Clinical Case Report

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Cardiovascular risk factors in patients with combined central retinal vein occlusion and cilioretinal artery occlusion

Case report

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Abstract

Rationale: To analyze cardiovascular risk factors and comorbidity of acute unilateral visual loss due to combined central retinal vein occlusion (CRVO) and cilioretinal artery occlusion (CLRAO).

Patient concerns: Among patients with retinal vein or artery occlusion hospitalized at the Department of Ophthalmology between January 2011 and August 2017, subjects with combined CRVO/CLRAO were selected. All of them underwent ophthalmologic and cardiologic examination, including fluorescein angiography, optical coherence tomography, 12-lead electrocardiogram, transthoracic and transesophageal echocardiography, carotid Doppler sonography, cerebral magnetic resonance imaging, and a panel of laboratory tests.

Diagnoses: Four subjects with coexisting CRVO and CLRAO were found among 146 patients with retinal vein or artery occlusion. There were no other types of concomitance of CRVO and retinal artery occlusion.

Interventions: All patients were treated with low molecular heparin in a full dose for 2 weeks, then with 1 mg/kg once daily for the next 2 weeks, followed by acetylsalicylic acid 75 mg/kg/d. Other medication included long-term statins, angiotensin-converting-enzyme inhibitor in 3 patients and beta-blocker in one patient.

Outcomes: All patients with CRVO/CLRAO presented multiple cardiovascular risk factors, including hypertension, obesity, hyperlipidemia, chronic nicotine addiction, and a positive family history of coronary artery disease or stroke. In all of them, echocardiography revealed left ventricular hypertrophy and atherosclerotic lesions in the descending aorta; in addition, 3 patients had insignificant atherosclerotic plaques in the carotid artery. Also, in 3 subjects, focal ischemic cerebral changes were diagnosed.

Lessons: Patients with combined CRVO and CLRAO present numerous cardiovascular risk factors and abnormalities on imaging examinations, which should be routinely evaluated and treated.

Abbreviations: ASA = acetylsalicylic acid, BCVA = best-corrected visual acuity, CLRAO = cilioretinal artery occlusion, CRVO = central retinal vein occlusion, ECG = electrocardiogram, HELLP = hemolysis, elevated liver enzymes, a low platelet count, IOP = intraocular pressure, IVFA = intravenous fluorescein angiography, LMWH = low molecular weight heparin, MRI = magnetic resonance imaging, OCT = optical coherence tomography, TEE = transesophageal echocardiography, TTE = transthoracic echocardiography.

Keywords: cardiovascular risk factors, central retinal vein occlusion, cilioretinal artery occlusion

1. Introduction

Combined central retinal vein occlusion (CRVO) and cilioretinal artery occlusion (CLRAO) is an uncommon variant of retinal vascular disease, which causes sudden unilateral visual acuity loss.[1] It was first described by Oosterhuis in 1968[2] and later by other authors.[3–7] The cilioretinal artery is a branch of the posterior ciliary artery, arising either directly from the posterior ciliary artery or from the choroid.[1] It is usually suggested that CLRAO occurs secondary to the raised capillary pressure caused by CRVO.[8,9] CRVO/CLRAO results in a significant increase in intraluminal pressure in the capillary bed, so CLRAO should be interpreted as a hemodynamic block.[1,10] Another hypothesis assumes that primary reduction in perfusion pressure of the cilioretinal and retinal arteries may lead to decreased retinal circulation[5,9,11,12] and subsequent venous stasis and thrombosis.[3] It is well known that the most important risk factors for CRVO are the same as those for atherosclerosis, including advanced age, hypertension, hyperlipidemia, diabetes, cigarette

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smoking, positive family history.[13,14] Other systemic predisposing factors include inherited and acquired thrombophilia, high blood viscosity, systemic vasculitis, and autoimmune disease.[10,14] The mechanism of action of the systemic factors may relate to the damage of the adjacent artery.[15] It is not well established whether the profile of the risk factors in patients with combined CRVO/CLRAO is similar to that observed in isolated CRVO or CRVO coexisting with central or branch retinal artery occlusion. Some authors have distinguished a subgroup of patients with CRVO or combined CRVO/CLARO, usually at a younger age, without obvious systemic disease.[1,9,13] Such a view, however, may, in part, be the result of incomplete assessment of the risk factors or even of rejected norm values of some investigated parameters.

The aim of the paper is to present the clinical picture and the cardiovascular risk factors of combined CRVO and CLRAO including transthoracic and transesophageal echocardiography, carotid Doppler sonography, cerebral magnetic resonance imaging (MRI), and a panel of laboratory tests, including thrombophilia screening.

