



Cerebral Arterial Stenosis in Patients with Spontaneous Intracerebral Hemorrhage

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Objective : Spontaneous intracerebral hemorrhage (ICH) and ischemic stroke share common vascular risk factors such as aging and hypertension. Previous studies suggested that the rate of recurrent ICH and ischemic stroke might be similar after ICH. Presence of cerebral arterial stenosis is a potential risk factor for future ischemic stroke. This study investigated the prevalence and factors associated with cerebral arterial stenosis in Korean patients with spontaneous ICH.

Methods : A total of 167 patients with spontaneous ICH were enrolled. Intracranial arterial stenosis (ICAS) and extracranial arterial stenosis (ECAS) were assessed by computed tomography angiography. Presence of ICAS was defined if patients had arterial stenosis in at least one intracranial artery. ECAS was assessed in the extracranial carotid artery. More than 50% luminal stenosis was defined as presence of stenosis. Prevalence and factors associated with presence of ICAS and cerebral arterial stenosis (presence of ICAS and/or ECAS) were investigated by multivariable logistic regression analysis.

Results : Thirty-two (19.2%) patients had ICAS, 7.2% had ECAS, and 39 (23.4%) patients had any cerebral arterial stenosis. Frequency of ICAS and ECAS did not differ among ganglionic ICH, lobar ICH, and brainstem ICH. Age was higher in patients with ICAS (67.6 ± 11.8 vs. 58.9 ± 13.6 years $p=0.004$) and cerebral arterial stenosis (67.9 ± 11.6 vs. 59.3 ± 13.5 years, $p<0.001$) compared to those without stenosis. Patients with ICAS were older, more frequently had diabetes, had a higher serum glucose level, and had a lower hemoglobin level than those without ICAS. Patients with cerebral arterial stenosis were older, had diabetes and lower hemoglobin level, which was consistent with findings in patients with ICAS. However, patients with cerebral arterial stenosis showed higher prevalence of hypertension and decreased kidney function compared to those without cerebral arterial stenosis. Multivariable logistic regression analyses showed that aging and presence of diabetes independently predicted the presence of ICAS, and aging, diabetes, and hypertension were independently associated with presence of cerebral arterial stenosis.

Conclusion : 19.2% of patients with spontaneous ICH had ICAS, but the prevalence of ECAS was relatively lower (7.2%) compared with ICAS. Aging and diabetes were independent factors for the presence of ICAS, whereas aging, hypertension, and diabetes were factors for the cerebral arterial stenosis.

Key Words : Cerebral hemorrhage · Diabetes · Hypertension · Cerebral arterial stenosis · Computed tomography angiography.

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INTRODUCTION

Spontaneous intracerebral hemorrhage (ICH) usually results from the rupture of small arteries in the brain and represents 10–30% of all strokes²⁰. ICH is associated with high rate of mortality and long-term disability in survivors. ICH and ischemic stroke share common vascular risk factors such as aging and hypertension. Secondary prevention of recurrence is the main treatment goal after prior stroke for both ischemic and hemorrhagic stroke. Importantly, several studies reported no differences of frequency of hemorrhagic or ischemic stroke recurrence after prior ICH^{7,8,26}. However, risk factors and features of recurrent stroke after ICH are not firmly established. Extracranial carotid stenosis is a well-known risk factor for stroke. Furthermore, it is widely accepted that intracranial cerebral arterial stenosis (ICAS) is more prevalent in Asians than in Caucasian stroke population, and 30–50% of stroke in Asians is suggested to be caused by ICAS^{3,25}. Therefore, detection of cerebral arterial stenosis, such as ICAS and extracranial cerebral arterial stenosis (ECAS) may have clinical significance for secondary stroke prevention in ICH patients. Although a previous study suggested that ICAS or ECAS occur in one-fifth of patients with ICH²², little is known of the prevalence and factors associated with cerebral arterial stenosis in patients with ICH.

We investigated the prevalence of ICAS and ECAS, and analyzed the factors predicting the presence of arterial stenosis in patients presenting with spontaneous ICH.

