

Clinical Article



# Analysis of Factors Related to Growth and Growth Patterns of Unruptured Intracranial Aneurysms

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**Conflict of Interest**

The authors have no financial conflicts of interest.

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## ABSTRACT

**Objective:** The goal of the present study was to identify factors related to the growth and growth patterns of unruptured intracranial aneurysms (UIAs).

**Methods:** Between January 2011 and December 2018, a total of 275 patients were diagnosed with UIAs in our institution. Of them, 91 patients were evaluated using computed tomography angiography, magnetic resonance angiography, or digital subtraction angiography. Aneurysm size, morphology, location, and its changes were investigated. Patient factors, including gender, history of stroke, smoking, hypertension, diabetes mellitus, and excessive alcohol consumption, were studied to identify factors associated with aneurysm growth.

**Results:** A total of 91 patients (121 aneurysms) with a mean follow-up duration of 37.2±23.9 months and a mean age of 64.0±11.4 years were included. The growth of unruptured aneurysms was identified in 23 patients (27 aneurysms, 22.3%). Regarding morphology, the diffuse growth pattern was the most common (12 aneurysms in 10 patients, 44.4%). Univariate analysis showed that patients with multiple aneurysms ( $p=0.010$ ), history of stroke ( $p=0.021$ ), and aneurysm location in the posterior circulation ( $p=0.029$ ) were significantly associated with aneurysm growth.

**Conclusion:** The growth of an UIA is associated with the history of stroke, posterior location, and multiplicity. Considering the risk of unruptured aneurysm growth, patients with such risk factors should receive additional attention during follow-up.

**Keywords:** Intracranial aneurysm; Growth; Risk factors

## INTRODUCTION

Unruptured intracranial aneurysms (UIAs) are common. They are diagnosed with higher frequencies as imaging techniques improve.<sup>17)</sup> Several investigators have suggested that approximately 3% of adults have UIA.<sup>28)</sup> Because mortality and morbidity are high after UIA rupture and during treatment of UIA, the natural history of UIA has been highlighted for decades.<sup>19)</sup>

Many previous studies have described that subarachnoid hemorrhage (SAH) is caused by intracranial aneurysm rupture in about 85% of cases and indicated that SAH has poor

prognoses despite various advancements in medical treatment.<sup>12,18)</sup> The mortality rate of SAH is about 40%–50%. Approximately 20% of patients who survive after SAH have critical complications such as neurological impairment and disability. Thus, clinical management of UIAs to prevent rupture is an important issue.<sup>18)</sup>

With improved ability of computed tomography and magnetic resonance imaging (MRI) scanning, the number of incidentally detected aneurysms is increasing.<sup>6)</sup> Despite longstanding investigations, many factors of the natural history of UIA remain unknown.

Although aneurysm growth is known to be associated with rupture, evidence for the growth and growth pattern of aneurysm is limited because few clinical studies are available.<sup>11)</sup> Many studies have analyzed risk factors for the growth and outcomes of an intracranial aneurysm based on aneurysm-specific information and patients-specific information.<sup>7,9,25)</sup> However, whether growth pattern of UIA could increase the risk of rupture remains controversial because of incomplete and conflicting data about the natural history of UIA. Hence, the decision about whether to treat UIA is often unclear in clinical practice. Thus, the objective of this study was to identify factors related to the growth of an aneurysm by retrospectively analyze outcomes including growth of patients with UIA.

## MATERIALS AND METHODS

### Patient population

Records of patients diagnosed with intracranial aneurysms in our institutions between January 2011 and December 2018 were reviewed. Inclusion criteria were: (1) adult patients, (2) at least one unruptured aneurysm, and (3) follow-up imaging time of at least 3 months. Although aneurysms were treated with either neurosurgical clip or interventional coil placement, if new UIA presented, it was included. A total of 456 aneurysms of 275 patients were examined in the study period. Of these 275 patients, 91 (121 UIAs) were continuously followed using magnetic resonance angiography (MRA), computed tomography angiography (CTA), or digital subtraction angiography (DSA) neurovascular images in our institutions.

Aneurysms with a history of hemorrhage were excluded. If patients failed to return for further follow-up visit, they were also excluded. Complete follow-up period was calculated from the date of initial diagnostic angiography to the date of the last follow-up.

