Large cerebral artery involvement in CADASIL

Abstract—The authors evaluated the involvement of large cerebral artery in 13 patients with cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) with angiography (12 MR and one conventional). Five patients (38%) showed stenosis: at the middle cerebral artery in three, vertebral artery in one, and the internal carotid artery in one. The stenosis persisted on follow-up angiogram in two patients. There were no differences in risk factors between patients with angiographic abnormality and those without, suggesting occasional involvement of large vessels in CADASIL.

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Eun J. Choi, MD; Choong G. Choi, MD; and Jong S. Kim, MD

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is a small vessel disease caused by mutations in the *Notch3* gene on chromosome 19. The clinical features include mood disorder, migraine with aura, recurrent subcortical infarcts, and vascular dementia.[1] Diffuse white matter hyperintensities, multiple lacunes, and microbleeds have been demonstrated on MRI.[2] A pathologic hallmark is a nonamyloid and nonatherosclerotic microangiopathy, which is associated with deposition of the granular osmiophilic material (GOM), degeneration of the vascular smooth muscle cells, and the stenosis of the lumen due to fibrotic thickening of the wall.[3] Although vascular abnormalities may involve the retina, peripheral nerve, skin, muscle, and visceral organs,[4] the brain is preferentially involved in these patients. Because small vessels are primarily involved, medium to large cerebral vessels have generally been considered normal.[5] However, a few angiographic studies have described involvement of distal cerebral arteries.[6] In this study, we evaluated the large cerebral artery involvement in patients with CADASIL.

Methods. Between January 2000 and January 2005, we studied 13 consecutive patients with CADASIL (two patients were sisters) of 12 families at the Department of Neurology, Asan Medical Center. They had at least one of the following symptoms: ischemic stroke or TIA, dementia, mood disturbances, and migraine with aura. In all patients, diagnosis was confirmed by identification of a mutation in the *Notch3* gene (n = 13) and by skin biopsy (n = 2). Vascular risk factors were recorded including hypertension (defined as receiving medication for hypertension or blood pressure >140/90 mm Hg on repeated measurements), diabetes mellitus (defined as receiving medication for diabetes mellitus, fasting blood sugar ≥126 mg/dL, or PP2 ≥200 mg/dL), cardiac disease, hypercholesterolemia (defined as receiving cholesterol-lowering agents or overnight fasting cholesterol level >200 mg/dL), current cigarette smoking (a current cigarette smoker or one who had quit less than 6 months previously), or heavy alcohol drinking (daily consumption of >60 g/day of alcohol).

Dementia was diagnosed according to *Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised* (DSM-III-R) criteria and Mini-Mental State Examination score <23. Migraine was diagnosed according to International Classification of Headache Disorder II. All patients underwent MRI and angiography (conventional angiography in one, MR angiography in 12). Follow-up MR angiograms were obtained in two patients to evaluate the change in stenosis. The vascular abnormality was confirmed by one neurologist and one neuroradiologist who independently assessed the patients' angiographic findings. The results were identical in all patients. Differences of the vascular risk factors or other variables between patients with angiographic abnormality and those without were assessed using Fisher's exact test and Mann-Whitney U test; $p < 0.05$ was regarded as significant.

Results. There were nine men and four women aged 40 to 69 (mean 55.0 ± 9.3 years (table 1). Vascular risk factors included hypertension in three patients, hypercholesterolemia in two, current cigarette smoking in four, and heavy alcohol drinking in one. Five patients did not have any conventional risk factors. Twelve patients had experienced TIA or completed strokes, eight had dementia, one had migraine, and four had mood disturbances.

The interval from the onset of the first CADASIL symptoms to the time of the angiogram evaluation ranged from 1 month to 9 years (mean 2.4 years). All patients had diffuse leukoaraiosis and multiple lacunes on bilateral subcortical white matters and basal ganglia, which were consistent with cerebral small vessel disease. Two patients (Patients 5 and 7) had additional territorial middle cerebral artery (MCA) infarcts on MRI. One of the two (Patient 7) did not have obvious angiographic abnormalities.

