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Title	The Impact of Atherosclerotic Factors on Cerebral Aneurysm Is Location Dependent : Aneurysms in Stroke Patients and Healthy Controls
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Citation	Journal of stroke & cerebrovascular diseases, 23(9), 2301-2307 https://doi.org/10.1016/j.jstrokecerebrovasdis.2014.04.019
Issue Date	2014-10
Doc URL	https://hdl.handle.net/2115/57774
Type	journal article
File Information	manuscript2.pdf

Hokkaido University Collection of Scholarly and Academic Papers : HUSCAP

The impact of atherosclerotic factors on cerebral aneurysm is location-dependent: Aneurysms in stroke patients and healthy controls

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Disclosure Statement

There is no conflict of interest to report.

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Running Title: The impact of atherosclerotic factors on aneurysms

Abstract

Previous studies have indicated that cerebrovascular diseases (CVDs) seem to increase the occurrence of unruptured intracranial aneurysms (UIAs). However, this may be explained by the fact that CVDs and UIAs share common risk factors, such as hypertension (HT) and smoking. To clarify the impact of atherosclerotic risk factors on cerebral aneurysmal formation, we explored the incidence of UIAs and their locations in healthy controls and patients with CVD, who frequently have atherosclerotic risk factors. This study included consecutive 283 asymptomatic healthy adults and 173 acute stroke patients, from patients diagnosed with acute cerebral hemorrhage or cerebral infarction and admitted to our hospital. The incidence, maximum diameter, and location of UIAs were evaluated, and we also investigated the following factors: age, gender, current smoking, HT, diabetes mellitus (DM), and dyslipidemia. UIAs were found in 19 of the total 456 subjects (4.2%), 11 of 283 healthy subjects (3.9%), and 8 of 173 stroke patients (4.6%). These differences are not statically significant. The incidence of MCA aneurysms was significantly higher in the CVD patients than in the healthy controls ($p=0.03$), and the incidence of paraclinoid aneurysms was significantly higher in the healthy controls than in the CVD patients ($p=0.03$). Moreover, higher incidences of HTs and CVDs in the MCA aneurysms than in the other locations of UIAs were observed. These results indicate that the impact of atherosclerotic factors on cerebral aneurysmal formation depends on their location, and that there is a stronger impact on MCA aneurysms than on para-clinoid aneurysms.

Keywords: cerebral aneurysms; location; atherosclerotic factor

Many studies have investigated risk factors for unruptured aneurysms [1-5]. These risk factors have been generally divided in two categories: congenital or inherited defects weakening the arterial wall, and atherosclerotic factors. Female sex, positive family history for subarachnoid hemorrhages (SAHs), previous history of unruptured intracranial aneurysms (UIAs), and polycystic kidney disease are all nonmodifiable risk factors for UIAs [5]. In contrast, hypertension (HT) and smoking are well-established modifiable risk factors; the evidence for other possible modifiable risk factors, such as dyslipidemia, diabetes mellitus (DM), and excessive alcohol use, are limited and sometimes conflicting [1, 2, 4, 5].

UIAs are incidentally found when a brain MRA is performed in asymptomatic healthy volunteers [6, 7]; UIAs in stroke patients are also incidentally detected [2, 5, 6, 8-10]. Some previous studies indicated that cerebrovascular diseases seem to increase the occurrence of UIAs [5, 11]. However, the relationship between UIAs in CVD patients and in healthy subjects still remains unclear. As far as we know, only one report evaluates whether or not UIAs are more frequent in CVD patients than in healthy controls [6]. They found no statistical differences in frequency of UIAs and their locations between the two groups. In their report, however, the incidence of internal carotid artery (ICA) aneurysms was found to be 47% in healthy controls and 28% in stroke patients, even though this difference is insignificant. This may suggest that nonmodifiable factors have stronger effects on ICA aneurysmal formation than arteriosclerotic risk factors, and that those atherosclerotic factors have stronger effects on other UIA locations. Thus, it may be possible that each risk factor has a different effect on each aneurysmal formation, due to their unique location..

To clarify the impact of atherosclerotic risk factors on cerebral aneurysmal formation, we explored the incidence of UIAs and their locations in healthy controls and patients with CVD, who frequently have atherosclerotic risk factors.