Patient medical records and their demographic information such as age and sex were obtained through our inpatient and outpatient electronic medical records system. Among included patients, data of patient factors (such as age, sex, history of stroke, hypertension, diabetes mellitus, current cigarette smoking, excessive alcohol consumption) and aneurysm factors (such as size, location, and morphology) were collected. Hypertension was defined as taking antihypertensive medication or blood pressure >140/90 mmHg on repeated measurement. Diabetes mellitus was defined as receiving diabetes mellitus medication or fasting blood glucose >126 mg/dL. History of smoking, excessive alcohol consumption, and family history were taken from patient-interviewed nurse report. Modalities and aneurysm factors were collected from follow-up imaging.

### Aneurysm factors

#### *Aneurysm size*

Based on various modalities, sizes of aneurysms were measured from images. The size of an aneurysm was measured based on the following 3 parameters: (1) neck width, a virtual line separating the aneurysm from the parental artery; (2) the maximum height from the neck to the dome tip; and (3) the maximum width of the dome perpendicular to its height. Aneurysm size change was calculated as the largest change of those 3 parameters (neck width, the maximum height, the maximum width). Aneurysm growth was defined as an increase of 1 mm in maximum dimension of aneurysm size change.

#### *Aneurysm location*

The location of the aneurysm was classified as internal carotid artery (ICA), anterior cerebral artery, anterior communicating artery (AcoA), middle cerebral artery (MCA), posterior communicating artery (PCoA), and posterior circulation including vertebral artery, basilar artery, posterior cerebral artery, anterior inferior cerebellar artery, and posterior inferior cerebellar artery. According to specific aneurysm locations, effects on aneurysm growth were compared with each other.

#### *Multiple aneurysms*

Multiplicity of intracranial aneurysm was counted in number. At least 2 aneurysm findings in a patient were defined as multiple aneurysms.

#### *Growth patterns of aneurysms*

Growth patterns of aneurysms were categorized according to follow-up images including CTA, MRA, and DSA findings. They were categorized into the following 5 types: (1) type 1, diffuse growing type; (2) type 2, focal growing, dome type; (3) type 3, focal growing, neck type; (4) type 4, multiple growing type; and (5) type 5, *de novo* type, accounting for new aneurysm formation at different areas. A diffuse growing type was defined as parallel wall bulging of the entire aneurysm wall. Focal growing type was defined as bulging of one part of aneurysmal components. These types were subdivided into dome and neck forms. A multiple growing type was defined as at least 2 bulges on the wall of aneurysm. *De novo* formation type accounted for new aneurysm formation in other areas of intracranial arterial vessels (**FIGURE 1**).

#### *Statistics*

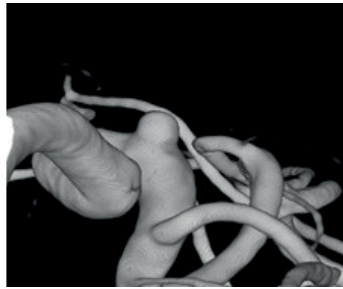
A 2-sample Student's *t*-test was applied to compare aneurysm growths of different groups. Univariate analyses were performed to assess categorical variables (for example, history of stroke, hypertension, diabetes mellitus, cigarette smoking, excessive alcohol consumption, and aneurysm multicity and location). Aneurysm growths were compared using the  $\chi^2$  test. The IBM SPSS statistics version 25 software (IBM Corp., Armonk, NY, USA) was used for statistical analyses with significance level set at 5%.

## RESULTS

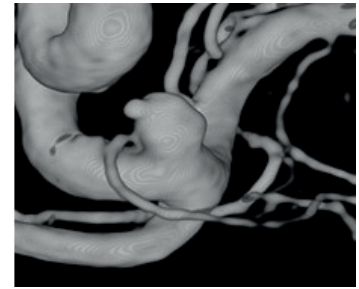
### Patient characteristics

Patients' medical history and characteristics of aneurysms are summarized in **TABLE 1**. A total of 91 patients (22 men and 69 women) with a mean age of  $64.0 \pm 11.4$  years (range, 44 to 89 years) were included. Their average follow-up duration was 37.2 months. The individual follow-up for aneurysm ranged from 2.1 to 81 months. Twenty-seven aneurysms

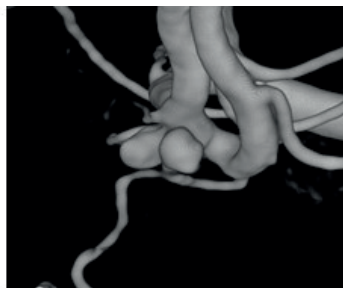
Type 1) Diffuse growth



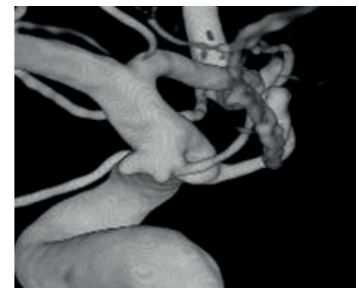
Type 2) Focal growth: dome



Type 3) Focal growth: neck



Type 4) Multiple growth



Type 5) *de novo* formation



**FIGURE 1.** Growth patterns according to aneurysm morphological change. Type 1: diffuse growth; Type 2: focal growth; dome; Type 3: focal growth; neck; Type 4: multiple growth; Type 5: *de novo* formation.

