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Retinal Vascular Obstruction and Asymptomatic Cerebral Infarction

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Purpose: The purpose of this study is to clarify the relationship between retinal vascular obstruction and asymptomatic cerebral infarction (ACI).

Methods: Forty-three patients (27 men and 16 women) with retinal vascular obstruction were examined by magnetic resonance imaging (MRI) at the Department of Ophthalmology of Nagasaki University Hospital in Nagasaki, Japan. Patients with a history of neurological signs and symptoms were excluded from this study. The control group consisted of 93 male and 49 female patients who were examined by MRI for routine brain screening examinations at the Takaki Neurosurgical Clinic in Fukuoka, Japan. We investigated the incidence of ACI, and the risk factors and characteristics of this condition.

Results: ACI was more common in patients with retinal vascular obstruction than in normal adults at all ages. The incidence of hypertension in the patients with ACI tended to be higher than in the patients without ACI.

Conclusion: ACI appears more frequently in patients with retinal vascular obstruction than in normal adults. Our results indicate that either retinal artery occlusion or retinal vein occlusion should be considered a sign of ACI and systemic diseases such as arteriosclerosis. **Jpn J Ophthalmol 2002;46:209–214** © 2002 Japanese Ophthalmological Society

Key Words: Asymptomatic cerebral infarction, hypertension, retinal vascular obstruction.

Introduction

Asymptomatic cerebral infarction (ACI) is sometimes seen in computed tomography (CT) and magnetic resonance imaging (MRI) of apparently healthy adults, and it is considered to be a sign of symptomatic cerebral disturbance. ACI is defined as cerebral infarction with no clinical cerebrovascular signs or symptoms.[1] A number of studies have examined the risk factors for ACI.[2–4] Many systemic factors such as hypertension, diabetes, and cardiovascular disease have been evaluated. They are consistent with those of retinal vascular obstruction. However, the relationship between ACI and retinal vascular obstruction has never been described,[3] and there is little information on the incidence of ACI in patients with retinal vascular obstruction, on the clinical features of such patients, or on the relationship between retinal vascular obstruction and ACI. The purpose of this study is to compare patients with retinal vascular obstruction and normal adults with respect to the incidence, characteristics and factors related to asymptomatic cerebral infarction.

Materials and Methods

Forty-three patients (27 men and 16 women) with retinal vascular obstruction were examined by MRI at the Department of Ophthalmology of Nagasaki University Hospital in Nagasaki, Japan, between January 1987 and August 1998. Patients with a his-

Received: May 21, 2001
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Published by Elsevier Science Inc.

0021-5155/02/$–see front matter
PII S0021-5155(01)00500-7

Jpn J Ophthalmol
Vol 46: 209–214, 2002

tory of neurological signs and symptoms were excluded from this study. Patients with retinal vascular obstruction were examined by MRI to determine whether or not they had had ACI. All patients with retinal artery occlusion (RAO) and retinal vein occlusion (RVO) were followed for more than 1 year. The control group consisted of 93 men and 49 women who had had MRI brain examinations as part of a routine check-up between January 1992 and August 1998 at Takaki Neurosurgical Clinic in Fukuoka. The MRI brain examinations of apparently healthy persons were performed because they requested screening for lesions such as cerebral infarctions, non-ruptured cerebral aneurysms, brain tumors, or congenital abnormalities. The images were taken in horizontal planes at the base of the anterior cranium. The same neurosurgeon at Takaki Neurosurgical Clinic read all the MRIs of patients and controls in a masked fashion.