2. Material and methods

About 146 patients with retinal vein or artery occlusion were hospitalized at the Department of Ophthalmology between January 2011 and August 2017. They underwent ophthalmologic and cardiovascular examination as well as a panel of laboratory tests, inter alia thrombophilia screening. Ophthalmologic assessment included measurements of the best-corrected visual acuity (BCVA) and intraocular pressure (IOP) by Goldmann applanation tonometry, slit lamp evaluation of the anterior eye segment performed after pupil dilation with 1% tropicamide, indirect ophthalmoscopy, intravenous fluorescein angiography (IVFA) after 5 mL of 10% sodium fluorescein solution bolus administration using a Zeiss fundus camera and optical coherence tomography (OCT) with the Topcon Triton Medical System. Cardiovascular assessment included electrocardiogram, transthoracic and transesophageal echocardiography (TEE), carotid Doppler sonography, cerebral MRI. Echocardiographic assessment comprised left ventricular hypertrophy, left ventricular contractile disturbances, valvular abnormalities, presence of a persistent foramen ovale, looking for thromboembolic material. The examination was performed using Vivid 7 dimension with sector, 3-dimensional and transesophageal probes. The quantification of the chambers and their function, evaluation of the valves and of a cardiac source of embolism were based on appropriate guidelines.[16–18] In detail, the atherosclerotic lesions of the descending aorta were graded according to the modified scoring system originally proposed by Fazio et al[19]: grade 0—no sign of atherosclerosis; grade 1—intimal thickening; grade 2—plaque <5 mm; grade 3—plaque >5 mm and/or "complex" plaque with ulcerated or mobile parts. Carotid artery Doppler sonography was done in accordance with the appropriate standards.[20] All examinations performed were routinely done, a written consent was given by patients for all examinations on admission and, additionally, before TEE and MRI. An analysis of the data was performed retrospectively. The patients' consent for every examination and for using their data in the publication was obtained. The study was conducted in consistence with the Declaration of Helsinki and the regulations of local IRB.

3. Results

Four subjects with coexisting CRVO and CLRAO were found. There were no other types of concomitance of CRVO and retinal artery occlusion. Ophthalmologic data of these patients are shown in Table 1. All patients presented as sudden painless deterioration of vision with a dark spot in the affected eye and were admitted to the Department of Ophthalmology with a 6 to 36-hour delay from the onset of symptoms. Fundus examination, IVFA and OCT in cases 1 and 2 represent a spectrum of the severity of the disease with mild to advanced retina edema and hemorrhage. (Fig. 1) Cardiologic information is collected in Table 2. All 4 patients presented multiple cardiovascular risk factors, including hypertension, obesity, chronic nicotine addiction, and a positive family history of coronary artery disease or stroke. In all of them, echocardiography revealed left ventricular hypertrophy and atherosclerotic lesions in the descending aorta (Fig. 2); in addition, 3 patients had insignificant atherosclerotic

Table 1

Ophthalmologic data of patients with combined central retinal vein occlusion and cilioretinal artery occlusion.

Age/sex	Symptoms, time from onset to 1st examination	BCVA, IOP	Fundus examination	IVFA	OCT
52/male	Sudden painless deterioration of vision, a dark spot in the right eye, 24 h	Counting fingers, 17 mm Hg	Optic disc edema, features of blanching of the retina in the ciliary – macular area, edema of the rest of the retina with multiple hemorrhages, and soft exudates	Moderately extended arteriovenous passage time, mild congestion with extended capillaries in the optic nerve region, hypofluorescence due to hemorrhage	Retinal edema
3/male	Sudden painless deterioration of vision, a dark spot in the right eye, 6 h	1.0, 14 mm Hg	Optic disc edema, features of blanching of the retina in the ciliary – macular area, small hemorrhages along the bottom of the vascular arcades	Cloudy retinal swelling, small leakage from disc and vein, infarction in cilioretinal territories	Slight retinal edema
82/female	Sudden painless deterioration of vision, a dark spot in the right eye,12 h	1/50, 19 mm Hg	Optic disc edema, features of blanching of the retina in the ciliary – macular area, petty hemorrhage, and soft exudates	ND	Mild retinal edema
31/male	Deterioration of vision, a dark spot in the right eye,36 h	1,0 15 mm Hg	OSptic disc edema, features of blanching of the retina in the ciliary – ,macular area, small hemorrhages and cotton wool spots	Moderately extended arteriovenous passage time, hypofluorescence due to hemorrhage	Slight retinal edema

BCVA = best-corrected visual acuity, IOP = intraocular pressure, IVFA = intravenous fluorescein angiography, ND = no data, OCT = optical coherence tomography.