(22.3% of total aneurysms) were enlarged in size (growing group) while 94 were unchanged (non-growing group) during follow-up. Total follow-up durations for growing and non-growing aneurysms were  $41.7 \pm 26.5$  months and  $35.6 \pm 23.1$  months, respectively, showing no significant ( $p=0.293$ ) difference between the 2 groups.

### Aneurysm factors

Aneurysms with growth were located in the ICA in 13 cases, the MCA in 2 cases, the AcoA in 4 cases, the PcoA in 3 cases, and in posterior circulation in 6 cases. And Aneurysm location in posterior circulation was significantly larger in the group with aneurysm growth than in the group without ( $p=0.029$ ) (TABLE 2).

Mean initial sizes of growing and non-growing aneurysms were  $4.1 \pm 1.9$  mm and  $4.1 \pm 2.3$  mm, respectively, showing no significant ( $p=0.965$ ) difference between the 2 groups. Although there was no significant difference in the initial size of aneurysm between aneurysms with growth and those without growth, growing aneurysms were enlarged by  $1.57 \pm 0.9$  mm at the end of follow-up.

Shapes of 27 aneurysms were as follows: type 1 in 12 aneurysms of 10 patients; type 2 in

**TABLE 1.** Characteristics of 121 aneurysms of 91 patients

Characteristics	Value
Patients-specific factors	
Number of patients (male/female)	91 (22/63)
Age (years)	64.0±11.4
Aneurysm-specific factors	
Number of aneurysms	121
Follow up duration (months)	37.2±23.9
Initial size (mm)	4.1±2.2
Multiplicity (Number of patients)	
Multiple aneurysm	28
Single aneurysm	63
Number in anterior circulation	108
ICA	57
MCA	24
ACA	8
AcoA	12
PcoA	7
Number in posterior circulation	13
VA + PICA	4
BA + SCA	7
PCA	2

Values are presented as mean ± standard deviation or number (%).

ICA: internal carotid artery, MCA: middle cerebral artery, ACA: anterior cerebral artery, AcoA: anterior communicating artery, PcoA: posterior communicating artery, VA: vertebral artery, PICA: posterior inferior cerebellar artery, BA: basilar artery, SCA: superior cerebellar artery, PCA: posterior cerebral artery.

**TABLE 2.** Univariate analysis for factors associated with aneurysm growth

Characteristics	With aneurysm growth	Without aneurysm growth	p-value
Patient information			
Number of patients	23	68	
Female	17	52	0.804
Male	6	16	
Age (years)	67.0±10.7	62.9±11.5	0.145
Median age (years)	68	64	
Single aneurysm	11	52	0.010*
Multiple aneurysm	12	16	
History of concomitant disease			
HTN	13	40	0.846
No HTN	10	28	
Hyperlipidemia	5	12	0.663
No hyperlipidemia	18	56	
Diabetes mellitus	7	17	0.609
No diabetes mellitus	16	51	
Stroke	7	7	0.021*
No stroke	16	61	
Current smoking	6	19	0.863
No current smoking	17	49	
Excessive alcohol consumption	6	21	0.663
No excessive alcohol consumption	17	47	
Aneurysm information			
Number of aneurysm	27	94	
Mean initial size (mm)	4.1±1.9	4.1±2.3	0.965
Size ≥5 mm	7	30	0.552
Size <5 mm	20	64	
Aneurysm location			
Anterior circulation	21	87	0.029*
Posterior circulation	6	7	

Values are presented as mean ± standard deviation or number (%).

HTN: hypertension.

\*p<0.05, statistically significant.

**TABLE 3.** Summary of 27 aneurysm growth patterns

Growth pattern	Value	HTN
Type 1: diffuse growth	12 (44.4)	8 (66.6)
Type 2: focal growth, dome	4 (14.8)	2 (50)
Type 3: focal growth, neck	1 (3.7)	1 (100)
Type 4: multiple growth	6 (22.2)	2 (33.3)
Type 5: <i>de novo</i> formation	4 (14.8)	2 (50)

Values are presented as number of cases (%).

HTN: hypertension.

