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Research Article

Cerebro-Cardiovascular Risk Factors are Equivalent for Retinal Ischemia and Cerebral Ischemia Patients with Carotid Artery Stenosis

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Abstract

Retinal ischemia associated with carotid artery stenosis is an important clinical sign for the prevention of repeated retinal and cerebral ischemic attacks. In this study, we compared the cerebro-cardiovascular risk factors of patients with symptomatic carotid artery stenosis presented with retinal ischemia and with cerebral ischemia. Forty-six patients were diagnosed with symptomatic carotid artery stenosis for five years in our institute. Sixteen patients (34.8%) presented with retinal ischemia, and 30 patients (65.2%) presented with cerebral ischemia. Retinal ischemia was divided into retinal artery occlusion (RAO: n=7, 15.2%), retinal vein occlusion (RVO: n=5, 10.9%) and retinal transient ischemic attack (RTIA: n=4, 8.7%). Stenosis more than 70% in the internal carotid artery was recognized in 62.5% of the patients with retinal ischemia (RAO: n=4, RVO: n=2, AF: n=4) and 73.3% of the patients with cerebral ischemia (p=0.45), and vulnerable plaque evaluated by ultrasonography was recognized in 42.9% of the patients with retinal ischemia (RAO: n=5, RVO: n=2, RTIA: n=2) and 33.3% of patients with cerebral ischemia (p=0.33). No significant difference were seen in the cardiovascular risk factors for hypertension, diabetes mellitus, dyslipidemia, smoking and previous cardiovascular events, and in the cerebrovascular risk factors for stenosis rate, vulnerable plaque, cerebral white matter lesions (WMLs), and impaired cerebrovascular reserve (CVR), between the patients with retinal ischemia and cerebral ischemia. Attentions to the future's stroke should be paid for patients with retinal ischemia of RAO, RVO and RTIA as well as patients with cerebral ischemia, because both patients could possess equivalent cerebro-cardiovascular risk factors.

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ABBREVIATIONS

RAO: Retinal Artery Occlusion; **Rvo:** Retinal Vein Occlusion; **Rtia:** Retinal Transient Ischemic Attack; **Ica:** Internal Carotid Artery; **Ht:** Hypertension; **Dm:** Diabetes Mellitus; **Wmls:** White Matter Lesions; **Cvr:** Cerebrovascular Reserve; **Tia:** Transient Ischemic Attack; **Ffa:** Fundus Fluorescein Angiography; **Mr:** Magnetic Resonance; **Flair:** Fluid Attenuated Inversion Recovery; **Dswmh:** Deep Subcortical White Matter Hyperintensity; **Cbf-Spect:** Cerebral Blood Flow – Single Photon Emission Computed Tomography; **Cea:** Carotid Endarterectomy; **Cas:** Carotid Artery Stenting; Or **Pta:** Percutaneous Transluminal Angioplasty

INTRODUCTION

Symptomatic carotid artery stenosis is a major cause of recurrent retinal and cerebral ischemic attack due to artery-to-artery embolism and impaired hemodynamics. Previous population-based studies have revealed that retinal ischemia, including retinal artery occlusion (RAO), retinal vein occlusion (RVO) and retinal transient ischemic attack (RTIA), is associated with carotid artery plaque [1-4]. The evaluation of carotid artery disease in patients with retinal ischemia is important for the prevention of repeated retinal and cerebral ischemic attacks. Retinal ischemia associated with carotid artery stenosis is a sight-threatening retinal vascular condition. It shares common risk factors with cardiovascular disease, including hypertension, diabetes mellitus, dyslipidemia and cigarette smoking, which cause the progression of atherosclerosis in the retinal and carotid arteries [4-7]. Therefore, the associations between retinal artery