The following items were studied: age, sex, MRI findings, and past histories of glaucoma, embolic disease, clotting abnormalities, hypertension, diabetes mellitus, and heart diseases. Diagnostic criteria for ACI are as follows: (1) despite vascular lesions in the brain, no neurological signs or symptoms, such as asymmetry of reflexes or cerebrovascular dementia; (2) no past history of cerebral apoplexy including transient ischemic attack; (3) confirmation of cerebral infarction by diagnostic imaging by computed tomography (CT) or MRI. MRIs were taken with a GE Sigma product (General Electric Medical Systems, Waukesha, WI, USA) at Nagasaki University Hospital and with a Hitachi MRP 20-1 product (Tokyo) at Takaki Neurosurgical Clinic. In this study the lesions considered to indicate ACI were 7.5 mm in diameter as evaluated by the same neurosurgeon. The patients were considered to have hypertension if they were already being treated for hypertension or found to have >160 mm Hg systolic or >90 mm Hg diastolic blood pressure at the time of examination. The patients were considered to have diabetes mellitus if they were already being treated for diabetes mellitus or found to have >110 mg/dL fasting glucose level. The patients were considered to have heart disease if they were being treated for heart disease or had an abnormal electrocardiogram. Nine of the 12 patients with RAO were admitted to our hospital and their coagulation and cholesterol levels were examined. Nine of the 31 patients with RVO were admitted to Nagasaki University Hospital, and their serum cholesterol levels were examined. Cross-sectional analysis and Welch's test were applied to the data obtained.

The study was performed according to the Declaration of Helsinki, and informed consent was obtained from each patient.

Results

Of the 43 patients with retinal vascular obstruction, 12 (8 men and 4 women) had RAO and 31 (19 men and 12 women) had RVO (Figure 1). The mean age of the patients with RAO was 60.8 years, ranging from 14 to 87 years, and that of the patients with RVO was 61.0 years, ranging from 37 to 79 years (Figure 1). The percentages of patients with RAO and ACI increased with age; from 50.0% in patients 41 to 50 years of age to 100% in those 61 years of age or older (Figure 2). The percentage of patients with RVO and ACI also increased with age; from 66.6% in patients aged 41 to 50 years of age to 87.5% in those 71 years of age or older (Figure 3).

None of the patients with RAO had a history of glaucoma. Of the 12 patients with RAO, 2 had vasculitis and their ages were in the fourth decade. None of the patients with RVO had a history of glaucoma, embolic diseases or clotting abnormalities.

There was no statistically significant difference in sex distribution between the patients with ACI and those without ACI. The traditional risk factors for stroke (hypertension, diabetes mellitus and heart disease)[2] in the patients with ACI were compared with those in the patients without ACI by cross-sectional examination ($P < .05$) (Figures 4 and 5). In the patient groups of both RAO and RVO, the incidence of hypertension in the patients with ACI is shown in Figures 4 and 5; it tended to be higher than in the patients without ACI. There was no such tendency in those with diabetes mellitus or heart disease. The serum cholesterol level was

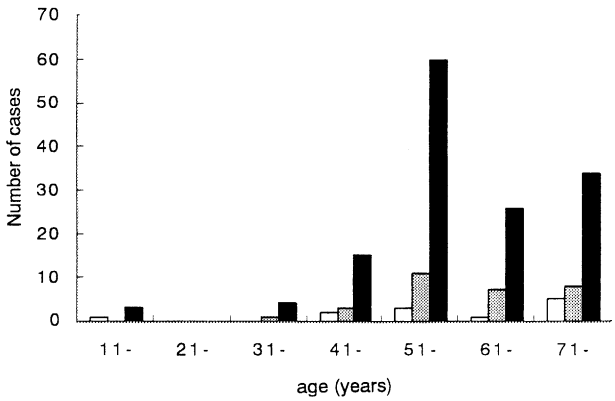

Figure 1. Age distribution of patients with retinal artery occlusion (RAO) or retinal vein occlusion (RVO), and controls. □: RAO, ▨: RVO; ■: control.