Patients and Methods

Patients

This study included consecutive 283 asymptomatic healthy adults (153 males and 130 females) and 173 acute stroke patients (111 males and 62 females) between April 2012 and March 2013. The present study was approved by the ethics committee of Kushiro Rousai Hospital.

A total of 283 asymptomatic healthy adults (the healthy group) underwent a physical check-up, including brain MRI and MRA in our hospital, during the study period. In Japan, "Brain Dock", a formalized screening system for asymptomatic brain diseases are popular and all these asymptomatic adults voluntarily paid and applied for brain dock at our hospital. Therefore, most of the subjects lived in the vicinity, and they volunteered for the examinations without any investigator's prejudiced selection.

Thus, there was nothing in their medical history that could bias the detection of UIAs. The healthy subjects who had experienced an MRA within 3 years or who had a past history of CVD were excluded.

A total of 173 patients (the CVD group) were diagnosed with an acute intracerebral hemorrhage ICH) or a cerebral infarction and were admitted to our hospital during the period. The patients were sub-classified into cardiac embolism, non-cardiac cerebral infarction, and intracerebral hemorrhage. For all patients, MRIs and MRAs were routinely performed within two weeks from onset. Those who could not undergo an MRI or an MRA, such as patients with pacemakers or those with severe damage and who died after discharge, were excluded from this study. Also excluded were patients with a past history of CVD or whose UIAs were found by previous examination. Consequently, there were no prejudiced selection criteria to detect UIAs in the stroke patients' clinical history.

Methods

Clinical data were collected from the patients' medical records. In this study, the authors used the following factors: age, gender, current smoking habit, HT (systolic blood pressure >140mm Hg or diastolic blood pressure >90 mm Hg) or current treatment status, DM (hemoglobin A_{1C} .6.5) or currently treatment status, and dyslipidemia (serum low-density lipoprotein cholesterol >140mg/dl) or current treatment status.

UIAs were diagnosed by a three-dimensional time-of–flight (3D TOF) MRA. The incidence, maximum diameter, and location of each UIA were evaluated. In this study, aneurysms longer than 3 mm were defined as UIAs. Aneurysmal locations were classified as follows: (1) intracranial-paraclinoid ICA (C2-3) aneurysm; (2) distal portion from posterior communicating artery bifurcation of ICA aneurysm, including internal carotid artery-posterior communicating artery (IC-PC) aneurysm and internal carotid artery-anterior choroidal artery (IC-AC) aneurysm; (3) middle cerebral artery (MCA) aneurysm; (4) anterior cerebral artery (ACA) aneurysm, including anterior communicating (A-com) artery and distal ACA aneurysms; and (5) posterior fossa aneurysms.

Statistics

All data are expressed as mean ± SD. Clinical variables—including age, gender, aneurysm size, location, smoking habit, HT, DM, and dyslipidemia—were compared by use of χ^2 test or unpaired t-test as appropriate. Multivariate logistic regression analysis was performed to determine whether the incidence of UIAs was associated with the clinical variables with a P value of <0.1 in univariate analysis. Differences with a P value of <0.05 were considered statistically significant.

Results

Clinical Data and incidence of UIAs

Characteristics of the patients and incidence of UIAs in this study are represented in Table 1. The mean age of all subjects was 63.1±12.8 ; the mean age for the healthy subjects was 58.3±10.6; the mean age for the stroke patients was 71.2±9.5; the percentage of males was higher in stroke patients than in healthy subjects. There are significant differences in age and gender between the two groups. Moreover, history of HT and DM and smoking habit were more frequently observed in the stroke patients than in the healthy subjects (67.1%, 30.6%, and 30.1% in the stroke patients versus 23.7%, 9.2%, and 18.0% in the healthy subjects, respectively) with significant differences. Thus, there were significant differences in risk factors between the two groups.

UIAs were found in 19 of the total 456 subjects (4.2%), 11 of the 283 healthy subjects (3.9%), and 8 of the 173 stroke patients (4.6%). In the stroke patients, UIAs were recognized in 0 of 51 (0%) with cardiac embolisms, 3 of 79 with non-cardiac infarctions (6.3%), 5 of 43 with ICH (7.0%). The incidence of UIAs was slightly higher in the stroke patients, although this difference is not statically significant by univariate analysis.

