matthé E. Retinal Changes in Different Grades of Retinal Artery Occlusion: An Optical Coherence Tomography Study. INVEST OPHTH VISUAL 2017;58(12):5209.
18. Ikeda F, Kishi S. Inner neural retina loss in central retinal artery occlusion. Japanese JPN J OPHTHALMOL 2010;54(5):423-429.
19. Wenzel DA, Kromer R, Poli S, Steinhorst NA, Casagrande MK, Spitzer MS, Schultheiss M. Optical coherence tomography-based determination of ischaemia onset–the temporal dynamics of retinal thickness increase in acute central retinal artery occlusion. ACTA OPHTHALMOL 2020.
20. Ochakovski GA, Wenzel DA, Spitzer MS, Poli S, Härtig F, Fischer MD, Dimopoulos S, Schultheiss M. Retinal oedema in central retinal artery occlusion develops as a function of time. ACTA OPHTHALMOL 2020;98(6):e680-e684.
21. Chu YK, Hong YT, Byeon SH, Kwon OW. In vivo detection of acute ischemic damages in retinal arterial occlusion with optical coherence tomography: a “prominent middle limiting membrane sign”. Retina 2013;33(10):2110-2117.
22. Matthé E, Eulitz P, Furashova O. ACUTE RETINAL ISCHEMIA IN CENTRAL VERSUS BRANCH RETINAL ARTERY OCCLUSION: Changes in Retinal Layers' Thickness on Spectral-Domain Optical Coherence Tomography in Different Grades of Retinal Ischemia. Retina 2020;40(6):1118-1123.
23. Chen H, Xia H, Qiu Z, Chen W, Chen X. Correlation of optical intensity on optical coherence tomography and visual outcome in central retinal artery occlusion. Retina 2016;36(10):1964-1970.
24. Chen S-N, Hwang J-F, Chen Y-T. Macular thickness measurements in central retinal artery occlusion by optical coherence tomography. Retina 2011;31(4):730-737.
25. Yusuf I, Fung TH, Wasik M, Patel C. Transient retinal artery occlusion during phacoemulsification cataract surgery. Eye 2014;28(11):1375-1379.
26. Page PS, Khattar NK, White AC, Cambon AC, Brock GN, Rai SN, James RF. Intra-arterial thrombolysis for acute central retinal artery occlusion: a systematic review and meta-analysis. FRONT NEUROL 2018;9:76.
27. Mac Grory B, Nackenoff A, Poli S, Spitzer MS, Nedelmann M, Guillon B, Preterre C, Chen CS, Lee AW, Yaghi S. Intravenous Fibrinolysis for Central Retinal Artery Occlusion: A Cohort Study and Updated Patient-Level Meta-Analysis. Stroke 2020;51(7):2018-2025.
28. Schrag M, Youn T, Schindler J, Kirshner H, Greer D. Intravenous fibrinolytic therapy in central retinal artery occlusion: a patient-level meta-analysis. JAMA NEUROL 2015;72(10):1148-1154.
29. Schultheiss M, Härtig F, Spitzer MS, Feltgen N, Spitzer B, Hüsing J, Rupp A, Ziemann U, Bartz-Schmidt KU, Poli S. Intravenous thrombolysis in acute central retinal artery occlusion–a prospective interventional case series. PLOS ONE 2018;13(5):e0198114.

30. Dumitrascu OM, Newman NJ, Biousse V. Thrombolysis for central retinal artery occlusion in 2020: time is vision! J NEUROPH 2020;40(3):333-345.
31. Hadanny A, Maliar A, Fishlev G, Bechor Y, Bergan J, Friedman M, Avni I, Efrati S. Reversibility of retinal ischemia due to central retinal artery occlusion by hyperbaric oxygen. CLIN OPHTHALMOL (Auckland, NZ) 2017;11:115.
32. Murthy R, Grover S, Chalam K. Sequential spectral domain OCT documentation of retinal changes after branch retinal artery occlusion. CLIN OPHTHALMOL (Auckland, NZ) 2010;4:327.
33. Yu S, Pang CE, Gong Y, Freund KB, Yannuzzi LA, Rahimy E, Lujan BJ, Tabandeh H, Cooney MJ, Sarraf D. The spectrum of superficial and deep capillary ischemia in retinal artery occlusion. AM. J OPHTHALMOL 2015;159(1):53-63. e2.