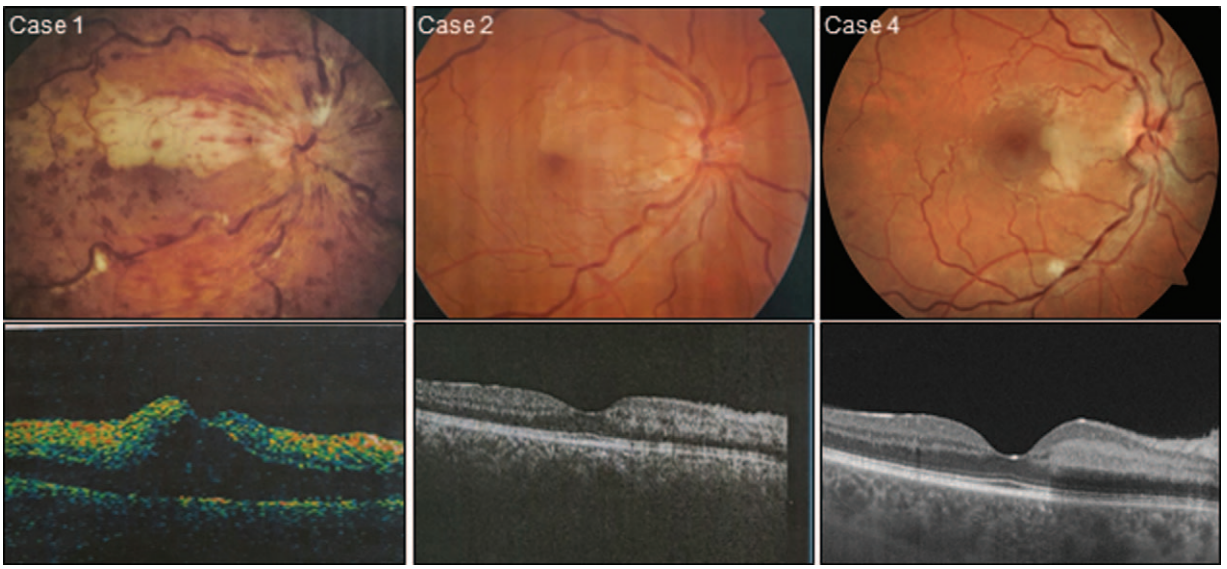

Figure 1. Fundus picture and optical coherence tomography of patients No 1, 2, and 4 (see Table 1).

Table 2

Cardiovascular assessment of patients with combined central retinal vein occlusion and cilioretinal artery occlusion.

Age/sex	Cardiovascular risk factors	Echocardiography (TTE, TEE)	Cerebral MRI	Carotid artery sonography
52/male	Hypertension, hyperlipidemia, obesity, smoking, family history*	LVH (SW: 12 mm, PW: 12 mm), EF: 60%, atherosclerotic lesions in the descending aorta – grade 2, PFO	Two ischemic foci (largest – 12 mm	Noncritical atherosclerotic plaques, IMT: 1.5 mm
43/male	Hyperlipidemia, obesity, hyperhomocysteinemia, smoking, family history*	LVH (SW: 12 mm, PW: 11 mm), EF: 64%, atherosclerotic lesions in the descending aorta – grade 2, PFO	A few small ischemic foci	Normal, IMT: 0.9 mm
82/female	Hypertension, hyperlipidemia, obesity, family history†	LVH (SW: 15 mm, PW: 13 mm), EF: 45% (inferior and posterior wall hypokinesia), not significant valvular changes, atherosclerotic lesions in the descending aorta – grade 3	Multiple ischemic foci (largest – 10 mm	Noncritical atherosclerotic plaques, IMT: 1.5 mm
31/male	Hyperlipidemia, obesity, previous smoking, family history*, other: intensive sport practice (powerlifting)	LVH (SW: 12 mm, PW: 11 mm), EF: 63%, atherosclerotic lesions in the descending aorta – grade 2	Normal	Small atherosclerotic plaques, IMT: 1.2 mm

EF = ejection fraction; abnormal value <52% for men, <54% for women, IMT = intima-media thickness (abnormal value >1.0 mm), LVH = left ventricular hypertrophy, MRI = magnetic resonance imaging, PFO = persistent foramen ovale, PW = posterior wall thickness (normal range: as above), SW = septal wall thickness (normal range: 0.6–1.0 mm for men, 0.6–0.9 mm for women), TEE = transesophageal echocardiography, TTE = transthoracic echocardiography.