Risk factors for UIA formation are represented in Table 2. Occurrence of HT and CVD were slightly higher in the subjects with UIAs. Multivariate logistic regression analysis was performed to determine whether the incidence of UIAs was associated with the clinical variables, such as gender and age, with a P value of <0.1 in univariate analysis. The female ratio was the only significant variable associated with incidence of UIAs (p=0.042).

Location

The characteristics of the UIAs found in this study are shown in Table 3. In the 11 aneurysms found in the healthy group, there were 5 para-clinoid aneurysms. Meanwhile, in the 10 aneurysms of the 8 patients detected in the CVD Group, there were 7 MCA aneurysms in 5 patients.

According to univariate analysis using χ^2 test, the incidence of MCA aneurysms was significantly higher in the CVD group than in the healthy group (p=0.03), and the incidence of paraclinoid aneurysms was significantly higher in the healthy group than in the CVD group (p=0.03).

Considering the distinction of location (Table 4A), we found significantly higher incidence of HT (p=0.033) and CVD (p=0.041) in the MCA aneurysms. We also found a lower incidence of CVD in the para-clinoid ICA aneurysms (p=0.045). Risk factors for MCA aneurysm formation are represented in Table 4B. Occurrence of HT and CVD were higher in the subjects with MCA aneurysms, with a P value of <0.1 in univariate analysis. Their odds ratios were rather high at 7.6 and 8.2, respectively. However, multivariate logistic regression analysis showed no significant differences in those variables associated with incidence of MCA aneurysms, probably because of the small number of each aneurysm location.

Illustrative case

A 62 year-old female smoker with HT was admitted with left cerebellar infarction, due to atherosclerotic change of the left vertebral artery (Fig. 1A-B). Bilateral MCA aneurysms were found by MRA on admission (Fig. 1C). An intraoperative photograph of the left MCA aneurysm shows atherosclerotic changes in the parent artery and an aneurysm (arrows in Fig. 1D)

Discussion

In this study, we observed significantly higher incidences of MCA aneurysms in stroke patients than in healthy adults, and we found higher incidences of HT and CVD in the MCA aneurysms than in the other UIAs. Meanwhile, incidence of paraclinoid aneurysms were significantly higher in the healthy controls than in the stroke patients, while there was a significantly lower incidence of CVD in the para-clinoid ICA aneurysms than in the others. Therefore, it is suggested that the impact of

atherosclerotic factors on cerebral aneurysmal formation depends on their location, and that these factors have stronger impact on MCA aneurysms than para-clinoid aneurysms. Although this is a relatively small study, this report is unprecedented in that it explores the differences of location with respect to the impact of atherosclerotic factors.

Incidence of UIAs

In the present study, incidental UIAs were found in 3.9% of healthy subjects. Previous studies have determined the prevalence of UIAs as being about 2 to 6.5 % of the general population [5, 7, 12]. In the study of UIAs by Nakagawa et al., out of 400 Japanese volunteers who underwent an MRA, 27 asymptomatic UIAs were found in 26 subjects (6.5%) [7]. Iwamoto et al. reported prevalence of UIAs as being 4.6% in a Japanese community, based on a consecutive autopsy series [12]. Meta-analysis conducted by Valk et al. reported the incidence of UIAs as being 2 to 4% and the prevalence ratio as being 1.7 for atherosclerosis [5].

Here, incidental UIAs found in stroke patients was measured at 4.6%, which is slightly higher than in 3.9% of healthy controls. Previous studies indicate that cerebrovascular diseases (CVDs) seem to increase the occurrence of UIAs [5, 11]. However, this may be clarified by the fact that CVDs and UIAs share common risk factors, such as HT and smoking. Some report a higher prevalence of UIAs in patients with ICA stenosis, and they speculate that atherosclerosis can generate morphological changes causing fibrous tissue deposition, leading to weakened vessels, dilation, and aneurysmal formation [2, 11, 13]. Several Japanese studies have reported UIAs in 3.2 to 5% in the patients with cerebral infarction and 3.2-4.7% in those with cerebral hemorrhaging [6, 14, 15].