ischemia (RAO, RTIA) and carotid artery stenosis can be explained pathophysiologically. However, the association between RVO and carotid artery stenosis has not been established. Recent studies examining the association between the retinal microcirculation and cardiovascular risk factors, including carotid artery disease, revealed that retinal vascular signs, such as retinal arteriovenous nicking and a wider retinal venular caliber, were associated with carotid artery disease [1,6,8-11]. Therefore, retinal ischemic symptoms caused by RVO as well as RAO and RTIA are important clinical signs for the evaluation of occult carotid artery stenosis. In the present study, we analyzed retrospective data in patients with symptomatic carotid artery stenosis who presented with retinal ischemia or cerebral ischemia. We compared the cerebro-cardiovascular risk factors of patients with retinal ischemia to those of patients with cerebral ischemia. The pathophysiology of RVO associated with carotid artery stenosis is discussed based on the anatomical structure of retinal vessels and cerebro-cardiovascular risk factors.

MATERIALS AND METHODS

Patients

Forty-six patients with symptomatic carotid artery stenosis were diagnosed in our institute for five years. Sixteen patients presented with the onset of retinal ischemia, and 30 patients presented with the onset of cerebral ischemia. Retinal ischemia was divided into RAO, RVO and RTIA. Cerebral ischemia was divided into transient ischemic attack (TIA) and cerebral infarction. Hypertension, diabetes mellitus, dyslipidemia, cigarette smoking and previous cerebro-cardiovascular events were examined as cardiovascular risk factors, and stenosis rate, plaque characteristics, cerebral white matter lesions (WMLs) and cerebrovascular reserve (CVR) were examined as cerebrovascular risk factors. Risk factors in retinal ischemia and cerebral ischemia associated with symptomatic carotid artery stenosis were compared. Patients with more than 30% of carotid artery stenosis were included in this study.

Definition of retinal ischemia and cerebral ischemia

Retinal findings were examined by an ophthalmologist using fundus microscopy and fundus fluorescein angiography (FFA). RAO was defined as occlusion of the central or a branch retinal artery that could be characterized by a whitish, edematous retina and a cherry-red spot. FFA demonstrated delayed filling of the affected retinal artery. RVO was defined as occlusion of the central or a branch retinal vein that could be characterized by retinal and papilla edema, scattered retinal hemorrhage and venous dilation. FFA demonstrated retinal capillary obliteration. RTIA was defined as a transient monocular visual loss associated with retinal ischemia that continued for seconds to a few minutes. Fundus microscopy demonstrated no acute abnormal findings, including occlusion of the retinal artery or vein. Cerebral infarction and TIA were diagnosed by neuroradiologists and neurosurgeons based on clinical symptoms and abnormal findings obtained by magnetic resonance (MR) imaging, MR angiography and ultrasonography.

Cardiovascular risk factors

Hypertension, diabetes mellitus, dyslipidemia, cigarette smoking and previous cerebro-cardiovascular events were examined as cardiovascular risk factors. Hypertension was defined as systolic blood pressure > 140 mmHg, diastolic blood pressure > 90 mmHg, or current use of antihypertensive medication. Diabetes mellitus was defined as > 200 mg/dl of serum glucose, > 6.5% of HbA1C, use of insulin or oral hypoglycemic medication or diagnosis by a physician. Dyslipidemia was defined as low-density lipoprotein cholesterol > 139 mg/dL, triglyceride levels > 150 mg/dL, or use of lipid-lowering medication. Smoking was defined as a Brinkman index > 400.

Cerebrovascular risk factors

Evaluation of stenosis rate and plaque characteristics: Carotid arterial ultrasonographies were examined by a medical technologist and cardiologist. The data obtained by MR angiography and digital subtraction angiography (DSA) were analyzed by a neuroradiologist and a neurosurgeon. The stenosis rate of the origin of the internal carotid artery was measured according to the protocol of the North American Symptomatic Carotid Endarterectomy Trial (NASCET) using ultrasonography, MR angiography or DSA [12]. Stenosis in the cavernous and petrous portion of the internal carotid artery was also measured according to the protocol of NASCET using MRA or DSA. The plaque characteristics of the origin of the internal carotid artery were evaluated using ultrasonography (patients with retinal ischemia: n=14, patients with cerebral ischemia: n=27). Vulnerable plaques were defined as echolucent plaques, intraplaque hemorrhages, or mobile plaques with or without ulcer formation [13,14].