* Of myocardial infarction.

† Of stroke.

plaques in the carotid artery. Also, in 3 subjects, focal ischemic cerebral changes were diagnosed (Fig. 3). All patients were treated with low molecular weight heparin (LMWH) in a full dose for 2 weeks, then with 1 mg/kg once daily, followed by acetylsalicylic acid (ASA) 75 mg/d. Other medications included long-term statins (rosuvastatin, atorvastatin for the next 2 weeks, or simvastatin), angiotensin-converting-enzyme inhibitor (ramipril) in 3 patients, and beta-blocker (carvedilol) in patient number 3. During a 2 to 60-month follow-up period, the oldest patient developed unstable angina.

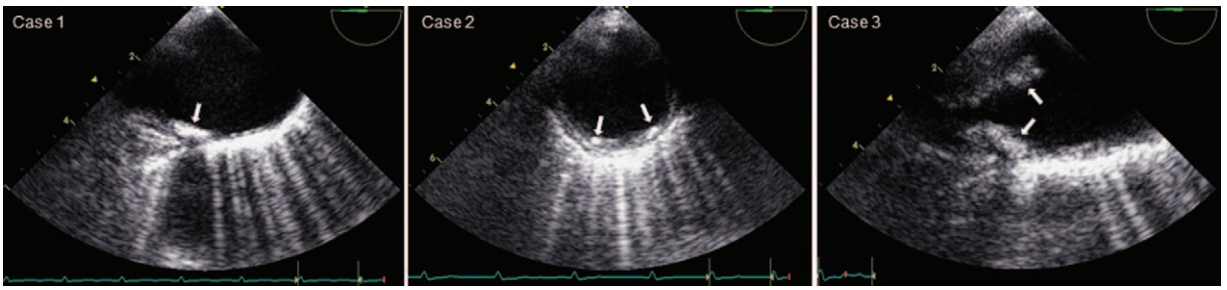

Figure 2. Atherosclerotic lesions of the descending aorta on transesophageal echocardiography (arrows) in patients No 1 to 3.

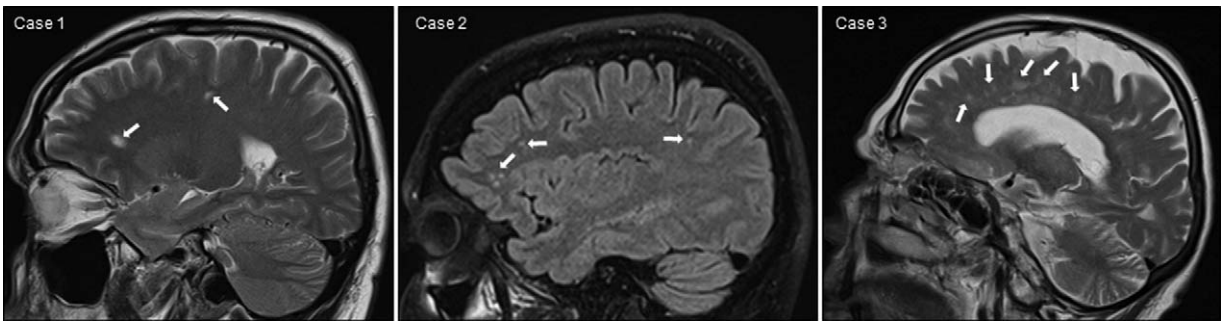

Figure 3. Ischemic foci on magnetic resonance imaging (arrows) in patients No 1 to 3.

4. Discussion

There are 3 different types of combined retinal vein and artery occlusions: CRVO with central retinal artery occlusion (CRAO), CRVO with branch retinal artery occlusion (BRAO) and CRVO with CLRAO.[10] While the most frequent cause of isolated CRAO or BRAO is of embolic etiology, in CRAO or BRAO coexisting with CRVO emboli are rarely or never found.[10] At the same time, Schmidt suggests that the profile of the factors predisposing to combined CRVO/CRAO or CRVO/BRAO differs from that observed in isolated CRVO with the prevalence of immunological diseases, malignancies, and other causes of coagulopathies.[10]