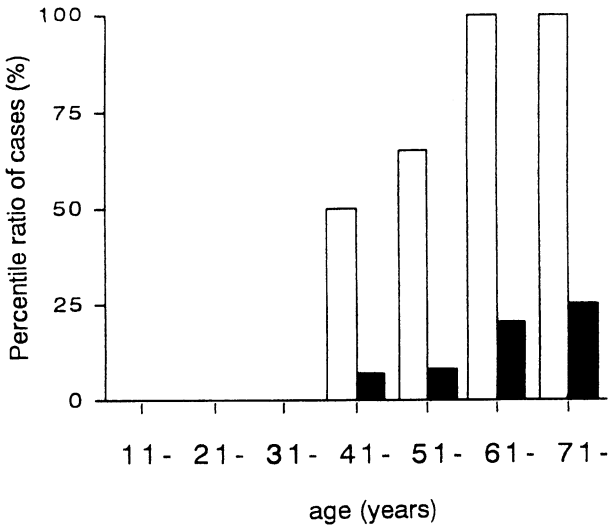

Figure 2. Age distribution of asymptomatic cerebral infarction patients with retinal artery occlusion (RAO) and controls. □: RAO, ■: control.

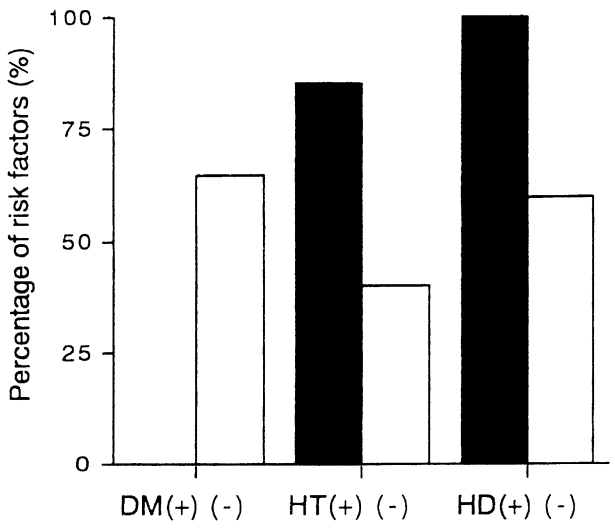

Figure 4. Percentage of traditional risk factors (hypertension, diabetes mellitus, heart disease) for asymptomatic cerebral infarction in patients with retinal artery occlusion. DM: diabetes mellitus, HT: hypertension, HD: heart disease. □: risk factor −, ■: risk factor +.

compared in patients with and without ACI by Welch's test. In the RAO group, there was no statistically significant difference in the serum cholesterol level or the hematological findings between patients with and without ACI. In the RVO group, there was no statistically significant difference in the serum cholesterol level between the patients with and those without ACI.

The types of cerebral infarction are shown in Table 1. The most common type of ACI seen in MRIs was lacunar infarction. Of the 12 patients with RAO, one had multiple infarctions. None of the patients with retinal vascular obstruction had cortical infarction.

The percentage of normal adults with ACI increased with age from 13.3% in adults aged 41 to 50

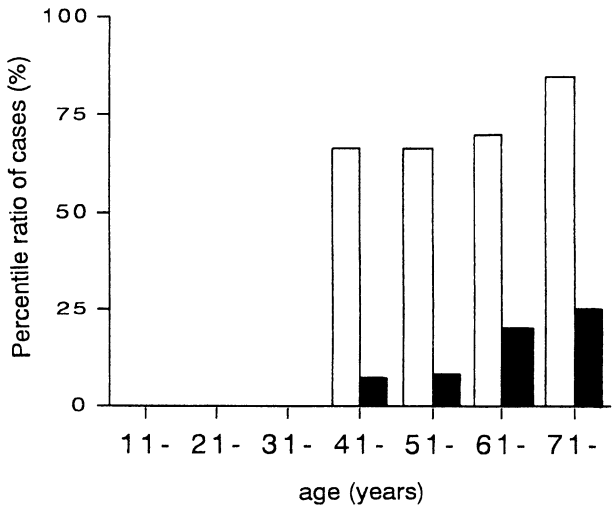

Figure 3. Age distribution of asymptomatic cerebral infarction patients with retinal vein occlusion (RVO) and controls. □: RVO, ■: control.