Deep white matter lesions (WMLs): MR imaging of the brain was performed in all patients to evaluate the small-vessel changes of the deep white matter, which have been reported to be associated with retinal microvascular abnormalities [15]. T1 weighted imaging (repetition time: 450 ms, echo time 14 ms), T2 weighted imaging (repetition time: 2500 ms, echo time 90 ms) and fluid attenuated inversion recovery (FLAIR) imaging (repetition time; 6000 ms, echo time; 100 ms) was used to estimate periventricular hyperintensity (PVH) and deep subcortical white matter hyperintensity (DSWMH) [16]. These were graded from 0 to 4 using set standards. PVH exhibits white matter hyperintensities on T2-weighted imaging and FLAIR imaging, and isointensities on T1-weighted imaging in contact with the ventricular wall. PVH were classified as follows. Grade 0: absent or only a "rim"; grade 1: limited lesion-like "caps"; grade 2: irregular "halo"; grade 3: irregular margins and extension into the deep white matter; grade 4: extension into the deep white matter and the subcortical portion. DSWMH exhibits hyperintensities in the deep white matter on T2 weighted imaging and FLAIR imaging, and isointensities on T1 weighted imaging that are separated from the ventricular wall. DSWMH were classified as follows. Grade 0: absent; grade 1: ≤3 mm, small foci and regular margins; grade 2: ≥3 mm, large foci; grade 3: diffusely confluent; grade 4: extensive changes in the white matter. Hyperintensities of greater than grade 2 were defined as deep WMLs.

Cerebral blood flow – single photon emission computed tomography (CBF-SPECT): For CBF-SPECT imaging, 500 MBq/kg of Technetium-99m ethyl cysteinate dimer (Tc-99m ECD; FUJIFILM RI pharma, Japan) was injected intravenously into the

patients, and the basal acquisition was started after 7 minutes. Ten minutes before the end of basal SPECT acquisition, 15 mg/kg of acetazolamide was injected intravenously. Seven minutes after the end of the basal study acquisition, 500 MBq/kg of Tc-99m ECD was injected, and the acquisition of the stress study began after 7 minutes. A multi-detector SPECT machine (E. CAM, Siemens Medical, Malvern, PA, USA), and a high-solution collimator (LEHR, Siemens Medical, Malvern, PA, USA) was used for acquisition. Forty five step-and-shoot images per detector were acquired with intervals of 4° for 20 seconds per each step. The Butter-worth pre-correction filter and the Chang method were used for pre-attenuation and post-attenuation corrections. The Ramp filter was used for reconstruction. The image matrixes were 128 × 128, and the pixel sizes 3.3mm. The slice thickness was 6.6 mm. The cut off was 0.61 cycle/cm. SPECT images were generated using the patlack plot method by a nuclear physician. Rest CBF (C rest) and acetazolamide-activated CBF (C acetazolamide) in the region of the middle cerebral artery were calculated using a three-dimensional stereotactic ROI template (3DSRT: FUJIFILM RI pharma, Japan) [17]. CVR was calculated using the following equation:

CVR = C acetazolamide – C rest / C rest × 100.

Impaired CVR was defined as less than 10% CVR in at least one-third of the region of the middle cerebral artery, excluding the cerebral infarct area evaluated by MR imaging.

Treatment

Anti-platelet therapy with or without carotid endarterectomy (CEA), carotid artery stenting (CAS), or percutaneous transluminal angioplasty (PTA) was performed for the prevention of retinal or cerebral ischemic attack recurrence. CEA or CAS was performed in patients with severe stenosis in the origin of the internal carotid artery, considering the stenosis rate, plaque characteristics and operative risk. PTA was performed in patients with stenosis in the petrous or cavernous portion of the internal carotid artery.