MATERIALS AND METHODS

Patients

Patients with spontaneous ICH who were admitted to a tertiary university hospital were included. Patients were retrospectively identified from the neurosurgical database for ICH between January 2009 to December 2012. The inclusion criteria were as follows: 1) spontaneous ICH within 24 hours of presumed symptom onset, 2) patients underwent computed tomography angiography (CTA), and 3) age >18 years. The exclusion criteria were ICH due to secondary causes like arteriovenous malformation, Moyamoya disease, traumatic ICH, aneurysm, neoplasm, and hemorrhagic conversion of cerebral infarction. The local institutional review board ap-

proved this retrospective study and waived the need for informed consent.

CTA and cerebral arterial stenosis

CTA was used to analyze the presence of intracranial and extracranial stenosis. All patients underwent multi-detector CTA, which was performed using a Brilliance 40-channel CT v2.2 (Philips Medical System, Best, The Netherlands) with the following parameters: 120 kVp, 300 mA, 0.8 mm slice thickness, 0.3 mm slice acquisition interval, a pitch of 0.67, and intravenous administration of 150 mL of iodinated contrast media (Omnipaque 300) at a rate of 4.0–4.5 mL/s under the control of an auto-injection protocol. Imaging data were transferred to two computer workstations (Extended Brilliance Workspace v3.0 and Rapidia v2.8) for post-processing.

Stenosis was determined as the ratio of the diameter at the segment of most severe stenosis divided by the diameter of a proximal or nearby normal segment²¹. More than 50% stenosis was defined as arterial stenosis. We analyzed stenosis for intracranial artery and extracranial artery. Intracranial arteries that were evaluated were the intracranial segment of internal carotid artery, basilar artery, anterior cerebral artery, middle cerebral artery, and posterior cerebral artery. Extracranial stenosis was analyzed in the extracranial portion of the internal carotid artery. We excluded the extracranial and intracranial vertebral arteries from this analysis since the hypoplastic vertebral arteries are frequently found in normal subjects, which make it difficult to differentiate between non-specific hypoplasia and atherosclerotic stenosis. Location of ICH were categorized as lobar (cortical and subcortical), ganglionic (putamen and thalamus), and infratentorial (brainstem and cerebellum).

Clinical characteristics

The Glasgow coma scale was recorded to assess the initial neurological status on admission, and patient's functional outcome at discharge and 90 days were assessed using the Glasgow outcome scale (1 to 5, good recovery to death). Hypertension was defined as a self-reported use of blood pressure-lowering medication or history of hypertension or blood pressure >160/100 mmHg at least 1 week after stroke onset. Diabetes mellitus was defined present if patient was taking hypoglycemic medication or had a random glucose

level ≥ 200 mg/dL. Dyslipidemia was defined when using anti-lipidemic agent or total cholesterol level ≥ 220 mg/dL or low-density lipoprotein cholesterol level ≥ 160 mg/dL. Current cigarette smoking was considered a positive smoking habitus. The estimated glomerular filtration rate (eGFR) was calculated using the equation proposed by the MDRD study group¹³⁾.

Statistical analysis

Baseline characteristics and location of ICH were compared between patients with ICAS and without ICAS. We also compared patients with cerebral arterial stenosis (defined as presence of ICAS and/or ECAS) and those without cerebral arterial stenosis. Baseline characteristics and location of ICH were compared using chi-square test and the Student t-test, as appropriate. Multivariable analyses were performed via multiple logistic regression to determine the factors associated with presence of ICAS and cerebral arterial stenosis. In multivariable analysis, variables with $p < 0.2$ from the univariate analysis

and biologically plausible variables were selected as potential factors for statistical analysis. All analyses were performed using PASW statistics version 18.0 (IBM Corp., Armonk, NY, USA).

