Prevalence and characteristics of unruptured cerebral aneurysms in ischemic stroke patients

Ji Hwa Kim

Department of Medicine

The Graduate School, Yonsei University

Prevalence and characteristics of unruptured cerebral aneurysms in ischemic stroke patients

Directed by Professor Kyung-Yul Lee

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Ji Hwa Kim

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Ji Hwa Kim is approved.

Thesis Supervisor : Kyung-Yul Lee

Thesis Committee Member#1 : Sang Hyun Suh

Thesis Committee Member#2 : Joonho Chung

The Graduate School
Yonsei University

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Thank you very much.

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ABSTRACT

Prevalence and characteristics of unruptured cerebral aneurysms in ischemic stroke patients

Ji Hwa Kim

Department of Medicine

The Graduate School, Yonsei University

(Directed by Professor Kyung-Yul Lee)

Introduction: The prevalence of unruptured cerebral aneurysms (UCAs) in ischemic stroke patients has not been investigated. We aimed to measure the prevalence and characteristics of UCAs in acute ischemic stroke (AIS) and to compare it with general population. And we evaluated factors associated with cerebral aneurysm in ischemic stroke patients.

Materials and Methods: We retrospectively reviewed brain magnetic resonance angiography (MRA) of 955 patients with AIS, and 2118 controls who had taken

brain MRA as part of a health check-up. We investigated the prevalence, size, location and risk factors of the subject for UCAs.

Results: UCAs were found in 74 patients with AIS (7.7%) and in 79 people for health check-up (3.7%). Prevalence of UCAs was high in AIS group than health check-up (OR 2.17, 95% CI 1.56-3.01, $p < 0.001$), especially in the age of 7th decade. The mean diameter of the aneurysms was larger in AIS group than health check-up group (3.95 mm *vs* 3.10 mm, $p = 0.010$). The UCAs were mostly located in the internal carotid artery and there were no significant differences in distribution pattern between groups. Multivariate analysis showed that only previous hypertension ($p = 0.028$) correlated with the increased prevalence of UCAs in stroke patients.

Conclusion: This study showed higher prevalence and larger size of UCAs in AIS patients than in general population. Hypertension was associated coexistence of cerebral aneurysm and ischemic stroke.

Key words : cerebral aneurysm, ischemic stroke, prevalence, magnetic resonance angiography

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I. INTRODUCTION

Cerebral aneurysm is an abnormal focal pouch-like dilatation of cerebral artery. The most dreaded complication of unruptured cerebral aneurysms (UCAs) is subarachnoid hemorrhage associated with high morbidity and mortality.[1,2] Therefore, there is a great deal of interest in detecting UCAs and in exploring their natural history which have exerted influence on screening and treatment of UCAs.[3]

The reported prevalences of UCAs vary between 0.2 and 9% of the population.[4-14] This wide range in prevalence may be due to variations in evaluation methods and demographics. First, there were methodological differences between studies

like study design, study tools, imaging tools, patient selection and the aneurysm types. Second, the differences in patient demographic may have also influenced the results, and the prevalence of aneurysms could actually be changing due to increasing comorbidity.

There are many common risk factors between cerebral aneurysm and ischemic stroke and there were some studies showing that the proportion of patients with aneurysms were higher in patients with internal carotid artery stenosis than in the general population.[15-19] However, the frequency of cerebral aneurysms in ischemic stroke patients has not been investigated. The purpose of this study was to evaluate the prevalence of UCAs in acute ischemic stroke (AIS) patients and to compare it with that of a health check-up (HC) population. In addition, we compared the characteristics of the detected UCAs in both groups. We also aimed to evaluate factors related to occurrence of UCAs in AIS patients.