Statistics

All values are expressed as the mean ± standard deviation (S. D.). Continuous data between groups were compared using the chi-square test. Differences with a value of $p < 0.05$ were considered as statistically significant.

RESULTS

Incidence of RAO, RTIA, and RVO

Forty-six patients with symptomatic carotid artery stenosis were diagnosed at the onset of retinal ischemia or cerebral ischemia. 16 patients (34.8%) presented with retinal ischemia and 30 patients (65.2%) presented with cerebral ischemia. Patients with retinal ischemia were divided into RAO (n=7, 15.2%), RVO (n=5, 10.9%) or RTIA (n=4, 8.7%). 2 patients with retinal ischemia had a stenosis in the intracranial internal carotid artery (ICA) portion and 14 patients had a stenosis in the cervical ICA portion. The 3 patients with cerebral ischemia had a stenosis in the intracranial ICA portion and 27 patients had a stenosis in the cervical ICA portion. (Table 1)

Cerebro-cardiovascular risk factors

There were no significant differences in cardiovascular risk factors (hypertension, diabetes mellitus, dyslipidemia, cigarette smoking and previous cardiovascular events) between the patients with retinal ischemia and those with cerebral ischemia. Stenosis more than 70% in the internal carotid artery was recognized in 62.5% of the patients with retinal ischemia (RAO: n=4, RVO: n=2, RTIA: n=4) and 73.3% of the patients with cerebral ischemia (p=0.45), and vulnerable plaque evaluated by ultrasonography was recognized in 42.9% of the patients with retinal ischemia (RAO: n=5, RVO: n=2, RTIA: n=2) and 33.3% of patients with cerebral ischemia (p=0.33). Deep WMLs, defined as more than grade 2 PVH or DSWMH, were recognized in 18.8% of patients with retinal ischemia and 16.7% of the patients with cerebral ischemia. Findings of less than 10% CVR, as evaluated by acetazolamide-activated CBF-SPECT, were recognized in 33.3% of the patients with retinal ischemia and 58.6% of the patients with cerebral ischemia. There were no significant differences in these cerebrovascular risk factors between the two groups. (Table 2)

Table 1: Summary of retinal ischemia and cerebral ischemia patients with symptomatic carotid artery stenosis.

	Onset		Total
	Retinal ischemia (RAO, RVO, RTIA)	Cerebral ischemia	
Symptomatic ICA stenosis	16 (34.8 %) (7, 5, 4)	30 (65.2 %)	46 (100 %)
Intracranial ICA stenosis	2 (0, 1, 1)	3	5
Cervical ICA stenosis	14 (7, 4 3)	27	41

RAO: Retinal Artery Occlusion, Rvo: Retinal Vein Occlusion, Rtia: Retinal Transient Ischemic Attack, Ica: Internal Carotid Artery.

Treatment

Eight patients (50%, RAO: n=3, RVO: n=2, AF: n=3) with retinal ischemia and 22 patients (73.3%) with cerebral ischemia were treated by CEA, CAS or PTA (no significant difference).

DISCUSSION

Our retrospective data revealed that 34.8% of patients with symptomatic carotid artery stenosis presented with onset of retinal ischemia. Visual disturbances due to RAO and AF could be caused by an impaired blood supply to the retina associated with an artery-to-artery embolism derived from the vulnerable carotid artery plaque, or by a hemodynamic disorder derived from severe carotid artery stenosis. There are many reports about the association between retinal arterial ischemia and carotid artery disease [1,3,4]. In addition, the association between retinal venous ischemia and carotid artery disease has been controversial. However, Wong, et al. reported that 27.3% of RVO was related to carotid artery plaque and that RVO was significantly related to hypertension, smoking, and arteriovenous nicking in the retina and carotid artery plaque. They explained the atherosclerosis of retinal artery causal might cause stenosis and occlusion in the adjacent retinal veins [4]. In addition, the Rotterdam and MCRS studies revealed that retinal venular widening was strongly associated with ipsilateral severe extracranial carotid artery stenosis [8,11]. These studies indicated that reduced retinal blood flow caused by severe carotid artery stenosis was

Table 2: Comparison of cerebro-cardiovascular risk factors between retinal ischemia and cerebral ischemia patients.