4 aneurysms of 4 patients; type 3 in 1 aneurysm of 1 patient, type 4 in 6 aneurysms of 5 patients, and type 5 in 4 aneurysms of 3 patients (**TABLE 3**).

Multiple aneurysms were significantly more common in patients with aneurysm growth than in those without ( $p=0.010$ ) (**TABLE 2**).

The mean age of 23 patients with aneurysm growth was 67.0 years. Of these 23 patients, 17 patients were females. Single aneurysms were found in 11 patients. There was no significant difference in the proportion of patients by sex or age.

The proportion of patients with a history of stroke was significantly ( $p=0.021$ ) larger in the group with aneurysm growth than in the group without aneurysm growth (**TABLE 2**). There was no significant difference in the proportion of patients with hypertension, hyperlipidemia, diabetes mellitus, current smoking, or excessive alcohol consumption between the group with aneurysm growth and the group without aneurysm growth.

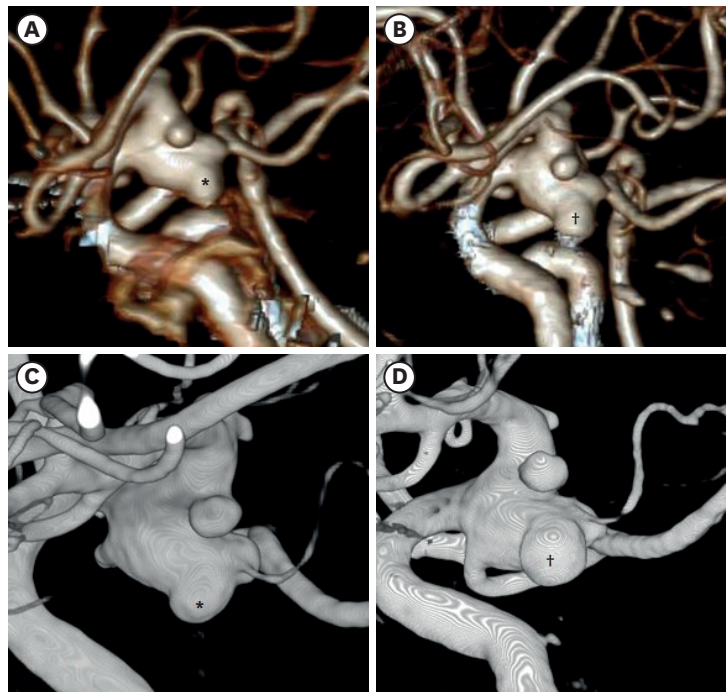
As a result of comparing growth type and hypertension, the incidence of hypertension was the most common in those with type 3 growth pattern. As follow, type 1 growth pattern was 66.6%, type 2 and type 5 was 50%, and type 4 was 33.3% (**TABLE 3**).

### Case illustration

A 74-year-old woman visited our center with recent headache and dizziness for one month. CTA was performed. It revealed 2 unruptured aneurysms. A left posterior communication artery aneurysm had a maximum diameter of 7.8 mm with a daughter sac and a left anterior choroidal artery aneurysm had a maximum diameter of 3.1 mm (**FIGURE 2**). A year later, focal enlargement of the aneurysm with a maximum diameter of 9.1 mm at the left posterior communication artery junction was detected. A type 3 focal growth on the neck of the aneurysm was found. Because the patient was concerned about its rupture, we elected to conduct yearly observations by performing angiography.

## DISCUSSION

This study showed an overall incidence of aneurysm growth of 22.3% during a mean follow-up of  $37.2 \pm 23.9$  months. Several studies have directly reported the incidence of growth in UIA. Matsubara et al.<sup>13</sup> have reported that 10 (6.0%) of 166 aneurysms are increased in size during a follow-up period of 17.7 months. So et al.<sup>22</sup> have reported that 95 (33.3%) of 285 aneurysms are increased in size during a follow-up period of 15.9 months. These studies also showed differences in patient homogeneity and follow-up periods. So et al.<sup>22</sup> have



**FIGURE 2.** This figure shows a case of aneurysm focal growth pattern. (A, C) Volume-rendered CT angiograms and 3D reconstructive of digital subtraction angiography at first diagnosed. (B, D) Volume-rendered CT angiograms 3D reconstructive of digital subtraction angiography 1 year later.

\*Initially diagnosed left posterior communication artery aneurysm; †Growing of left posterior communication artery aneurysm 1 year later.

also indicated that the cumulative incidence of growth is increased by years. Their study suggests that the incidence of growth will be increased with longer follow-up period. Our study showed that growth rate of unruptured intracranial aneurysms was 22.3%, which was relatively high compared to previous studies. It was thought that a long observation period might lead to a high incidence of growth.