Five patients (38%) had angiographic abnormalities. Three patients showed MCA stenosis: M1 portion in two and M2 portion in one. There were proximal internal carotid artery (ICA) stenosis in one and distal vertebral artery (VA) stenosis in one patient (figure). Poorly visualized right VA in Patient 2 with ICA stenosis was considered a hypoplasia rather than occlusion of the vessel.

Patient 3 who presented with memory impairment and mood disturbances, but without clinical symptoms of stroke showed stenosis of the M1 portion of the left MCA. Follow-up MR angiogram four months later showed persistent stenosis of the MCA. Patient 5 did not show definite angiographic abnormalities at the time of first stroke. Two

From the Department of Neurology (Dr. E.J. Choi), University of Korea College of Medicine, Guro Hospital, Departments of Radiology (Dr. C.G. Choi) and Neurology (Dr. Kim), University of Ulsan College of Medicine, Asan Medical Center, Seoul, Korea.

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Address correspondence and reprint requests to Dr. Jong S. Kim, Department of Neurology, Asan Medical Center, 388-1, Pungnap-dong, Songpa-gu, Seoul 138-736, South Korea; e-mail: jongskim@amc.seoul.kr

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Table 1 *Summary of the patient characteristics*

Patient/age, y/sex	*Notch3* mutation	Risk factors	Symptoms	Interval, y*	Pattern of MRI lesions	Angiographic findings
1/55/M	R75P†	Hypertension hypercholesterolemia	S, D	2	Multiple lacunes, WMH	Right distal VA stenosis
2/69/M	R544C	None	S	1	Multiple lacunes, WMH	Right ICA stenosis
3/60/F	R133C	None	D, Mo	3	Multiple lacunes, WMH	Left MCA M1stenosis
4/46/M	C988Y†	Hypertension, Current smoking	S, D	6	Multiple lacunes, WMH	Right MCA M2 stenosis
5/52M	R110C	None	S	2	Multiple lacunes, WMH MCA territorial infarct	Right MCA M1 stenosis
6/56/F	R75P†	Hypercholesterolemia	S	9	Multiple lacunes, WMH	Normal
7/66/M	R75P†	Hypertension	S, D	1	Multiple lacunes, WMH MCA territorial infarct	Normal
8/46/M	R544C	Current smoking	S, D, Mo	0.1	Multiple lacunes, WMH	Normal
9/40/M	R133C	Current smoking	S, D, Mo	1	Multiple lacunes, WMH	Normal
10/49/F	C174R	None	S, M	1	Multiple lacunes, WMH	Normal
11/47/F	C174R	None	S	0.1	Multiple lacunes, WMH	Normal
12/60/M	R75P†	Current smoking	S, D	3	Multiple lacunes, WMH Petechial hemorrhages	Normal
13/69/M	R587C†	Alcohol	S, D, Mo	2	Multiple lacunes, WMH	Normal

* From the onset of symptom to evaluation of angiogram.
† Novel mutation.

S = stroke or TIA; D = dementia; M = migraine; WMH = white matter hyperintensity lesions; VA = vertebral artery; ICA = internal carotid artery; Mo = mood disturbances; MCA = middle cerebral artery.

years later when she developed left hemiparesis, a stenosis of the M1 portion of the right MCA was found. Diffusion weighted MRI at this time showed scattered ischemic lesions on the right MCA territory. Follow-up angiogram four months later showed persistent MCA stenosis (figure).

When the patients with angiographic abnormality and those without were compared, there were no differences in the age, sex, mean duration of the disease, and the frequency of vascular risk factors (table 2).

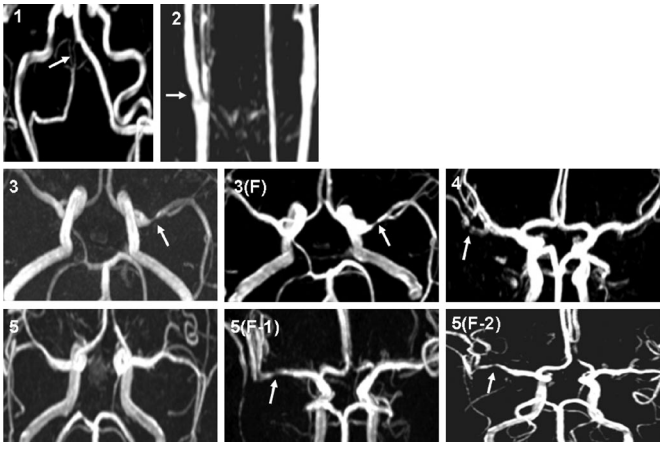

Figure. MR angiograms showing stenosis of cerebral arteries (Patients 1, 2, 3, 4, and 5). The initial angiogram of Patient 5 shows no definite abnormalities, but the follow-up images 2 years later show focal stenosis of the right middle cerebral artery (Patient 5 [F-1]). The stenosis persists in Patients 3 (F) and 5 (F-2). Number indicates Patient number. F = follow-up images.

