

Clinical Diagnosis in Central Retinal Vein Occlusion

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Abstract

With unhealthy eating habits and the aging of society, there has been an increase of lifestyle-related diseases such as hypertension, hyperlipidemia, and diabetes, which are important risk factors for central retinal vein occlusion (CRVO). The condition is classified into non-ischemic CRVO and ischemic CRVO, with the ischemic form being associated with an increased risk of neovascularization and having a poor prognosis. Therefore, it is important to differentiate non-ischemic from ischemic CRVO as an initial step of management. However, assessment of retinal ischemia is difficult in the acute phase of CRVO. Examinations of ocular function (visual acuity, visual field tests, relative afferent pupillary defect, and electroretinography) and morphology (ophthalmoscopy, fluorescein angiography, and optical coherence tomography) are employed to differentiate non-ischemic CRVO from ischemic CRVO. Using these functional and morphological examinations, identification of retinal ischemia is not so difficult. If a simple and rapid method of measuring vascular endothelial growth factor (VEGF) in aqueous humor is established, we may not only use this for differentiation between non-ischemic and ischemic CRVO, but also to decide the indications and predict the response to anti-VEGF therapy.

Introduction

In recent years, with an unhealthy diet, lack of exercise, and aging of society, there has been an increase of lifestyle-related diseases such as hypertension, hyperlipidemia, and diabetes, which are important risk factors for retinal vein occlusion (RVO), including branch RVO (BRVO) and central RVO (CRVO) (Figure 1a and 1b) [1]. BRVO and CRVO affect an estimated 180,000 eyes per year in the United States, making RVO the second most common retinal vascular disorder after diabetic retinopathy [2]. While BRVO occurs in approximately 80% of these patients, CRVO is associated with more significant loss of vision than BRVO [2-4]. Thus, CRVO is a potentially serious retinal disease that can lead to severe visual impairment.

The Central Vein Occlusion Study evaluated visual function in non-ischemic CRVO and ischemic CRVO combined [5,6]. However, the clinical pictures of these two types of RVO are quite different. Non-ischemic CRVO does not provoke ocular neovascularization (NV), unless there is another associated disease that can cause it, such as diabetic retinopathy or ocular ischemia [7]. The retinopathy associated with non-ischemic CRVO is self-limited and resolves after a variable period [8]. Thus, non-ischemic CRVO is a relatively benign disease without a risk of NV, although it causes visual impairment associated with macular edema [9]. The main long-term complication is the development of a permanent central scotoma (with normal peripheral vision) if chronic edema leads to secondary degenerative changes of the macula. Also, some eyes may progress to ischemic CRVO [1].

In contrast to non-ischemic CRVO, ischemic CRVO is associated with an increased risk of NV and has a worse prognosis. Neovascular glaucoma occurs in 40-45% of patients with ischemic CRVO [7]. There is some risk of retinal and/or optic disc NV, which can produce vitreous hemorrhage [7]. Furthermore, when ischemic CRVO is associated with macular edema, there is little chance of the visual acuity recovering because the macula is the vital region of the retina for detailed vision, especially the fovea that consists entirely of cones, [10] and macular ganglion cells can rapidly suffer irreversible damage due to ischemia [9,11]. Thus, even if macular edema is improved by vitreous surgery or other treatments, improvement of visual acuity is unlikely. These differences between non-ischemic and ischemic CRVO make it evident that the clinical implications of the two conditions are also very different, with the former being comparatively benign and the

latter being a threat to vision. Therefore, it is important to differentiate non-ischemic CRVO from ischemic CRVO as an initial step in the management of this condition.

Clinical Examinations for Differentiating Non-ischemic from Ischemic CRVO

Differentiation of non-ischemic CRVO from ischemic CRVO is often attempted on the basis of fluorescein angiography (FA) alone. In the acute phase, however, FA has limitations because capillaries cannot be observed due to the presence of retinal hemorrhage. Accordingly, it is important to differentiate non-ischemic CRVO from ischemic CRVO by also employing the following examinations as required.

Functional Examinations

There are four functional examinations, which are assessment of visual acuity, visual field testing, assessment of a relative afferent pupillary defect (RAPD) and electroretinography (ERG).

