Different Vascular Risk Factors Associated with Cervical and Cerebral Atherosclerotic Steno-occlusions in Patients with Acute Ischemic Stroke

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Abstract

Background: Besides race-ethnicity, the role of other risk factors that can be related to the distribution of cerebral atherosclerosis has been controversial. We determined if there were vascular factors related to the extra- and intracranial atherosclerosis in ischemic stroke patients.

Methods: We studied 856 consecutive patients with ischemic stroke admitted to our two hospitals over a 5-year period. We excluded patients who had potential cardiogenic source of embolism. The information about potential vascular risk factors, such as age, sex, arterial hypertension, diabetes mellitus, hyperlipidemia, cigarette smoking, and alcohol consumption, was obtained from medical records. We determined the location and severity of atherosclerotic lesions on MR angiography (MRA). The presence of atherosclerotic lesion in intracranial cerebral arteries and extracranial carotid artery was defined as 50% or more narrowing of luminal diameter or occlusion on MRA. We compared the vascular risk factors between patients with extra- and/ or intracranial atherosclerosis and those with no atherosclerotic lesion.

Results: The intracranial atherosclerotic lesion on MRA was found in 355 patients (41.5%). Of the other patients 61 (7.1%) had steno-occlusive extracranial carotid artery disease, and 78 (9.1%) had combined extracranial carotid and intracranial atherosclerotic lesions. Multivariate logistic regression analyses showed that hyperlipidemia was associated with the extracranial carotid atherosclerosis (OR, 4.12; 95% CI, 1.21-9.11; p<0.01), but that diabetes mellitus was only associated with intracranial atherosclerosis (OR, 3.26; 95% CI, 1.45 – 6.52; p<0.01).

Conclusion: Our data suggest that the factors associated with extra- and intracranial artery lesion were different. Diabetes mellitus may be associated with the development of intracranial atherosclerosis, which is predominant in Korean stroke patients.

Introduction

Intracranial atherosclerosis has been more often found in Asians, Hispanics, and African Americans, compared with Caucasians [1,2]. Inzitari et al. [3] reported that race was the only factor that was independently associated with the location of the atherosclerosis in the cohort of the EC/IC study. However, in the Northern Manhattan Stroke Study, non-white race was not an independent risk factor for intracranial atherosclerosis [4]. The information on whether race is an independent factor for these lesions has been less well-studied. Besides race-ethnicity, the role of other risk factors that can be related to the distribution of atherosclerosis is also under debate. Most previous studies included different race populations and sought a difference between races or between populations with intracranial lesions and those with extracranial lesions [5,6].

Although race plays an important role in determining the sites at which disease is predominant, we speculate that factors other than race determine whether a patient develops occlusive cerebrovascular disease. All of our patients were from a single racial population (Korean) and racial differences did not influence our results.

We reviewed the findings on MR angiography (MRA) in each patient with ischemic stroke and compared potential vascular risk factors between patient subgroups according to the locations of atherosclerotic lesions. We sought specific vascular factors that influenced the distribution of the atherosclerotic lesions and determined if there were the factors related to the extra- and intracranial atherosclerosis in Korean stroke patients.

Methods

The patients were identified from a prospectively collected computerized stroke registry of 1212 consecutive patients with ischemic stroke who were admitted to Eulji University Hospital between May 2011 and April 2014. We excluded 271 patients

who had potential cardiogenic sources of embolism such as atrial fibrillation, valvular heart disease, sick sinus syndrome, myocardial infarction and 15 who had stroke due to unusual cause such as venous stroke, moyamoya disease, arterial dissection, and vasculitis. We also excluded 70 patients who did not undergo MRA. Finally, 856 patients were included in this study.