Discussion. We found that as many as five of 13 (38%) patients had angiographic abnormality in large cerebral arteries. Considering that patients with CADASIL frequently suffer from migraine,[1] angiographic abnormalities, especially those shown in patients with MCA diseases, may have been caused by transient vasospasm. However, this is unlikely because follow-up angiography in two of these patients demonstrated persistent abnormalities. Because two of the five patients with angiographic abnormalities (40%) had at least one vascular risk factor, part of our observation may be due to the concomitant presence of atherosclerosis. However, the other three patients did not have any risk factors. Moreover, there was no difference in the age or risk factors between patients with large vessel abnormality and those without. Therefore, it seems possible that the large cerebral artery involvement shown in angiographic studies represents irreversible vascular change caused by CADASIL as in arterioles.[3]

Although more than 400 patients with CADASIL have been reported worldwide, angiographic abnormalities in the cerebral vessels have been rarely reported.[6] Multifocal segmental stenosis of cerebral arteries similar to primary angiitis of the CNS[6] and coronary artery occlusion[7] were described in patients

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Table 2 *Comparison of the patients with angiographic abnormality and those without*

	Mean age ± SD, y	Mean duration of disease ± SD, y	Hypertension, n = 3	Hypercholesterolemia, n = 2	Alcohol, n = 1	Current smoking, n = 4
Abnormality present (n = 5)	56.4 ± 8.6	2.8 ± 1.9	2	1	0	1
Abnormality absent (n = 8)	54.1 ± 10.3	2.1 ± 2.9	1	1	1	3

with CADASIL. Regarding the pathology of cerebral vessels, the data have been conflicting. One study did not demonstrate the stenosis of cerebral vessels,[8] whereas another described increased thickness of the wall of white matter arterioles and the presence of stenosis of vascular lumen.[3] One autopsy study reported the presence of GOM deposition with relatively preserved vascular smooth muscle cells in the aorta, carotid, and renal arteries.[4] Recently, the presence of atherosclerotic changes in the basilar artery, ICA, and anterior, middle, and posterior cerebral arteries were described in Japanese patients with CADASIL who did not have any vascular risk factors.[9] Therefore, a large cerebral artery abnormality may represent accelerated atherosclerosis in the presence of endothelial cell damage associated with GOM deposition, although we do not know what triggers large vessel diseases in particular patients.

Our study has limitations. The number of patients was small, a pathologic study was not performed, and conventional angiography was performed in only one patient. However, conventional angiography has usually been avoided in patients with CADASIL because of the high rate of complications.[10] Further studies are warranted to elucidate the precise incidence of large cerebral vessel involvement in patients with CADASIL. Pathologic verification of the stenotic vessel character is also needed.

Finally, even in those with angiographic abnormality, our patients' symptoms were mainly caused by cerebral small vessel diseases. Only one patient (Patient 5) had territorial infarction due to the MCA stenosis. Therefore, although our data showed a relatively high frequency of large cerebral vessel involvement, they do not refute the fact that it is a small vessel disease that is clinically responsible in the majority of patients with CADASIL.

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Correction

Cellular telephones and the risk for brain tumors

During a review of the data analyzed in the article "Cellular telephones and the risk for brain tumors" (*Neurology* 2005;64:1189–1195) by Christensen et al., a recoding of the data yielded a change in the distribution of nonresponders among controls. Some controls previously coded as excluded due to ineligibility were recoded as nonresponders and consequently the participation rate changed from 64% to 52%. This correction of coding errors does not change the main result of the analysis but underscores the overall conclusion that more meaningful and generalizable results will be obtained when the pooled Interphone study results are reported as a whole.

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