RESULTS

Present study included 187 patients with spontaneous ICH. Of them, 20 patients who did not undergo CTA were excluded from this analysis. The main reason for not performing CTA was irritability and/or unstable patient condition due to acute stroke. Therefore, 167 patients were finally included. Mean age was 61.3 ± 13.6 years. Sixty five (38.9%) were female, 59.3% had hypertension, 16.8% had diabetes, 19.2% had dyslipidemia, and 23.4% were current smoker (Table 1).

Among the 167 patients who underwent CTA, 32 (19.2%) had at least one ICAS, and 15 (9%) had multiple ICAS (Table 2). Extracranial carotid stenosis was detected in 12 (7.2%) patients, and 39 (23.4%) patients had cerebral arterial stenosis (ICAS and/or ECAS). Patients with ICAS were older, more frequently had diabetes, and had a higher initial serum glucose level than those without ICAS. Hemoglobin level was lower in patients with ICAS (Table 3). However, other vascular risk factors and laboratory finding did not differ between the two groups. Location of hemorrhage (lobar, ganglionic, and infratentorial) and volume of ICH also did not differ between the patients with and without ICAS. Patients with cerebral arterial stenosis (ICAS and/or ECAS) were older, had diabetes

Table 1. Baseline characteristics

	Value (n=167)
Female sex	65 (38.9)
Age (years)	61.3 ± 13.6
Hypertension	99 (59.3)
Diabetes	28 (16.8)
Dyslipidemia	32 (19.2)
Previous stroke	29 (17.4)
Current smoking	39 (23.4)
Initial GCS	12.6 ± 3.3
Discharge GOS	3.3 ± 0.7
3 months GOS	3.4 ± 0.9
Leukocyte (mm^3)	9244 ± 3874
Hemoglobin (g/dL)	14.1 ± 1.8
Serum glucose (mg/dL)	148.1 ± 53.1
Total cholesterol (mg/dL)	182.5 ± 44.4
HDL cholesterol (mg/dL)	55.0 ± 18.6
LDL cholesterol (mg/dL)	111.5 ± 40.7
Triglyceride (mg/dL)	105.8 ± 81.2
Serum creatinine (mg/dL)	0.93 ± 0.48
eGFR (mL/min/1.73m^2)	89.7 ± 28.5

Values are presented as mean \pm standard deviation or number (%). GCS : Glasgow coma scale, GOS : Glasgow outcome scale, HDL : high-density lipoprotein, LDL : low-density lipoprotein, eGFR : estimated glomerular filtration rate

Table 2. Radiological features

	Value (n=167)
Location of ICH	
Ganglionic	118 (70.6)
Lobar	28 (16.8)
Brainstem/cerebellum	21 (12.6)
Intracranial stenosis	32 (19.2)
Middle cerebral artery	19 (11.4)
Posterior cerebral artery	2 (1.2)
Internal carotid artery	12 (7.2)
Basilar artery	6 (3.6)
Multiple stenosis	15 (9)
Extracranial stenosis	12 (7.2)

Values are presented as number (%). ICH : intracerebral hemorrhage

and lower hemoglobin level, which is consistent with the findings of patients with ICAS. However, patients with cerebral arterial stenosis had higher prevalence of hypertension and decreased kidney function estimated by eGFR compared to those without cerebral arterial stenosis (Table 4).

Multivariable logistic regression analyses showed that aging and presence of diabetes independently predicted the presence of ICAS. However, other factors including hypertension and dyslipidemia were not associated with the presence of ICAS (Table 5). Factors independently predicting the presence of cerebral arterial stenosis using multivariable logistic regression

Table 3. Comparison between patients with intracranial stenosis and those without stenosis