II. MATERIALS AND METHODS

1. Patient selection

This retrospective, cross-sectional study was conducted in a tertiary university hospital. Patients were classified into two groups for study. AIS group included patients with acute ischemic stroke who were admitted to the hospital and took brain magnetic resonance angiography (MRA) from January 2011 to December 2014. Excluded from the study were patients with (1) transient ischemic attack

(TIA); (2) pacemaker implantation or bionic ear; (3) pregnancy; and (4) denial of taking brain MRA or poor general condition to take brain MRA. HC group was control group who had taken brain MRA from January 2011 to December 2012 as part of health examination. Patient data including age, gender, past medical history (hypertension, diabetes, hyperlipidemia, previous stroke history, smoking and family history of cerebrovascular disease), and follow-up data were obtained from medical records. In AIS group, stroke subtypes were decided according to TOAST classification as large-artery atherosclerosis, cardioembolism, small vessel occlusion, other determined etiology, or undetermined.[20]

2. Image acquisition

All 3-dimensional time-of-flight MRA (3D-TOF MRA) examinations were done on one of two 3.0T MRI system (Discovery MR750, GE Medical Systems, Milwaukee, WI, USA; Achieva, Philips Medical Systems, Best, The Netherlands). 3D-TOF MRA was performed with following parameters: repetition time/echo time, 23/2.5; flip angle, 20 degrees; field of view, 210 x 185; 4 slabs (176 slices); slice thickness, 1.4 mm; matrix, 416 x 224; and acquisition time, 5 minutes and 9 seconds for Discovery MR750, and repetition time/echo time, 25/3.5; flip angle, 20 degrees; field of view, 250 x 198; 1 slab (170 slices); slice thickness, 1.4 mm; matrix, 832 x 414; and acquisition time, 6 minutes and 52 seconds for Achieva. The acquired image data sets were then

transferred to a workstation (Aquarius iNtuition Edition version 4.4.6.85.2800; TeraRecon, Inc, San Mateo, Calif), in which reconstruction with maximum intensity projection and volume rendering was performed.

3. Image interpretation

We defined UCAs as abnormal focal outpouchings of cerebral arteries.[1] First, patients with incidentally detected cerebral aneurysm (or suspicious aneurysm) were identified from the radiology reports. And then, the images of these patients were independently reviewed once again by one neuroradiologist and one neurologist. In cases of discordant results, a consensus interpretation by the two readers was made. Patients with known UCAs prior to the MRA were also included regardless of the treatment. Patients were excluded if they had fusiform, traumatic, and mycotic aneurysms or extradural location. In cases of patients who additionally undergo digital subtraction angiography (DSA) to confirm the aneurysm and/or treatment plan, we use the DSA result as a reference.

Aneurysm size was recorded as the largest diagonal measurement. Aneurysm locations were classified as internal carotid artery (ICA), anterior cerebral artery, anterior communicating artery, middle cerebral artery (MCA), posterior communicating artery and vertebrobasilar artery. In addition, multiplicity of the aneurysm and the presence of a daughter sac were analyzed. In patients with multiple aneurysms, one index aneurysm with the largest size was selected for

analyzing one's aneurysmal characteristics like size and location.

4. Standard protocol approvals, registrations, and patient consents

This retrospective study design and protocol was approved by the Institutional Review Board (IRB). Written informed consent from the patient was not obtained due to retrospective design and IRB approved it.

5. Statistical analyses

Differences in two groups were evaluated using Student t test (for continuous variables) and Chi-square test (for categorical variables). Odd ratio (OR) was derived from Chi-square test with 95% confidence intervals (CI). The age-matched prevalence rate of UCA was analyzed by the Cochran-Mantel-Haenszel test. Linear regression analyses were performed to test the relation between aneurysm size and age. The association between coexistence of UCA and various covariates in group 1 were tested using logistic regression test. All P values were 2-sided and were considered statistically significant if they were 0.05 or less. These analyses were performed using the SPSS version 20.0 (SPSS Inc., Chicago, IL, USA). In addition, relationship between age and the prevalence of UCAs examined by the Cochran–Armitage trend test which was conducted by using SAS, version 9.2 (SAS Institute, Cary, North Carolina).