Two sets of MRA using the three-dimensional time-of flight technique were performed separately at the circle of Willis level, which shows the intracranial arteries and the cervical carotid levels, that showed the extracranial arteries. We determined the location and severity of atherosclerotic lesions on MRA. The percentage of stenosis was calculated using the luminal diameter at the point of great stenosis to the normal part of the artery just distal to the narrowing [7]. The presence of atherosclerotic lesion was defined as 50% or more narrowing of luminal diameter or occlusion on MRA. The origin of the vertebral artery could not be accurate evaluated because of the limitation of MRA that did not include the origin of vertebral artery. Angiographic findings were interpreted by two readers blinded to clinical data, and an acceptable level of agreement for the presence of an occlusive lesion on was found (k = 0.92, p< 0.05). In case of disagreement, the reading was determined by consensus.

Demographic data and potential vascular risk factors for each patient were obtained from the stroke database and medical records. Hypertension was defined as a systolic blood pressure ≥140 mmHg and/ or a diastolic blood pressure ≥90 mmHg based on repeated measurements or previous diagnosis and antihypertensive drug use. Diabetes mellitus was diagnosed if patients had a history of insulin or oral hypoglycemic agent use, or if fasting blood glucose was above 7.0 mmol/L (126 mg/dL). Hyperlipidemia was defined if patients had previous diagnosis and cholesterol-lowering drug use, or if total serum cholesterol level on admission to the hospital was above 5.7 mmol/L (220 mg/dL). We also collected information on smoking (current or past) and heavy alcohol consumption (≥2 drinks per day).

A χ^2 test was used to assess a difference of categorical data between the subgroups. The numbers of expected frequencies in each cell of the contingency table were more than 5. Group means were compared by the 2-tailed t test. Normality of each variable was observed on the Kolmogorov-Smirnov test.

Logistic regression models were used to assess the independent factor related to the site of the atherosclerotic lesions (intracranial atherosclerosis, extracranial carotid atherosclerosis, or combined extracranial carotid and intracranial atherosclerosis), and to estimate odds ratio (OR) and the 95% confidence interval (CI). To adjust for the effects of other factors, age (≥ 65 years) was fitted as independent dichotomous variables. We used logistic regression models including the potential 7 variables above, with the Bonferroni correction used for multiple comparisons when appropriate. The Hosmer-Lemeshow goodness-of fit χ^2 test was used to assess the model fit. Reference group for all models comprised patients without atherosclerotic lesion. The values of p < 0.05 were considered significant. All statistical analyses were performed with the use of commercially available software (SPSS-PC, Version 14.0; SPSS Inc, Chicago, Ill).

Results

Of the 856 patients, 362 (42.3%) had no atherosclerotic lesion in intracranial arteries or extracranial carotid arteries. The intracranial steno-occlusive lesion was found in 355 patients (41.5%) and 61 (7.1%) had the extracranial carotid artery disease on MRA. The combined extracranial carotid and intracranial atherosclerotic lesions were found in 78 patients (9.1%). The intracranial steno-occlusive lesion was most frequently encountered in the middle cerebral artery (MCA) and the atherosclerotic lesions of MCA were found in 142 patients (16.5%). The steno-occlusive lesions in intracranial internal carotid artery (ICA), MCA, or basilar artery (BA) were found in 246 patients.

On univariate analysis (**Table 1**), diabetes mellitus was more often found in the patients with intracranial atherosclerotic lesions alone than in those without atherosclerotic lesion (35.5% vs. 19.5%; p<0.0001). The other demographic data and risk factors did not show a significant difference between the two groups. Compared to the patients without atherosclerotic lesion, the patients with extracranial carotid disease showed higher hyperlipidemia (39.1% vs. 15.5%, p<0.0001). In the patients with combined extracranial carotid and intracranial steno-occlusive lesions, the prevalence of diabetes mellitus (44.4% vs. 19.5%, p<0.0001) and hyperlipidemia (31.5% vs. 15.5%, p=0.003) were higher than in the patients without atherosclerotic lesion (**Table 1**).

Table 1 Different vascular risk factors according to the locations of atherosclerotic lesion on MR angiography.