	With stenosis (n=32)	Without stenosis (n=135)	p-value
Age (years)	67.6±11.8	58.9±13.6	0.004
Female sex	14 (43.8)	51 (37.8)	0.533
Hypertension	24 (75)	75 (56.8)	0.059
Diabetes	11 (34.4)	17 (12.9)	0.004
Dyslipidemia	7 (21.9)	25 (18.9)	0.707
Previous stroke	6 (18.8)	23 (17.4)	0.86
Current smoking	6 (18.8)	33 (25)	0.456
Initial GCS	12.4±3.6	12.6±3.2	0.83
Discharge GOS	3.1±0.9	3.4±0.7	0.062
3 months GOS	3.1±1.1	3.5±0.8	0.014
Initial SBP (mmHg)	183±35	174±38	0.273
Leukocyte (mm ³)	8887±5248	9329±3486	0.653
Hemoglobin (g/dL)	13.5±1.9	14.2±1.8	0.033
Serum glucose (mg/dL)	168±52	143±52	0.017
Total cholesterol (mg/dL)	177±44	183±45	0.459
HDL cholesterol (mg/dL)	52±13.6	55.7±19.6	0.327
LDL cholesterol (mg/dL)	110.8±39.5	111.7±41.1	0.912
Triglyceride (mg/dL)	92.5±76.8	108.9±82.2	0.327
Serum creatinine (mg/dL)	1.2±0.9	0.9±0.2	0.102
eGFR (mL/min/1.73m ²)	81.8±36.7	91.5±25.9	0.082
Location of ICH			0.981
Ganglionic	23	95	
Lobar	5	23	
Brainstem/Cerebellum	4	17	

Values are presented as mean±standard deviation or number (%). GCS : Glasgow coma scale, GOS : Glasgow outcome scale, SBP : systolic blood pressure, HDL : high-density lipoprotein, LDL : low-density lipoprotein, eGFR : estimated glomerular filtration rate

analysis were aging, diabetes, and hypertension. Multivariable logistic regression analysis for ECAS was not done since the sample size of patients with ECAS (n=12) was not enough to demonstrate the effect in multivariable modeling.

DISCUSSION

Present study shows that 19.2% of patients with spontaneous ICH had ICAS. Multivariable analysis identified aging

Table 4. Comparison between patients with cerebral arterial stenosis (presence of intracranial and/or extracranial stenosis) and those without cerebral arterial stenosis

	With stenosis (n=39)	Without stenosis (n=128)	p-value
Age (years)	67.9±11.6	59.3±13.5	<0.001
Female sex	15 (38.5)	50 (39.1)	0.946
Hypertension	29 (74.4)	70 (54.7)	0.041
Diabetes	13 (33.3)	15 (12)	0.002
Dyslipidemia	9 (23.1)	23 (18)	0.52
Previous stroke	8 (20.5)	21 (16.4)	0.596
Smoking current	9 (23.1)	30 (23.4)	0.906
Initial GCS	12.5±3.4	12.6±3.2	0.982
Discharge GOS	3.2±0.8	3.4±0.7	0.13
3month GOS	3.2±0.9	3.5±0.8	0.039
Initial SBP (mmHg)	182±36	174±38	0.26
Leukocyte (mm ³)	8980±5077	9326±3442	0.692
Hemoglobin (g/dL)	13.6±1.8	14.2±1.8	0.046
Serum glucose (mg/dL)	164±54	143±52	0.034
Total cholesterol (mg/dL)	181±48	183±43	0.794
HDL cholesterol (mg/dL)	54.8±15.6	55.0±19.4	0.946
LDL cholesterol (mg/dL)	112.2±45.2	111.3±39.4	0.913
Triglyceride (mg/dL)	90.7±75.1	110.4±82.7	0.21
Serum creatinine (mg/dL)	1.1±0.9	0.9±0.2	0.057
eGFR (mL/min/1.73m ²)	80.2±33.7	92.6±26.1	0.018
Location of ICH			0.511
Ganglionic	26	92	
Lobar	6	22	
Brainstem/Cerebellum	7	14	

Values are presented as mean±standard deviation or number (%). GCS : Glasgow coma scale, GOS : Glasgow outcome scale, SBP : systolic blood pressure, HDL : high-density lipoprotein, LDL : low-density lipoprotein, eGFR : estimated glomerular filtration rate, ICH : intracerebral hemorrhage

Table 5. Multivariable logistic regression analysis for presence of intracranial stenosis and cerebral arterial stenosis (presence of intracranial and/or extracranial stenosis)