Visual acuity

It was reported that 81% of patients with non-ischemic CRVO have a visual acuity of 20/200 or better versus only 7% of patients with ischemic CRVO, and that a visual acuity of 20/400 or worse shows the highest sensitivity (91%) and specificity (88%) with respect to differentiating ischemic from non-ischemic CRVO within 3 months after the onset [11]. Therefore, it has been proposed that if a patient's visual acuity is 20/200 or better during the acute phase of CRVO, the patient probably has non-ischemic CRVO. However, the opposite is not

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necessarily true because visual acuity is not only influenced by macular changes associated with CRVO but also by opacities of the ocular media, optic nerve lesions, and amblyopia.

Visual field testing

Measurement of visual acuity primarily reflects fovea function, but CRVO affects the entire retina and not just the fovea (Figure 1b). Therefore, retinal sensitivity is decreased over the entire macular region in CRVO patients with macular edema [12,13]. Since almost all CRVO patients have a central scotoma, useful differentiating information is only provided by examination of the peripheral visual fields. Therefore, quantitative dynamic visual field tests (Goldmann perimetry) are suitable, while quantitative static visual field tests are not. It has been reported that 71% of patients with non-ischemic CRVO can see all 3 targets (I-2e, I-4e, and V-4e) during Goldmann perimetry. In contrast, only 8% of patients with ischemic CRVO can see all 3 targets, 18% can only see V-4e, and 10% cannot see any target [11]. In addition, patients with ischemic CRVO show visual field defects at a rate of 100% for I-2e, 96–100% for I-4e, and 71–82% for V-4e during the initial 12-month period after the onset, while the corresponding data for patients with non-ischemic CRVO are 54–78%, 38–48%, and 12–17%, respectively. Thus, when peripheral vision is markedly abnormal, CRVO is more likely to be of the ischemic type, although examining the visual fields will not provide reliable information if the patient has an unrelated retinal or optic nerve lesion.

RAPD

This simple test is a highly useful and reliable functional method for objective differentiation of ischemic CRVO from non-ischemic CRVO [11,14,15]. It is often overlooked in daily practice because the pupil is frequently dilated for funduscopy, although confirmation of RAPD is simple and easy. RAPD is recorded in log units of neutral density filters as described elsewhere. Servais et al. [14] reported that the sensitivity and specificity of RAPD for detection of ischemic CRVO were 80 and 97%, respectively [11]. Thus, if RAPD is prominent, CRVO is more likely to be ischemic, although it is essential to have a normal contralateral eye, as well as normal optic nerves and pupils bilaterally.

Electroretinography

This objective functional test is also very useful for differentiating the two types of CRVO. The b wave reflects the function of the inner layer of the retina because this wave is thought to originate from the Mueller cells [16]. The b wave is absent or its amplitudes are reduced in the presence of retinal ischemia. In patients with ischemic CRVO, it has been reported that the b-wave amplitude is (1) reduced to less than 60% of the normal mean value, (2) is reduced by at least one standard

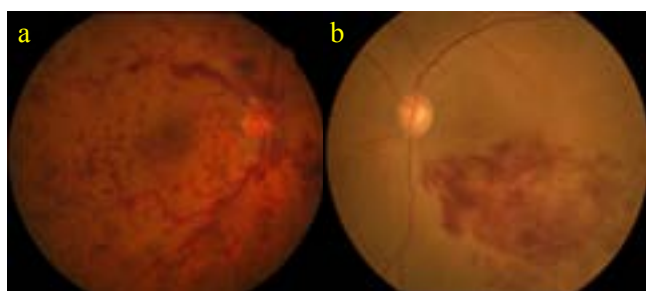


Figure 1: Fundus photographs of BRVO (a) and CRVO (b)
(a) Fan-shaped retinal hemorrhage. (b) Retinal hemorrhages spreading radially.