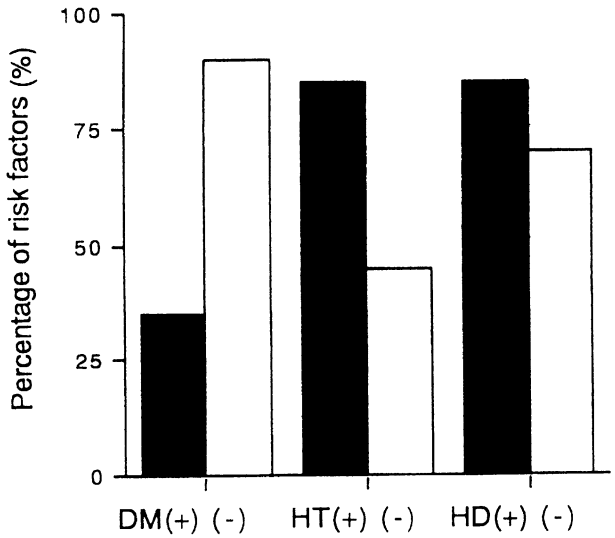

Figure 5. Percentage of traditional risk factors (hypertension, diabetes mellitus, heart disease) for asymptomatic cerebral infarction in patients with retinal vein occlusion. DM: diabetes mellitus, HT: hypertension, HD: heart disease. □: risk factor −, ■: risk factor +.

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Table 1. Types of Cerebral Infarction in Patients with Retinal Artery Occlusion (RAO) and Retinal Vein Occlusion (RVO)*

Type of Infarction	RAO	RVO	Total
Lacunar	8 (88.9)	23 (100)	31 (96.9)
Multiple	1 (11.1)	0 (0)	1 (3.1)
Cortical	0 (0)	0 (0)	0 (0)

*Values in parentheses are percentages.

years to 23.5% in those older than 71 years of age (Figures 2, 3). There was no tendency in the incidence of each traditional risk factor mentioned above in control adults with and without ACI. None of these risk factors was found to be significantly correlated with the incidence of ACI in this study.

Discussion

There is little information about the relationship between retinal vascular obstruction and ACI. Wijman et al[5] reported the incidence of cerebral microembolism detected by transcranial Doppler ultrasonography in patients with clinical evidence of retinal ischemia, including transient monocular blindness, central and branch retinal artery infarction, and ischemic oculopathy. Microembolisms were detected in 40.0% of middle cerebral arteries in the study group and in 9.2% of the controls. However, there have been no reports on the relationship between retinal vascular obstruction, including RAO and RVO, and ACI detected by MRI.

The MRI apparatus used in the present study for the detection of retinal vascular obstruction can visualize 1–2-mm lesions with 1.5 tesla resolution, but for the one used for health examinations the lesion must be 7.0 mm with 0.2 tesla resolution. The difference between the two apparatuses is too great to compare the patient group with the health screening group. However, it is very difficult to get an apparently healthy control group examined with a high quality MRI apparatus because such an apparatus is not usually used for health screening. In spite of this obstacle, the findings of the present study suggest that ACI occurs prior to the onset of retinal vascular obstruction.

The incidence of ACI in healthy adults is reported to increase with age.[3,4] ACI was found in 14.1% of healthy adults, and its incidence increased with age in this study. The incidence in healthy adults in the present study was similar to that in previous reports.[3,4] The present study indicates that the incidence of ACI in patients in the RAO and RVO groups is significantly higher at all ages than that in healthy adults. The incidence of ACI in patients with both RAO and RVO also increased with age. Although RAO has been reported to be related to systemic vascular disturbances, especially cerebral infarction,[6,7] RVO has not been shown to be related to cerebral infarction. We found that the incidence of ACI was also higher in RVO patients than in controls. The results suggest that not only RAO but also RVO is related to cerebral infarction, especially ACI.

The most frequent type of ACI in the MRIs of patients with RAO and RVO was lacunar infarction. Our results suggest that patients with RAO and RVO have a high possibility of having asymptomatic lacunar infarction.