III. RESULTS

1. Characteristics of the subjects

A total 1258 patients with suspected ischemic stroke were admitted to our hospital. Among these patients, TIA (n = 203), pacemaker implantation (n = 2), bionic ear (n = 1) and too poor general condition to take brain MRI (n = 2) were excluded. Eventually, remaining 955 patients with ischemic stroke and 2118 controls who had taken brain MRA as part of a health check-up were enrolled to the study. The baseline characteristics of patients in each group are shown in Table 1. The mean age of AIS group was significantly older than HC group (64.9 ± 14.1 *vs* 53.9 ± 9.6). Other risk factors including hypertension, diabetes, hyperlipidemia, previous stroke history, smoking and a family history of cerebrovascular accident were significantly more common in AIS group.

Table 1. **Baseline characteristics of the subjects**

characteristics	**AIS (n=955)**	**HC (n=2118)**	***P* Value**
Age, mean ± SD, y	64.9±14.1	53.9±9.6	<0.001
Male, *n* (%)	586 (61.4%)	1188 (56.1%)	0.06
Hypertension, *n* (%)	600 (62.8%)	622 (29.4%)	<0.001
Diabetes, *n* (%)	289 (30.3%)	241 (11.4%)	<0.001
Hyperlipidemia, *n* (%)	134 (14.0%)	189 (8.9%)	<0.001

characteristics	AIS (n=955)	HC (n=2118)	*P* Value
Previous stroke, *n* (%)	170 (17.8%)	20 (0.9%)	<0.001
Smokers, *n* (%)*	417 (43.7%)	710 (33.5%)	<0.001
Family history of stroke, *n* (%)	94 (9.8%)	44 (2.1%)	<0.001

* includes current smoker and ex-smoker

AIS: acute ischemic stroke, HC: health check-up

2. Prevalence of UCAs

UCAs were found in 74 patients in AIS group (7.7%; 38 men and 36 women; age 43 to 91 years, mean 67.2 ± 11.2) and in 79 people in HC group (3.7%; 35 men and 44 women; age 37 to 76 years, mean 57.2 ± 8.8). Prevalence of UCAs was higher in AIS group than HC group (OR 2.17, 95% CI 1.56-3.01, $p < 0.001$).

In an age-matched comparison, the prevalence of UCAs was higher in AIS group than HC, based on the Cochran-Mantel-Haenszel test (OR 1.79, 95% CI 1.24-2.60, $p = 0.002$). When categorized according to age by decade, there was significant difference in prevalence between the two groups only in the 7th

decade (Table 2). The prevalence of aneurysm was higher in women than in men in both groups, and the prevalence increased significantly with increasing age in the HC group especially in women. On the other hand, one peak appeared in the 7th decade in the AIS group (10.5%) for both males (8.6%) and females (14.7%)

Table 2. Age- and sex-specific prevalence of unruptured cerebral aneurysms

	Acute ischemic stroke group						Health check-up group						*P* Value*
	Men		**Women**		**Total**		**Men**		**Women**		**Total**		
Age (y)	Pop, *n*	UCA, *n* (%)	Pop, *n*	UCA, *n* (%)	Pop, *n*	UCA, *n* (%)	Pop, *n*	UCA, *n* (%)	Pop, *n*	UCA, *n* (%)	Pop, *n*	UCA, *n* (%)	
<50	99	3 (3.0)	38	3 (7.9)	137	6 (4.4)	371	8 (2.2)	282	8 (2.8)	653	16 (2.5)	0.212
50-59	146	8 (5.5)	42	3 (7.1)	188	11 (5.9)	522	16 (3.1)	390	20 (5.1)	912	36 (3.9)	0.240
60-69	162	14 (8.6)	75	11 (14.7)	237	25 (10.5)	224	8 (3.6)	209	11 (5.3)	433	19 (4.4)	0.002†
≥70	179	13 (7.3)	214	19 (8.9)	393	32 (8.1)	71	3 (4.2)	49	5 (10.2)	120	8 (6.7)	0.541
total	586	38 (6.5)	369	36 (9.8)	955	74 (7.7)	1,188	35 (3.0)	930	44 (4.7)	2118	79 (3.7)	<0.001†
***p* Value of trend‡**		0.138		0.932		0.118		0.325		0.038†		0.024†	

* *P* value obtained by Chi-square test for comparisons between acute ischemic stroke group and health check-up group.