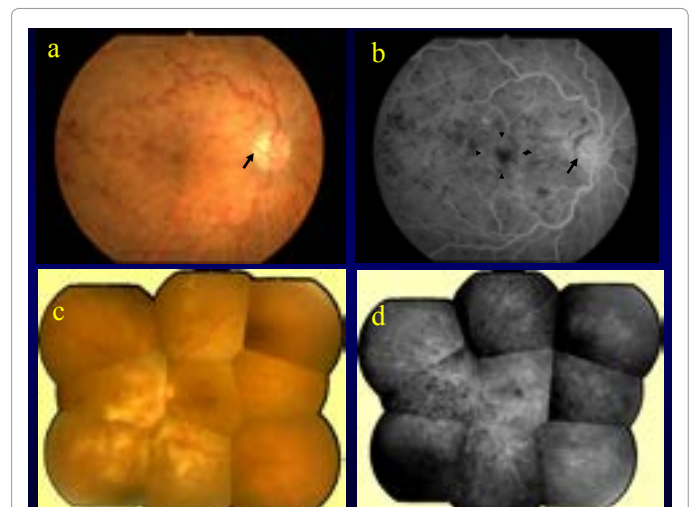


Figure 2: Ophthalmoscopy and fluorescein angiography in CRVO
(a) Optociliary vessels are seen on the optic disc (arrow). (b) Despite neovascularization on the optic disc, fluorescein leakage is absent (arrow). Cystoid macular edema is present with persistent fluorescein leakage (arrowhead). (c) Retinal cloudiness is observed, although there is little retinal hemorrhage. (d) Hyper permeability of a capillary and a nonperfused area are seen.

deviation below the normal mean value, or (3) the ratio between the CRVO eye and the normal contralateral eye is less than 60–70% [15]. Therefore, if an abnormal b wave is observed on the full-field ERG, CRVO is more likely to be of the ischemic type.

Morphologic examinations

There are three examinations in this category, which are ophthalmoscopy, FA, and optical coherence tomography (OCT).

Ophthalmoscopy

CRVO causes brush-shaped splinter hemorrhages because there is considerable bleeding into the nerve fiber layer of the retina (Figure 1b). Generally, retinal hemorrhage is mild with non-ischemic CRVO, and there is much more retinal hemorrhage with the ischemic type. However, some non-ischemic patients have extensive bleeding, while some patients with severe retinal ischemia have little bleeding. Therefore, assessment of retinal hemorrhage shows limited usefulness for distinguishing non-ischemic CRVO from ischemic CRVO [11].

It is possible that ischemic CRVO will cause neo vascularization at the optic disc, while it is less likely that non-ischemic CRVO will lead to neo vascularization at the disc, but optociliary vessels that represent retinal-choroidal or retina – retinal anastomoses are rarely found (Figure 2a and 2b) [8]. In addition, CRVO is more likely to be ischemic when retinal cloudiness is observed (Figure 2c and 2d).

FA

In patients with non-ischemic CRVO, blood flow in the retinal artery is normal, but venous flow is delayed in the initial image. In non-ischemic CRVO, FA shows phlebotasia, absence of nonperfused areas, and obstruction of fluorescence due to bleeding. When leakage of fluorescein occurs due to hyperpermeability of the veins and capillaries, cystoid macular edema is likely (Figure 2b). In ischemic CRVO, capillaries are not often observed on FA because bleeding obscures these vessels. Areas of low fluorescence may be due to either bleeding

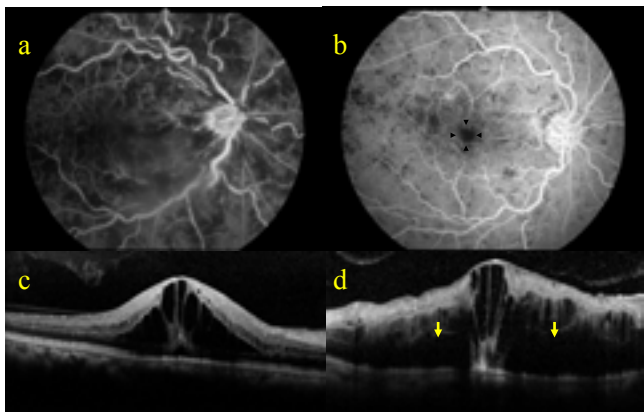


Figure 3: Fluorescein angiography and optical coherence tomography in CRVO

(a) Because retinal hemorrhage is persistent, observation of capillaries is difficult. (b) Expansion of FAZ is seen (arrowhead). (c) Non-ischemic CRVO: Retinal swelling and cystoid changes are present. (d) Ischemic CRVO: Serous retinal detachment (arrow) is present in addition to retinal swelling and cystoid changes.

or nonperfusion (Figure 3a). In such cases, we need to separate non-ischemic CRVO from ischemic CRVO by employing functional examinations mentioned above.