The most frequent type of ACI in normal adults was lacunar infarction, and its incidence is reported to be approximately 80% of all lacunar infarctions.[8] Silent lacunar infarction is often asymptomatic and is found in elderly Japanese patients with hypercoagulability, endothelial cell damage and high Lp(a) levels.[9] However, in our study groups and controls, there was no statistically significant difference in the serum cholesterol level or the hematological findings between patients with and those without ACI. Lacunar infarcts have been defined by Fisher as small, deep cerebral infarcts resulting from occlusion of small penetrating cerebral arteries. Lacunar infarcts range in size from very small (3 to 4 mm) to large (1.5 to 2.0 cm).[10] Loeb et al[11] studied 383 consecutive patients with stroke and ischemic lesions on CT scan for the characteristics of symptomatic cerebral infarction and ACI. The larger infarctions tended to be symptomatic, whereas the very small ones were liable to be asymptomatic unless they were strategically located in a sensory or motor tract. In other words, ACI is assumed to be a sign of symptomatic cerebral infarction. Generally speaking, risk factors for ACI are similar to those for stroke such as symptomatic cerebral infarction.[2] There are various etiologies of lacunar infarction: microvascular diseases, such as lipohyalinosis and microatheromata,[12] as well as microemboli, microaneurysms, and arteritis.[13–15]

Persons with retinal emboli are at an increased risk of stroke-related death. In previous reports, patients with RAO most frequently had symptomatic cortical infarction.[16] This may be related to the fact that one of the causes of RAO and cortical infarction is thrombosis due to atherosclerosis. In patients without cardiac embolic sources, cerebral microembolism is frequently present on the same side as the retinal ischemia, particularly during the week after the onset of symptoms. Cerebral microembolism is often associated with se-

vere stenosis or occlusion of the ipsilateral carotid artery.[5] In this study, patients with RAO and RVO did not have asymptomatic cortical infarction. This means that cortical infarction tends to cause symptoms depending on its location in the brain and its size.

Kogure et al[16] reported that cerebral infarction was detected in 25% of the patients with RAO. Nakao et al[17] reported that the onset of symptomatic cerebral infarction of patients with RAO was mainly before the onset of RAO. The onset of symptomatic cerebral infarction in patients with RVO was mainly after the onset of RVO. The times of onset of RAO and symptomatic cerebral infarction were close to each other. Nakao stated that these results indicated a close relationship between arterial occlusion in the fundus and cerebral infarction, and that atheromatous arteriosclerosis seemed to be the common risk factor. On the other hand, there was only a slight relationship between RVO and stroke. Although cerebral vessels of patients with RAO are stenotic and obstructed,[18–20] the incidence of stroke in patients with RVO is not high.[1,21] The incidence of ACI in patients with RVO has not been reported yet. In our study, the incidence of ACI in patients with RVO was 64.5%, much higher than in normal adults.

ACI was especially frequently found in MRIs of patients with a history of hypertension. Arteriosclerosis advances with age and hypertension. As the cause of RVO, a thickened arterial wall reduces the caliber of the adjacent vein in a common sheath.[22] The resulting stenosis slows blood flow and increases viscosity. These changes may lead to RVO. Arteriosclerosis caused by hypertension has something to do with both retinal vascular obstruction and ACI. In the groups of patients with RAO and RVO, the incidence of hypertension in those with ACI was apt to be higher than in those without ACI. That is, patients with RAO and RVO have risk factors including hypertension and ACI.

According to Shinkawa et al,[4] patients with silent infarctions had higher levels of certain risk factors such as increased systolic and diastolic blood pressure than did those without stroke but lower levels than did those with a history of clinical stroke. This suggests that individuals with silent infarcts may be ranked as a moderate risk group for stroke.[1] In the same way, our results suggest that patients with retinal vascular obstruction should be ranked as a moderate risk group for stroke. Especially, patients with retinal vascular obstruction and hypertension are in a high-risk group for stroke, so they should be treated systemically.