	OR	95% CI	p-value
Intracranial stenosis			
Age (per 1 year)	1.05	1.01–1.09	0.015
Female sex	0.79	0.29–2.17	0.647
Hypertension	2.49	0.88–7.01	0.085
Diabetes	3.09	1.12–8.56	0.03
Dyslipidemia	1.32	0.46–3.81	0.607
Prior stroke	0.53	0.16–1.71	0.285
Smoking	1.66	0.51–5.42	0.4
Hemoglobin	0.89	0.68–1.16	0.38
eGFR	0.99	0.98–1.01	0.689
Cerebral arterial stenosis			
Age (per 1 year)	1.07	1.03–1.12	0.001
Female sex	0.53	0.20–1.41	0.201
Hypertension	2.95	1.09–7.95	0.032
Diabetes	3.33	1.21–9.16	0.02
Dyslipidemia	1.66	0.61–4.56	0.323
Prior stroke	0.57	0.18–1.74	0.322
Smoking	2.53	0.84–7.62	0.099
Hemoglobin	0.9	0.69–1.18	0.445
eGFR	0.99	0.98–1.01	0.345

OR : odds ratio, CI : confidence interval, eGFR : estimated glomerular filtration rate

and diabetes as independent factors associated with the presence of ICAS. Compared with ICAS, extracranial carotid stenosis was less frequently found (7.2%). Any presence of cerebral arterial stenosis (presence of ICAS and/or ECAS) was observed in 23.4% of the patients. Aging, hypertension, and diabetes were factors for the presence of cerebral atherosclerosis.

Evidence of cerebral atherosclerosis in patients with spontaneous ICH has been sparsely investigated until recently. A Japanese study reported that 13% of patients had ICAS and 9% had ECAS (combining extracranial carotid artery and extracranial vertebral artery)²²⁾. However, the prevalence of cerebral atherosclerosis in patients with ICH has not been reported in the western population. It is well known that ICAS is more prevalent in Asians than in Caucasian stroke population³⁾, and reportedly causes up to 30–50% of ischemic strokes in Asians²⁵⁾. Several studies investigated the prevalence of asymp-

tomatic ICAS in patients presenting with ischemic stroke in another vascular territory. Coexisting asymptomatic ICAS was highly prevalent (27%) in patients with ischemic stroke enrolled in the WASID trial¹⁸⁾. ICAS was reported in 10% and was symptomatic in 7% of Norwegian ischemic stroke/TIA population¹⁵⁾. However, the prevalence of asymptomatic ICAS in subjects without stroke is not well established. Transcranial Doppler study in subjects with vascular risk factors showed that 12% had ICAS with increasing prevalence that correlated with the increasing number of vascular risk factors²⁴⁾. A prevalence study of ICAS in a non-stroke population showed that aging was associated with ICAS, reflecting the strong relationship between aging and atherosclerotic burden. Although we do not know the real prevalence of ICAS in different population groups (ischemic stroke, ICH, and non-stroke), the prevalence of ICAS in patients with ICH as shown in our study is comparable to previously-reported prevalence of asymptomatic ICAS in those with ischemic stroke.

The risk of recurrent stroke in patients with symptomatic ICAS is among the highest of the stroke subtypes¹¹⁾. A recent randomized controlled trial in patients with ICAS reported a risk of any recurrent stroke or death of 17.5% at 1 year and 19.8% at 2 years despite best medical management⁶⁾. However, despite the high risk of subsequent vascular events in patients with symptomatic ICAS, the significance of asymptomatic ICAS remains unknown. The risk of stroke from asymptomatic stenosis is thought to be relatively low¹⁸⁾, however, other study showed asymptomatic ICAS is significant risk factor for future stroke¹⁶⁾. Furthermore, presence of asymptomatic ICAS may portend advanced atherosclerosis and could be a risk marker for subsequent vascular event as suggested by high prevalence of coronary artery disease in patients with symptomatic ICAS^{1,17)}. It is, therefore, possible that the presence of asymptomatic ICAS in patients with ICH may suggest higher risk of ischemic vascular event despite incident hemorrhagic stroke.