Risk factors	Location of atherosclerotic lesions			
	Absent (n=362)	Intracranial cerebral arteries alone (n=355)	Extracranial carotid artery alone (n=61)	Extracranial carotid and intracranial cerebral arteries (n=78)
Age, mean (SD), y	67.7 (8.1)	68.3 (10.6)	69.3 (8.5)	69.4 (9.4)
Sex, male	178 (49.2)	167 (47.0)	32 (52.5)	43 (55.1)
Hypertension	256 (70.7)	253 (66.2)	42 (69.6)	53 (68.5)
Diabetes mellitus	70 (19.5)	126 (35.5)**	11 (17.4)	35 (44.4)**
Hyperlipidemia	56 (15.5)	79 (22.3)	24 (39.1)**	25 (31.5)**

Heavy alcohol consumption	31 (8.6)	37 (10..5)	6 (9..4)	8 (9.8)
Cigarette smoking	142 (39.1)	116 (32.7)	24 (39.5)	31 (40.1)

Data are given as number (percentage) of patients unless otherwise indicated. Reference group for three models comprises patients without atherosclerotic lesion (n=362). *, significant p-value determined by the χ^2 and t-test with the Bonferroni correction (x3); *P<0.05; **P<0.01.

On multivariate logistic regression analysis (**Table 2**), diabetes mellitus was only associated with the intracranial atherosclerosis (OR, 3.26; 95% CI, 1.45 to 6.52; p=0.003; Hosmer-Lemeshow goodness-of-fit χ^2=10.86; df=8; P=0.61). On the other hand, hyperlipidemia was associated with extracranial carotid atherosclerosis (OR, 4.12; 95% CI, 1.21 – 9.11, p=0.009; Hosmer-Lemeshow goodness-of-fit χ^2=8.30; df=8; P=0.82). In the patients with combined extracranial carotid and intracranial atherosclerosis, diabetes mellitus (OR, 3.01; 95% CI, 1.47-6.15; p=0.001), and hyperlipidemia (OR, 2.54; 95% CI, 1.12-5.57, p=0.03) also showed significant differences, compared to those without atherosclerotic lesion.

Table 2 Odds ratio and confidence interval on multivariate logistic regression according to the presence of the atherosclerotic lesions.

Risk factors	Odd ratio (95% confidence interval)		
	Intracranial steno-occlusion alone (n=355)	Extracranial carotid steno-occlusion alone (n=61)	Extracranial carotid and intracranial steno-occlusions (n=78)
Old age, (≥65 years)	1.41 (0.89 - 2.13)	3.21 (0.60 - 5.11)	2.02 (0.44 - 6.29)
Male sex	0.98 (0.61 - 1.55)	0.83 (0.24 - 2.87)	0.73 (0.33 - 1.62)
Hypertension	0.95 (0.63 - 1.44)	0.93 (0.32 - 2.72)	0.89 (0.43 - 1.86)
Diabetes mellitus	3.26 (1.45 - 6.52)**	0.58 (0.21 - 2.22)	3.01 (1.47 - 6.15)**
Hyperlipidemia	1.44 (0.87 - 2.37)	4.12 (1.21 - 9.11)**	2.54 (1.12 - 5.57)*
Heavy alcohol consumption	1.84 (0.93 - 3.64)	3.96 (0.81 - 9.29)	3.21 (0.91 - 8.76)
Cigarette smoking	0.72 (0.44 - 1.16)	0.85 (0.22 - 3.27)	0.85 (0.37 - 1.93)

Reference group for all models comprises patients without atherosclerotic lesion. *, significant p-value determined by logistic regression models with the Bonferroni correction (x3); *P<0.05; **P<0.01.

Diabetes mellitus was also the only associated factor with the intracranial atherosclerosis in 246 patients who had steno-occlusive lesions only in intracranial ICA, MCA, or BA, compared to those without intracranial steno-occlusive lesion. (OR, 2.30; 95% CI, 1.45 to 3.66; p=0.001; Hosmer-Lemeshow goodness-of-fit χ^2=9.79; df=8; P=0.89).

Discussion

Our results showed that diabetes mellitus was the significant factor associated with intracranial atherosclerosis. Diabetes mellitus has been well known as a major risk factor for ischemic stroke. It is known from case-control studies of stroke patients and prospective epidemiological studies that diabetes has an independent effect on ischemic stroke with an increased relative risk in diabetics ranging from 2 to nearly 6-fold [8].