Apart from CLRAO associated with CRVO, 2 other etiologically distinct types of CLRAO have been reported: nonarteritic CLRAO alone and arteritic CLRAO associated with giant cell arteritis or with ischemic optic neuropathy.[21–23] Combined CRVO and CLRAO represents 27%[23] to 62%[1] of all CLRAOs. In 1 retrospective study, 33 eyes with CLRAO over a 10-year period were diagnosed, including 9 cases of CLRAO combined with CRVO.[23] The largest group based on 38 eyes with CRVO/CLRAO was reported by Hayreh et al.[1]

Most publications focus on the interpretation of the pathomechanism of combined CRVO/CLRAO, which still remains unclear.[6,7,11] Observation of the clinical course of the particular cases gives arguments for the initiating role of CRVO, after which an evolution of arterial occlusion is observed.[24] The probability of CLRAO should grow with the increasing severity of CRVO.[25] It is also possible that the incidence of combined CRVO and CLRAO is grossly underestimated.[26] On the other hand, the 1st occurrence of CLRAO seems to confirm the hypothesis concerning primary arterial affection.[27] In evidence of arterial vasospasm, related to an increased contractility of the retinal arteries, initial retinal blanching along the cilioretinal artery followed by signs of venous stasis can be observed.[9,28] Brazitikos et al[9] distinguish 2 types of combined CRVO/CLRAO in relation to cilioretinal artery filling pattern in IVFA. Patients with delayed filling were older and had systemic risk factors, while in subjects with normal cilioretinal filling systemic disease was not revealed. Recovery of visual acuity in this group was expected. Contrary to this observation, Keyser et al[12] suggest that otherwise healthy patients often presented prolonged retinal artery inflow and, after an initial improvement of vision, recurrent episodes of visual loss may occur.

The most important risk factors for CRVO (and combined CRVO/CLRAO), widespread among the population, are the same as those for atherosclerosis: advanced age, hypertension, hyperlipidemia, diabetes, cigarette smoking, a positive family history.[1,14] In some studies, including the highest number of patients with CRVO or CRVO/CLRAO, hyperlipidemia was diagnosed in an unexpectedly low percentage.[1,13] However, it should be pointed out that norm values may evolve with time. Systemic predisposing factors can also include inherited and acquired thrombophilia, systemic vasculitis, and autoimmune disease and other illnesses or clinical situations (Table 3).

Rarely is combined CRVO/CLRAO reported in otherwise healthy subjects,[1,9,12] although at least some of these patients did not undergo full diagnostics panel including TEE, cerebral MRI or thrombophilia screening ,or had atypical burdens such as intensive sport practice. It is important to consider uncommon (e.g., Flammer syndrome) or common but so far unrecognized risk factors (e.g., hypertension). Fluctuation of the blood pressure is probably an unacknowledged risk factor for CRVO/CLRAO occurrence.

Table 3

Risk factors for central retinal vein occlusion (including combined central retinal vein occlusion and cilioretinal artery occlusion).

Atherosclerotic risk factors	Inherited/acquired thrombophilia	Systemic vasculitis or autoimmune disease	Other
Hypertension (Blood pressure fluctuation)	Factor V Leiden	Systemic lupus erythematosus	High blood viscosity
Hyperlipidemia	Prothrombin mutation	Mixed connective tissue disease	Hemodialysis
Diabetes obesity	Hyperhomocysteinema	Behçet disease	HELLP syndrome
Metabolic syndrome	Dysplasminogenemia malignancies	Wegener granulomatosis	Postpartum period
Cigarette smoking	Hormone replacement therapy and oral contraceptive use	Giant-cell arteritis	Sleep apnea syndrome
Family history	Other thrombogenic medication		Flammer syndrome
			High altitude
			Sildenafil use
			Intensive sport practice
			Local (glaucoma, injury)

HELLP = hemolysis, elevated liver enzymes, a low platelet count.

There are some controversies as to antithrombotic therapy for CRVO.[15,29] Hayreh et al[29] suggest no benefit from treatment with antiplatelets or anticoagulants; they have even observed a significantly greater severity of retinal hemorrhages among aspirin users than among nonusers. According to the latest guidance for the management of venous thrombosis in unusual site, LMWH may be considered for acute phase treatment of RVO in selected patients; further long-term treatment with ASA should be based on individual indications for primary or secondary prevention of cardiovascular disease.[15]

5. Conclusion

Patients with combined CRVO and CLRAO present numerous cardiovascular risk factors and abnormalities on imaging examinations, which should be routinely evaluated and treated. Combined CRVO and CLRAO require combined ophthalmologic and cardiovascular care.

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