† Significant value

‡ *P* value of trend was calculated using the Cochran–Armitage trend test.

Pop: population, UCA: unruptured cerebral aneurysm, Pr: prevalence.

3. Characteristics of UCA

The mean diameter of the UCAs was larger in AIS group than in HC (3.95 mm *vs* 3.10 mm; $p = 0.010$). As shown in Figure 1, the size increased with age in AIS group ($R^2 = 0.127$, $p = 0.002$) but not in HC group ($R^2 = 0.018$, $p = 0.241$). In addition, large (> 7 mm) aneurysms were more common in AIS group than HC (8.1% *vs* 6.3%). The mean diameter of UCAs was larger in women than men in both groups, but the difference was not significant (AIS group, 4.48 ± 2.74 mm vs. 3.49 ± 1.80 mm; $p = 0.069$ and HC group, 3.32 ± 1.85 vs. 2.82 ± 1.35; $p = 0.182$).

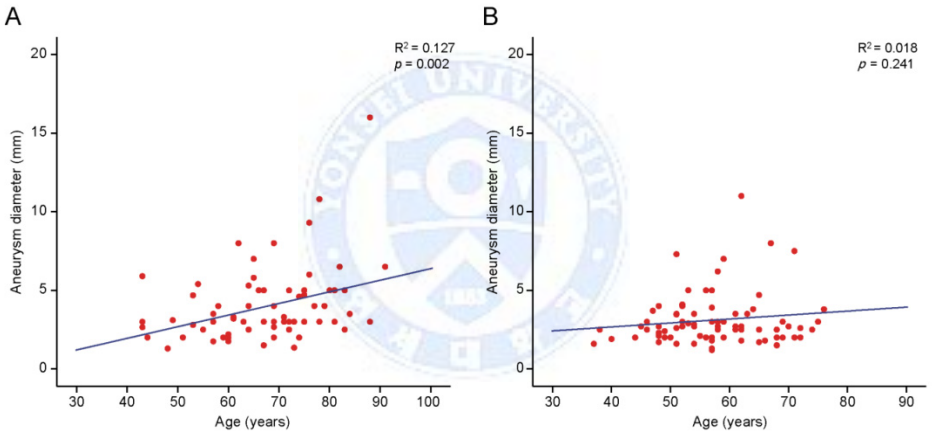

Figure 1. The relation between the size of unruptured cerebral aneurysms and age in acute ischemic stroke group (A) and health check-up group (B). The regression lines are y = 0.074x - 1.009 (A) and y = 0.025x + 1.663 (B) where y is aneurysm size (mm) and x is age (years).

The most common site of UCAs was the distal ICA and the next was MCA with no significant differences in distribution pattern between groups (Table 3). Analyzing size of aneurysms by location, mean diameter was significantly larger in AIS group than HC group only in ICA (Table 3). Multiple aneurysms were found in 15 patients (20.3%) in AIS group and 11 patients (13.8%) in HC group (p = 0.281). Two patients of each group had daughter sac.

Table 3. Incidence and size of aneurysms by location

		ICA	MCA	A-com	P-com	VB	ACA
AIS	**n**	39	14	9	7	5	0
	(%)	(52.7%)	(18.9%)	(12.2%)	(9.5%)	(6.8%)	(0%)
	size, mm	3.6 ± 1.7	4.8 ± 3.5	3.4 ± 1.3	4.0 ± 3.2	4.8 ±2.8	.
HC	**n**	53	8	7	6	2	3
	(%)	(66.3%)	(10.0%)	(8.8%)	(7.5%)	(2.5%)	(3.8%)
	size, mm	2.9 ± 1.0	2.8 ± 1.8	4.3 ± 2.4	5.0 ± 3.5	2.3 ± 0.4	2.2 ± 0.4
p* Value		0.012	0.147	0.328	0.605	0.272	.

Data are mean ± SD unless otherwise indicated.

* For comparison of size of the aneurysms between AIS group and HC group.