Location

In this study, there were more MCA aneurysms in stroke patients and less paraclinoid aneurysms in healthy adults. Contrary to our results, Ishikawa et al. found no statistical differences in the

frequency of UIAs and their locations between the two groups [6]. As mentioned before, however, ICA aneurysms were found to be greater in healthy controls than in stroke patients with no statistical significance in their report. Moreover, several Japanese studies [16-20] have also demonstrated a higher incidence of MCA aneurysms in stroke patients; but this may be caused by biased selection criteria that detects UIAs in the background of stroke patients. In this study, however, there were no biased stroke patient selection criteria.

Risk factors

Many studies have determined risk factors for UIAs, such as female sex, positive family history for SAHs or UIAs, polycystic kidney disease, and atherosclerotic factors, including HT and smoking [1-5]. In most of those studies, however, the risk factors were investigated for general UIAs, without distinguishing location. As in Ishikawa et al[6], our study compares UIAs in CVD patients to those in healthy controls. These studies demonstrate that female sex is the only independent risk factor for overall UIAs. However, by distinguishing locations, our study demonstrates a significantly higher incidence of HT and CVD in MCA aneurysms and a lower incidence of CVD in para-clinoid ICA aneurysms. Therefore, some of the factors may be offset by the general evaluation for UIAs, as there can be differences in the impact on aneurysmal formation between the locations. Several reports suggest that the risk factors for aneurysmal formation depend on their locations [21-24]. Inagawa et al. conducted a community-based study and found more ruptured A-com aneurysms in men and relatively more in those who smoked or drank than those with aneurysms at other sites [22]. Moreover, paraclinoid aneurysms are infrequent lesions with very specific particularities, namely, that there are found in an extremely high ratio of females to males and at a relatively younger age [23, 24]. They speculate that those aneurysms may be mainly influenced by nonmodifiable factors and hemodynamic stress [23], which have a stronger impact on paraclinoid aneurysms than other

aneurysms.

Furthermore, the present study saw a higher incidence of CVD in the MCA aneurysms as an independent factor. In our recent study [10], annual risk of cerebral infarction or intracerebral hemorrhage after clipping of unruptured aneurysms was much higher than that in the general population. Moreover, although we did not describe their detailed location in the article , there were 8 patients with MCA aneurysms out of 10 patients who had experienced symptomatic cerebrovascular events in the long-term follow-up periods after clipping surgery for UIAs. Therefore, it may be possible that CVD is directly associated with unruptured aneurysm formation, especially MCA aneurysms, and not due to common risk factors, such as HT and smoking.

This study has limitations, in that the number of patients was relatively small. This reduces the generalizability of the results, especially in investigating distinct locations. Larger studies are needed to confirm that impacts on UIA formation are contingent upon their location.

Conclusions

We found a higher incidence of MCA aneurysms and a lower incidence of para-clinoid aneurysms in stroke patients than in healthy adults. There were also more HT and CVD in those with MCA aneurysms. These results may suggest that impact of atherosclerotic factors on cerebral aneurysmal formation is location dependent, and that they have a stronger impact on MCA aneurysms than para-clinoid aneurysms.

Acknowledgements

The authors deeply thank Momoe Miyamoto for her secretarial work.