In the CVO study, ischemic CRVO was defined by retinal capillary nonperfusion over an area of more than 10 disc diameters [17]. However, Hayreh has reported that ischemic CRVO should be defined by retinal capillary nonperfusion of more than 30 disc diameters, [11] because it has been clearly demonstrated that eyes with less than 30 disc diameters of retinal capillary nonperfusion and no other risk factors have a low risk of developing iris/angle NV, 'whereas eyes with 75 disc diameters or more are at highest risk' [18,19].

In the chronic stage, judgment of the nonperfused area and existence of neovascularization is clear on FA. When staining of the retinal vein walls and fluorescein leakage are persistent, it means that retinal ischemia still exists. Furthermore, expansion of the foveal avascular zone means macular ischemia (Figure 3b), and the visual prognosis of such patients is extremely poor.

Optical coherence tomography (OCT)

Based on recent technical progress, OCT studies have revealed various morphological changes associated with CRVO [20-22]. One of the reasons for a decrease of visual acuity due to CRVO is macular edema and the pattern of macular edema can be understood in detail using OCT (e.g. sponge-like retinal swelling, cystic changes, and serous retinal detachment) [21,22]. However, macular edema is observed in both non-ischemic CRVO and ischemic CRVO. In both non-ischemic and ischemic CRVO, the OCT findings in the acute phase frequently include sponge-like retinal swelling, cystic changes, and serous retinal detachment with bilateral symmetry around the fovea (Figures 3c and 3d). However, ischemic CRVO shows persistence of macular edema and tends to be associated with serous retinal detachment.

Molecular tests

In the recent CRUISE (Ranibizumab for the treatment of macular edema after Central Retinal Vein Occlusion Study: Evaluation of Efficacy and Safety) study, [23,24] anti-vascular endothelial growth factor (VEGF) therapy was found to be effective for macular edema

in patients with CRVO, suggesting that cytokines such as VEGF are associated with the pathogenesis of this macular edema. In fact, it has been reported that aqueous and vitreous levels of both VEGF and inflammatory cytokines, such as interleukin (IL)-6 and intercellular adhesion molecule 1 (ICAM-1), are increased in CRVO patients with macular edema, with levels of these cytokines being significantly higher in ischemic CRVO than in non-ischemic CRVO and also being significantly correlated with the severity of macular edema [25-28].

VEGF has a strong influence on vascular permeability, and its release from various retinal cells is induced by hypoxia [29,30]. Inflammatory cytokines, such as IL-6 and ICAM-1 also enhance vascular permeability and are induced by hypoxia as well as VEGF [25,27,31]. When CRVO occurs and retinal ischemia develops with vascular occlusion, production of various cytokines by retinal cells is induced, so that macular edema occurs due to enhancement of vascular permeability, suggesting that retinal ischemia is closely associated with the pathogenesis of macular edema in CRVO. When a patient has ischemic CRVO, expression of these cytokines is further enhanced, resulting in a marked increase of vascular permeability. This explains why ischemic CRVO is associated with persistent fluorescein leakage from retinal vein on FA, and also explains the degree of macular edema shown by OCT.

Among various cytokines, VEGF contributes most to the development of ischemia, [25-27] and the VEGF level in aqueous humor is correlated with that in vitreous fluid [32]. Therefore, CRVO is more likely to be ischemic when the vitreous VEGF level is high and this can be predicted by measuring the aqueous VEGF level.

Conclusion

Assessment of retinal ischemia may be difficult in the acute phase of CRVO. However, differentiation between ischemic and non-ischemic CRVO is not so difficult if we perform the functional and morphological examinations discussed in this article. If measurement of VEGF in aqueous humor by a simple and rapid test is established in the future, it may not only be used for the differentiation between non-ischemic and ischemic CRVO but also for deciding the indications and predicting the response to anti-VEGF therapy.

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