ICA: internal carotid artery, MCA: middle cerebral artery, A-com: anterior communicating artery, P-com: posterior communicating artery, VB: vertebrobasilar artery, ACA: anterior cerebral artery, AIS: acute ischemic stroke, HC: health check-up

4. Independent predictors of the UCAs in AIS patients

Age, female sex, hypertension, diabetes, hyperlipidemia, previous stroke history, smoking, family history of stroke were analyzed using logistic regression. Univariate and multivariate analysis showed that only previous hypertension (p = 0.028) correlated with the increased prevalence of UCAs in AIS patients but other risk factors were not associated (Table 4). There were no differences in the prevalenc of UCAs according to the ischemic stroke subtype by TOAST classification.

Table 4. Independent predictors of the unruptured cerebral aneurysms in acute ischemic stroke patients

Predictors	**Estimated OR**	
	Univariate (95% CI)	**Multivariate (95% CI)**
Age, per 1-year increase	1.01 (0.99-1.03)	1.82 (0.95-3.49)
Female sex	1.56 (0.97-2.51)	1.00 (0.99-1.03)
Hypertension	2.09 (1.19-3.65) *	1.94 (1.07-3.53) *
Diabetes	0.84 (0.50-1.44)	0.70 (0.40-1.20)
Hyperlipidemia	1.48 (0.80-2.73)	1.43 (0.75-2.71)
Previous stroke	1.30 (0.73-2.33)	1.15 (0.63-2.10)

Predictors	Estimated OR	
	Univariate (95% CI)	**Multivariate (95% CI)**
Smoking	0.93 (0.57-1.50)	1.46 (0.76-2.81)
Family history of stroke	0.95 (0.42-2.14)	1.11 (0.48-2.55)
TOAST		
LAA	Reference	Reference
CE	2.12 (0.99-4.49)	1.98 (0.92-4.22)
LAC	1.89 (0.89-3.99)	2.01 (0.97-4.49)

* Significant values

LAA: large-artery atherosclerosis, CE: cardioembolism, LAC: small vessel occlusion, SOD: Stroke of Other Determined Etiology, SUD: Stroke of Undetermined Etiology.

5. Follow-up data

The median follow up duration was 18.3 months (median 13.0, range 1-48 months) in AIS group, and 17.6 months(median 15.0, range 1-48 months) in HC. Eight of the 66 patients (12%) in AIS group were treated by clipping (n = 5) or coiling (n = 3), and 21 of the 75 (28%) patients in HC group were treated by clipping (n = 12) or coiling (n = 9). Among the patients without treatment, aneurysms were ruptured in 3 patients in AIS group, but not in HC group.

IV. DISCUSSION

Our overall prevalence UCAs in HC group is similar to recent systemic review published in 2011 which estimated the overall prevalence of UCAs to be 3.2% in a population without comorbidity (mean age, 50 years; 50% men).[6] It was higher than overall prevalence of 2.3% in previous review at 1998.[4] They explained it was due to correction for age and sex, and inclusion of more recent studies with higher quality imaging techniques. Most of recent studies about the prevalence of UCAs use MRA as method for evaluating. However, prevalences reported in these studies do not strictly reflect flawless general population. Because they evaluated volunteer participants[9,10] or patients underwent brain MRA for various reasons including diverse neurological conditions[11,14,21,22] Whereas in our study, the HC group has no neurologic symptom or other specific reason for taking brain MRA and this means they represent general population more closely. It makes the comparison with AIS group more precisely.

In this study, we have shown that prevalence of UCAs is higher in AIS group compared with HC group (7.7% *vs* 3.7%). We suppose it is due to high rate of risk factors related formation of cerebral aneurysm in AIS group. There has been controversy for the age-related increase in the prevalence of UCAs. Some studies[4,14] have reported that the prevalence of UCAs steadily increased with age in both genders, whereas other studies[8,21,23] found no age related increase in the prevalence of UCAs. Interestingly, our study showed age-related increase in

prevalence in only HC group, especially in female. On the other hand, decreased prevalence after peak in 7th decade is showed in AIS group. This discrepancy can be explained by high aneurysmal rupture risk and mortality unrelated to cerebral aneurysm in this age group of ischemic stroke patient.[24,25] Our study also showed the age-related increase in size of aneurysms in AIS group, but not in HC group. This may be because AIS patients have more risk factors associated with growth of the aneurysm.