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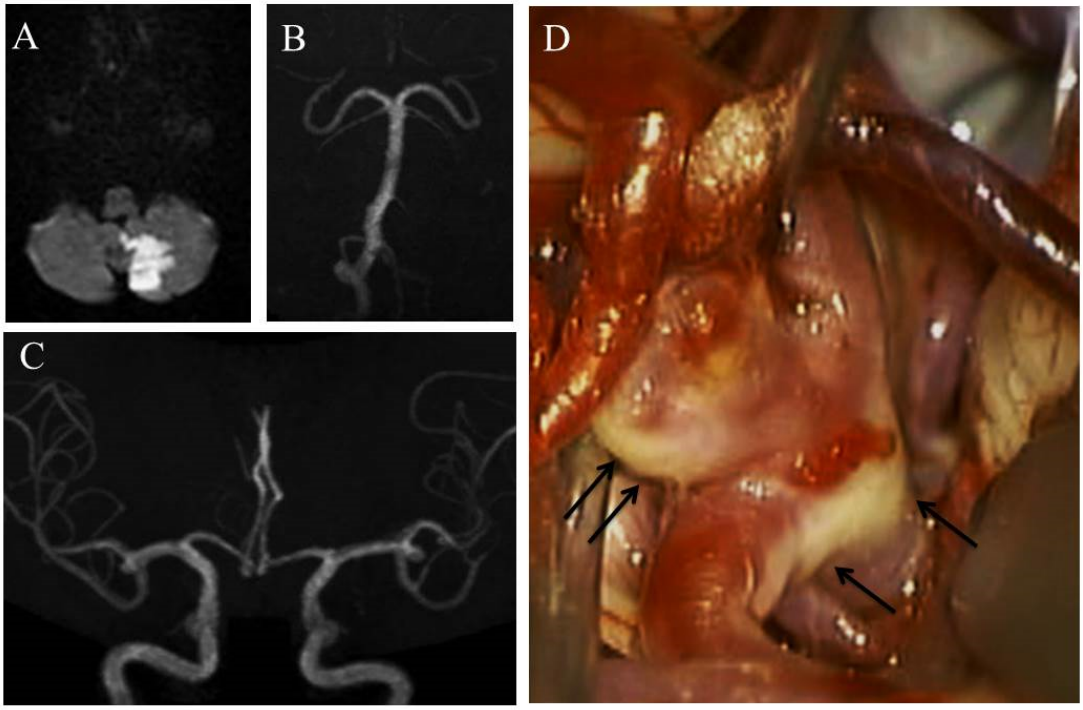
Figure 1. MRI diffusion-weighted image shows left cerebellar infarction (Fig.1A) and MRA illustrates atherosclerotic change of the left vertebral artery (Fig.1B). MRA on admission demonstrates the bilateral MCA aneurysms (Fig.1C). Fig.1D is an intraoperative photograph of the left MCA aneurysm when she underwent lipping surgery 6 months after the cerebellar infarction. It shows atherosclerotic changes in parent artery and aneurysm (arrows in Fig.1D).



	Total	Healthy group	CVD group	Cardiac embolism	Other infacction	ICH	Univariate (P<0.05) Healthy group vs CVD group
Number of patients	456	283	173	51	79	43	
Age mean in y±SD	63.2±12.8	58.3±10.6	71.2±12.0	76.0±11.5	70.0±10.7	71.2±12.0	<0.001*
Male/Female	264/192	153/130	111/62	31/20	53/26	27/16	0.03*
Hypertension	184 (40.4%)	67 (23.7%)	116 (67.1%)	28(54.9%)	53(67.1%)	35(81.4%)	<0.001*
Smoking	104 (22.8;%)	51 (18.0%)	53 (30.1 %)	13(25.5%)	25(31.7%)	15(34.9%)	0.002*
Dyslipidemia	69 (15.1%)	36 (12.7%)	33 (19.1%)	10(19.6%)	22(27.8%)	1(2.3%)	0.89
Diabetes mellitus	74 (16.2%)	26 (9.2%)	48(30.6%)	12(23.5%)	30(38.0%)	6(14.0%)	<0.001*
Aneurysm	19(4.2%)	11(3.9%)	8 (4.6%)	0	5(6.3%)	3(7.0%)	0.9

Table 1 Characteristics of the patients and incidence ofunruptured intracranial aneurysms

SD indicates standard deviation
CVD: cerebrovascular disease
ICH: intracerebral hemorrhage

	Total	Aneurysm(+)	Aneurysm(-)	Univariate OR (95% CI)	P<0.1	Multivariate P<0.05
Number of patients (aneurysms)	456	19 (21)	437			
Age mean in y±SD	63.2±12.8	67.1±7.8	63.0±12.9		0.03*	0.16
Male/Female(Male%)	264/192(57.9%)	7/12(36.8%)	257/180(58.8%)	0.41(0.15-1.05)	0.058*	0.042*
Hypertension	183 (40.1%)	9 (47.4%)	174(39.8%)	1.36(0.54-3.4)	0.51	
Smoking	104 (22.8;%)	3 (15.8;%)	101(23.1%)	0.62(0.18-2.2)	0.46	
Dyslipidemia	69 (15.1%)	2 (10.5;%)	67(15.3%)	0.64(0.15-2.8)	0.57	
Diabetes mellitus	74 (16.2%)	4 (21.1%)	70(16.0%)	1.4(0.45-4.3)	0.56	
CVD	173	8(42.1%)	165(37.8%)	1.2(0.47-3.0)	0.7	