ICH and ischemic stroke share common vascular risk factors such as aging and hypertension. Recurrent stroke after prior ICH could present as either hemorrhagic or ischemic subtypes, although the epidemiology and features of recurrent stroke after ICH are unclear. Recurrent ICH has been reported to occur more frequently than ischemic stroke after prior ICH^{2,9)}. However, other studies claimed that there are no differences of recurrence between hemorrhagic and ischemic

stroke or numerically higher rate of recurrent ischemic stroke after prior ICH^{7,8,26}). Which clinical characteristics represent higher risk for ischemic stroke among ICH population is still unknown. Therefore, secondary stroke prevention strategy for reducing ischemic stroke event in patients with prior hemorrhagic stroke has not been established. Our study showed that ICH patients with older age and diabetes have higher risk for ICAS, and those with diabetes and hypertension are at higher risk for cerebral atherosclerosis, which might have a clinical implication for preventing subsequent ischemic event in patients with prior ICH.

Lobar and non-lobar ICH are presumably caused by different types of microangiopathy, and risk factors for ICH may vary according to the location of ICH¹²). Regarding the location of ICH, lobar ICH frequently recurs as lobar ICH suggesting the participation of cerebral amyloid angiopathy as a main pathogenesis, but ganglionic ICH may have a chance of recurrence both as infarction and ganglionic ICH, suggesting the participation of intracranial atherosclerosis^{7,14,19}). However, the presence of cerebral arterial stenosis did not differ between patients with lobar and non-lobar ICH in the present study, and further larger sample size study is required to elucidate the association between cerebral arterial stenosis and location of ICH.

ICAS is more prevalent in Asian, and black people than in Caucasians. As well, small vessel disease such as hypertensive ICH and lacunar infarcts are more prevalent in Asians. In keeping with this epidemiologic association, patients with lacunar stroke often experience hemorrhagic stroke^{4,10}). The reasons for differing prevalence of ICAS, lacunar infarct, and ICH among populations remain unknown. Hypertension is the most important risk factor for small vessel disease and, it has been suggested that the role of hypertension may be greater in ICAS than in ECAS^{5,23}). Therefore, it can be speculated that hypertensive vascular damage might be the factor linking ICAS and ICH.

There are several limitations to our study. First, this was a retrospective cross-sectional analysis. Therefore, whether the presence of cerebral arterial stenosis implicate poor vascular prognosis or not could not be addressed and remains to be determined by further prospective investigation. Second, because the sample size was relatively small, the association of arterial stenosis and location of ICH was not determined in the present study. Further studies with a larger sample size are

required to analyze the relation of ICH pattern and arterial stenosis. Also, because of the relative scarcity of patients with extracranial carotid stenosis, we did not analyze the characteristics of patients with ICH and extracranial carotid stenosis. Third, other causes of arterial stenosis such as vasospasm after ICH could not be excluded because follow-up angiography was not done in most patients. Finally, although we investigated the prevalence of ICAS and ECAS in patients with ICH, prevalence of ICAS and ECAS in non-stroke population was not available in the present study. Therefore, significance of presence of arterial stenosis in ICH population compared to non-stroke population could not be clearly determined in the present study. Further study enrolling subjects with ICH, ischemic stroke, and non-stroke population are required to clarify the association between ICH and cerebral arterial stenosis.

CONCLUSION

This study showed that 19.2% of patients with spontaneous ICH had ICAS, but the prevalence of ECAS was relatively lower (7.2%) compared with ICAS. Aging and diabetes are factors associated with the presence of ICAS, and aging, diabetes, and hypertension are associated with the presence of cerebral arterial stenosis in patients with ICH. Because stroke recurrence could present as either ischemic or hemorrhagic stroke, further studies regarding the predictors of different subtypes of recurrent stroke should be undertaken in patients with ICH.

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