Large size and growth of UCAs are important determinants for eventual rupture of cerebral aneurysm.[1,26,27] Our study show higher prevalence, large size and growth of UCAs in AIS group than general population. All these factors imply the high risk aneurysmal rupture in ischemic stroke patients and when we decide treatment options of UCAs, these factors should be considered.

There are some limitations of this study. The diagnosis of UCAs is based on 3D-TOF. The gold standard in diagnostic work up of cerebral aneurysm is conventional angiography. Therefore there may be some cases with incorrect diagnosis in our study. However, there are many studies that describe the high diagnostic accuracy of 3D-TOF MRA with high sensitivity over 95% and high specificity from 89 to 97%.[28-30] Moreover most of recent studies used MRA for the validation tool because of its many benefits, such as noninvasive, and radiation free examination. In addition, we could not obtain the natural history of UCAs because of retrospective study design. A large prospective study is needed to define the natural history of UCAs in ischemic stroke patient

compared to general population. Lastly, this was single hospital-based, geographically and ethnically defined study.

V. CONCLUSION

UCAs were more common in the AIS patients than in the general population. The mean size of the aneurysms in AIS group was larger than in HC group and the size significantly increased with age only in the AIS group. Among the various risk factors, hypertension was correlated with the increased prevalence of aneurysms in the AIS group.

Ultimately, a follow-up study of UCAs in ischemic stroke patients is required. Because, they have more risk factors for aneurysmal rupture and most of them use antiplatelet or anticoagulation agents which can put them at risk for severe hemorrhage in the event of an aneurysm rupture. Thus, further study may assist treatment plans for ischemic stroke patients with UCAs.

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ABSTRACT(IN KOREAN)

허혈성 뇌졸중 환자에서 비파열 대뇌 동맥류의 빈도와 특성

<지도교수 이경열>

연세대학교 대학원 의학과

김지화

서론: 지금까지 허혈성 뇌졸중 환자에게서 비파열 뇌동맥류의 빈도에 대한 연구는 없었다. 우리는 급성 허혈성 뇌졸중 환자에게서 비파열 뇌동맥류의 빈도와 특성을 일반인과 비교하는 것을 목표로 하였다. 또한 허혈성 뇌졸중 환자에게서 동맥류가 있는 것과 관련된 요인을 조사하였다.

방법: 우리는 955명의 급성 허혈성 뇌졸중 환자들과 건강검진으로 뇌 자기공명혈관촬영을 시행한 2118명의 대조군의 뇌 자기공명혈관촬영을 후향적으로 연구하였다. 우리는 비파열 대뇌 동맥류의 빈도, 크기, 위치, 관련된 위험인자들을 조사하였다.

결과: 비파열 뇌동맥류는 뇌경색군에서 74명에서 나타났으며 (7.7%) 건강검진군에서는 79명에서 나타났다 (3.7%). 양 군을 비교하면 뇌경색 환자군에게서 빈도가 더 높았으며 (OR 2.17, 95% CI 1.56-3.01, $p < 0.001$), 특히 60대에서 유의하게 더 높았다. 동맥류의 평균 직경은

뇌경색군이 건강검진군에 비해 높았다 (3.95 mm *vs* 3.10 mm). 내경동맥에 위치한 뇌동맥류가 가장 많았고, 각 군에서 뇌동맥류의 분포에는 유의미한 차이가 없었다. 다변량 로지스틱 회귀분석에서 고혈압만이 (p = 0.028) 뇌경색 환자에게서 비파열성 뇌동맥류가 있는 것과 유의하게 연관이 있었다.

결론: 이 연구는 뇌경색 환자군에서 일반인에 비해 비파열 뇌동맥류의 빈도가 더 높다는 것을 보여준다. 또한 고혈압이 뇌경색 환자군에게서 뇌동맥류가 있는 것과 연관이 있었다.

핵심되는 말 : cerebral aneurysm, ischemic stroke, prevalence, magnetic resonance angiography