	Retinal ischemia, n=16 (%) (RAO=7, RVO=5, RTIA=4)	Cerebral ischemia, n=30 (%)	P value
Age	65.6±7.3 (67.9±7.3, 66.6±5.4, 60.3±9.9)	66.7±7.3	0.69
Men	13 (81.3) (6, 3, 4)	26 (86.7)	0.39
HT	15 (93.8) (7, 4, 4)	25 (83.3)	0.32
DM	9 (56.3) (5, 3, 1)	11 (36.7)	0.20
Dyslipidemia	9 (56.3) (5, 2, 2)	9 (30)	0.08
Cardiovascular events	6 (37.5) (3, 1, 2)	9 (30)	0.61
Cigarette smoking	6 (37.5) (4, 1, 1)	4 (13.3)	0.06
ICA stenosis > 70%	10 (62.5) (4, 2, 4)	22 (73.3)	0.45
Vulnerable plaque	9/14 (42.9) (5, 2, 2)	9/27 (33.3)	0.33
Cerebral WMLs	3 (18.8) (2, 1, 0)	5 (16.7)	0.86
Impaired CVR	5/15 (33.3) (3, 1, 1)	17/29 (58.6)	0.11

Abbreviations: Rao: Retinal Artery Occlusion, Rvo: Retinal Vein Occlusion, Rtia: Retinal Transient Ischemic Attack, Ht: Hypertension, Dm: Diabetes Mellitus, Wmls: White Matter Lesions, Cvr: Cerebrovascular Reserve.

compensated by the retinal venular widening. Based on those previous reports, it could be considered that impaired retinal circulation hemodynamics induced by carotid artery stenosis caused the occlusion of the retinal vein.

It is known that the retinal artery and vein are affected by cardiovascular risk factors such as hypertension, diabetes mellitus, dyslipidemia, and smoking. These cardiovascular risk factors are also associated with cerebral ischemia. Recent studies have indicated that retinal microvascular abnormalities are significantly related to high-grade cerebral WMLs, and the risk of stroke is higher in patients with both retinopathy and cerebral WMLs [15]. The present study revealed that 18.8% of patients with retinal ischemia presented with cerebral WML. In addition, 33.3% of patients with retinal ischemia had impaired CVR. There was no significant difference in the cerebral small-vessel abnormalities and hemodynamic disorder between the patients with retinal ischemia and cerebral ischemia. Few studies have compared the cerebral hemodynamics between retinal ischemia and cerebral ischemia patients with symptomatic carotid artery stenosis. Our data obtained from patients' profiles, stenosis rates, plaque characteristics, cerebral WMLs and impaired CVRs revealed that patients with retinal ischemia associated with carotid artery stenosis possessed equivalent cerebro-cardiovascular risk factors with the patients with cerebral ischemia associated with carotid artery stenosis.

The number of patients reported herein who presented with retinal ischemia associated with carotid artery ischemia might be relatively high compared to previous studies [18]. Most patients who presented to our hospital were asymptomatic, mildly symptomatic or were admitted for endovascular treatment. Patients with severe symptoms caused by cerebral infarction were rare. However, many patients with retinal ischemia who were admitted to the department of ophthalmology were referred to our department for the management of their carotid artery disease. Collaborations between physicians, ophthalmologists, neurologists and neurosurgeons are important for the diagnosis of retinal ischemia associated with carotid artery stenosis and to prevent future retinal and/or cerebral ischemic attacks.

CONCLUSION

Attentions to the future's stroke should be paid for patients with retinal ischemia of RAO, RVO and RTIA as well as patients with cerebral ischemia, because both patients could possess equivalent cerebro-cardiovascular risk factors.

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