However, the role of diabetes on intracranial atherosclerosis is not well known. Nishimaru et al. [9] reported that coronary artery disease was more common in American patients, but the frequency of diabetes mellitus was greater in Japanese patients. Sacco et al found that no difference between races in the proportion of patients with extracranial atherosclerotic stroke, while intracranial atherosclerosis was more frequently in African Americans and Hispanics than in Caucasians [10]. The greater prevalence of diabetes mellitus and hypercholesterolemia in African American and Hispanics accounted for the increased frequency of intracranial atherosclerotic stroke. They also mentioned the race-ethnic disparities in the impact of stroke risk factors in other study [11,12]. There was another report that type 2 diabetes mellitus was more common in native American, African Americans, Hispanic Americans, Asian Americans, Pacific Islander compared to European Americans [13]. These data indicating that diabetes mellitus is more frequent in Asians, Hispanics, and African Americans than Caucasians can partially explain the racial difference of intracranial atherosclerotic lesions. Recently several studies reported that diabetes was involved with the development of intracranial atherosclerosis [14,15]

One of the authors reported similar results that diabetes mellitus was associated with combined intracranial atherosclerosis in patients who had steno-occlusive extracranial carotid artery disease, although different study population and the other angiographic method were included [16].

Besides race-ethnicity, however, the role of other risk factors that can be related to the distribution of atherosclerosis is also under debate among past several studies. The risk factors related to intracranial atherosclerosis were hypertension, smoking, and serum cholesterol in some studies [17,18]. Other studies showed that hypertension, coronary artery disease, serum cholesterol, and smoking were associated with extracranial atherosclerosis [19-21]. Most previous studies included different race populations and sought a difference between races or between populations with intracranial lesions and those with extracranial lesions.

Patients with intracranial atherosclerosis tend to be older than patients with normal intracranial vessels, but younger than patients with extracranial atherosclerosis [3]. Our results showed no age difference according to the presence location of cerebral atherosclerosis. We speculate that evolving pattern of extra- and intracranial atherosclerosis in Asian patients may be different from that in Caucasians.

Intracranial atherosclerotic disease has been estimated to occur in about 10-65% of Asian patients [22], and accounting for 30-50% of all ischemic strokes [23], depending on the study methods and definition of intracranial atherosclerotic disease. The proportion of patients with intracranial atherosclerosis in this study seemed slightly higher than those of other studies. We considered a possibility of misclassification and overestimation of the frequency of intracranial atherosclerotic on MRA because there was a difficulty to discriminate between true atherosclerotic steno-occlusive lesion and agenesis or hypoplasia in some intracranial arteries, especially anterior cerebral arteries, vertebral arteries, or posterior cerebral arteries. Thus, we reanalyzed the data of patients with the steno-occlusive lesions in the MCA, ICA, or BA. It also showed the same result that diabetes was associated with atherosclerotic lesions in intracranial ICA, MCA, or BA.

Limitation

Some limitation in this study should be discussed. The main limitation is inherent to its cross-sectional design, that is; it does not permit the identification of true risk factors. The authors use 'factors associated with (or related to)' intra- and extracranial atherosclerosis instead of 'risk factor'. Most of the included patients were admitted to our hospital for acute stroke. Complete cardiac work-up cannot be performed in all patients. Moreover, cardioembolic mechanism cannot be completely excluded even if there is no definite abnormality in cardiac evaluation. Embolic occlusion with partial recanalization can angiographically resemble stenosis, especially in the acute phase of stroke. The other limitation was that results did not include quantitative information about each vascular factor, for example, the duration and severity of disease or exposure, or the effect of medication because of the retrospective review.

Conclusion

In conclusion, our data suggest that the factors related to extra- and intracranial arterial lesions are different. Diabetes mellitus may be associated with the development of intracranial atherosclerosis, which is predominant in Korean stroke patients.

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