Table 2 Risk factors for unruptured intracranial aneurysmal formation

SD indicates standard deviation
CVD: cerebrovascular disease

	Total	Healthy group	CVD group	Univariate (P<0.05) Healthy group vs CVD group
Number of patients (aneurysms)	19(21)	11 (11)	8 (10)	
Age mean in y±SD	67.1±7.8	64.5±6.9	70.1±8.0	0.09
Male/Female	7/12	3/8	4/4	0.31
History of hypertension	9 (47.4%)	3 (27.3%)	6(75.0%)	0.04*
Smoking	3 (15.8;%)	0 (0.0%)	3 (37.5 %)	0.03*
Dyslipidemia	2 (10.5;%)	2 (18.2%)	0(0%)	0.2
Diabetes mellitus	4 (21.1%)	2 (18.2%)	2(25.0%)	0.72
Size mean in mm±SD	4.9±2.3	4.7±3.1	5.1±1.0	0.71
MCA aneurysm	6(8)	1	5(7)	0.03*
IC-PC aneurysm	5	2	3	0.34
IC (C2-3) aneurysm	5	5	0	0.03*
A-com Aneurysm	1	1	0	0.38
distal ACA aneurysm	1	1	0	0.38
posterior fossa	1	1	0	0.38

Table 3 Review of the patients with aneurysm in this study

SD indicates standard deviation
CVD: cerebrovascular disease
MCA; middle cerebral artery, C2-3; paraclinoid aneurysm, IC-PC; internal carotid artery-posterior comunicating artery
A-com; anterior communicating arrtery, ACA; anterior cerebral artery

	Total	MCA	C2-3	others	Univariate (P<0.05) MCA vs the ohters	Univariate (P<0.05) C2-3 vs the others
Number of patients (aneurysms)	19(21)	6 (8)	5	8		
Age mean in y±SD	67.1±7.8	66.3±10.0	63.3±5.6	70.0±6.7	0.24	0.09
Male/Female	7/12	3/3	2/3	2/6	0.62	0.86
Hypertension	9 (47.4%)	5 (83.3%)	1(20.0%)	3 (37.5%)	0.03*	0.3
Smoking	3 (15.8;%)	2 (33.3%)	0 (0%)	1 (12.5%)	0.22	0.53
Dyslipidemia	2 (10.5;%)	0 (0%)	1(20.0%)	1 (12.5%)	0.31	0.47
Diabetes mellitus	4 (21.1%)	0 (0%)	0 (0%)	4 (50.0%)	0.26	0.53
CVD	8 (42.1%)	5 (83.3%)	0 (0%)	3 (37.5%)	0.04*	0.04*

Table 4 Characteristics of the aneurysm locacions

SD indicates standard deviation
CVD: cerebrovascular disease
MCA; middle cerebral artery, C2-3; paraclinoid aneurysm

	MCA Aneurysm(+)	No MCA Aneurysm	Univariate OR (95% CI)	P<0.1	Multivariate P<0.05
Number of patients (aneurysms)	6(8)	450			
Age mean in y±SD	66.3±10.0	63.0±12.9		0.4	
Male/Female(Male%)	3/3(50%)	261/189(58.0%)	0.70(0.14-3.5)	0.66	
Hypertension	5 (83.3%)	180(40.0%)	7.6(0.89-65.2)	0.08*	0.32
Smoking	2 (33.3%)	102(22.7%)	1.6(0.3-9.2)	0.56	
Dyslipidemia	0(0%)	69(15.3%)		0.29	
Diabetes mellitus	0(0%)	74(16.4%)		0.29	
CVD	5(83.3%)	168(37.3%)	8.2(0.95-71.2)	0.06*	0.46

Table 5 Risk factors for MCA aneurysm formation

SD indicates standard deviation
MCA middle cerebral artery
CVD: cerebrovascular disease