Small lacunar infarctions appear to be asymptomatic. We found that the patients with retinal vascular obstruction, such as RAO and RVO, had ACI before retinal vascular obstruction. Therefore, regardless of the existence of symptoms, patients with retinal vascular obstruction may be at high risk for cerebral infarction. Moreover, our results indicate that RAO and RVO should be suspected as signs of ACI, symptomatic cerebral infarction and systemic diseases such as arteriosclerosis. Our next research project will focus on whether or not ACI in a patient with retinal vascular infarction has any correlation with the patient's life span.

References

1. Rubinstein K, Johnes EB. Retinal vein occlusion: long-term prospects, 10 years follow up of 143 patients. Br J Ophthalmol 1976;60:148–50.
2. Chodosh EH, Foulkes MA, Kase CS, et al. Silent stroke in the NINCDS stroke data bank. Neurology 1988;38:1674–9.
3. Kase CS, Wolf PA, Chodosh EH, et al. Prevalence of silent stroke in patients presenting with initial stroke: The Framingham Study. Stroke 1989;20:850–2.
4. Shinkawa A, Ueda K, Kiyohara Y, et al. Silent cerebral infarction in a community-based autopsy series in Japan. The Hisayama Study. Stroke 1995;26:380–5.
5. Wijman CA, Babikian VL, Matjucha IC, et al. Cerebral microembolism in patients with retinal ischemia. Stroke 1998;29: 1139–43.
6. Liversedge LA, Smith VH. Neuromedial and ophthalmic aspects of central retinal artery occlusion. Trans Ophthamol Soc UK 1962;82:571–6.
7. Karjialainen K. Occlusion of the central retinal artery and retinal branch arterioles. Acta Ophthalmol 1971;109:75.
8. Huchi K. Treatment with asymptomatic cerebral infarction in brain health examination. Rinsho to Kenkyu (Clin Res) 1999; 76:2406–12.
9. Kario K, Matsuo T, Kobayashi H. 'Silent' cerebral infarction is associated with hypercoagulability, endothelial cell damage, and high Lp(a) levels in elderly Japanese. Thromb Vasc Biol 1996;16:734–41.
10. Fisher CM. Lacunar strokes and infarcts: a review. Neurology 1982;32:871–6.
11. Loeb C, Gandolfo C, Del Sette M, Conti M, Finocchi C, Calautti C. Asymptomatic cerebral infarctions in patients with ischemic stroke. Eur Neurol 1996;36:343–7.
12. Fisher CM. Capsular infarcts. The underlying vascular lesions. Arch Neurol 1979;36:65–73.
13. Mohr JP. Lacunes. In: Barnett HJM, Mohr JP, Stein JM, Yatsu FM, eds. Stroke. New York: Churchill Livingstone, 1986;475–92.
14. Miller VT. Lacunar stroke. A reassessment. Arch Neurol 1983;40:129–34.
15. Mohr JP. Lacunes. Stroke 1982;13:3–11.
16. Kogure S, Iijima H. Retinal arterial obstruction and systemic disorders. Nippon Ganka Gakkai Zasshi (Acta Soc Opthalmol Jpn) 1991;95:67–72.
17. Nakao Y, Komai Y, Udaka H, Tanaka S. Relationship between occlusion of fundus vessels and stroke. Nihon Ganka Kiyo (Folia Ophthalmol Jpn) 1982;33:544–8.
18. Bruno A, Jones WL, Austin JK, Carter S, Qualls C. Vascular

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outcome in men with asymptomatic retinal cholesterol emboli. A cohort study. Ann Intern Med 1995;122:249–53.

19. Hayreh SS. Occlusion of the central retinal vessels. Br J Ophthalmol 1965;49:626–45.
20. Hayreh SS. So-called central vein occlusion: I. Pathogenesis, terminology, clinical features. Ophthalmologica 1976;172:1–13.
21. Elman MJ, Bhatt AK, Quinan PM, Enger C. The risk for systemic vascular diseases and mortality in patients with central retinal vein occlusion. Ophthalmology 1990;97:1543–8.
22. Weinberg D, Dodwell DG, Fern SA. Anatomy of arteriovenous crossings in branch retinal vein occlusion. Am J Ophthalmol 1990;109:298–302.