This study showed various growth patterns of UIAs. Because there have been few studies directly addressing unpredictable aneurysm growth, recognition of factors associated with consecutive size and morphological changes is helpful for clinician to manage and evaluate increasing risk during follow-up. Based on followed-up unruptured aneurysms study, several research studies have suggested risk factors related to growth and morphological changes in aneurysm. Ujiie et al.<sup>26)</sup> have measured *in vivo* velocity profiles of daughter aneurysms. They found that vessel wall images differed between stable and growing UIAs. Also, several research studies have reported that the inflammatory status in aneurysm can affect flow and growth patterns.<sup>1,3)</sup> Authors assume that hemodynamics of aneurysmal sac could affect growing patterns of unruptured aneurysms. Thus, authors categorized and analyzed growth patterns of aneurysms in 5 types.

In this study, 27 growing UIAs were categorized to 5 patterns of aneurysm growth. Diffuse growth pattern was the most common in aneurysm growth. However, the sum of focal growth and multiple growth patterns showed comparable incidence. Recent histopathologic studies have reported that aneurysmal wall thickening accompanied by atherosclerosis, neovascularization, and infiltrations of inflammatory cells are important in the pathophysiology of weakness of the aneurysmal arterial wall.<sup>3,21)</sup> Additionally, aneurysmal

wall thickening patterns and wall hemodynamic stress may decide the growth pattern of aneurysms.<sup>23)</sup> As a result, most saccular UIA did not have a heterogeneous wall thickening pattern. Besides, UIAs with a focal growth (dome) type such as daughter sac formation showed heterogeneous aneurysmal wall thickening in histopathological study and MRA study.<sup>5)</sup> Focal growing of aneurysm wall component can be caused by extremely thin portion of the wall.

In our study, diffuse growth pattern has relatively high incidence of hypertension. This result suggests that the entire aneurysm wall growth might be related to hemodynamics and pressure stress of wall. On the other hand, in the case of other growth patterns, it is thought to be related to other reasons such as heterogeneous aneurysmal wall thickening pattern and inflammatory status of the aneurysmal sac. We found no statistical significance because the number of cases was small. Thus, a follow-up study on growth patterns and factors affecting aneurysm it is required.

In our study, we also found that aneurysm growth was related to a patient's history of stroke including transient ischemic attack. Because few studies have reported the relationship between cerebrovascular disease and aneurysm growth,<sup>4)</sup> further study is needed to help understand the relationship between other cerebrovascular diseases and intracranial aneurysms. However, some autopsy and angiography studies suggest that atherosclerotic change of intracranial vessels appears to increase the risk of incidental cerebral aneurysm formation.<sup>8)</sup> Accordingly, it could be postulated that the increased prevalence of UIAs in patients who had stroke history could be explained by shared risk factors including hypertension, smoking, atherosclerosis, and potentially internal carotid stenosis.

Several studies have recently shown that dome-neck ratio and aspect ratio of an unruptured aneurysm are associated with aneurysm growth and rupture.<sup>2,27)</sup> These studies concluded that the aspect ratio could be useful for predicting imminent aneurysmal ruptures.<sup>27)</sup> Besides, the dome-neck ratio of an initial unruptured aneurysm itself should be considered as risk factor for aneurysm growth.<sup>2)</sup> Additionally, multiple aneurysms have been more often reported in women, hypertensive, and older patients than in patients a single aneurysm.<sup>10,15)</sup> However, some authors have suggested that hypertension and age are not risk factors for development of multiple aneurysms.<sup>16)</sup> Despite of those reports, some presumptive studies have shown that polycystic kidney disease and other connective tissue disease are related to the occurrence of multiple aneurysms.<sup>20)</sup> Therefore, the presence of multiple aneurysms is considered an evidence for the weak aneurysmal arterial wall possibly of familial or inherited origin or due to hemodynamic stress in the wall. The incidence of multiple aneurysms has been associated with the resolution power of imaging technique or completeness of autopsy. It has been reported that small aneurysms may be observed during operation not seen on angiography.

The proportion of aneurysms located at the posterior circulation was significantly larger in the group with aneurysm growth (22.2%) than in the group without aneurysm growth (7.4%) ( $p=0.029$ ). Small aneurysms located in the posterior circulation have been reported to be associated with a significant risk of rupture.<sup>14)</sup> Several studies have shown that posterior circulation located aneurysm can increase the risk for UIA growth.<sup>4)</sup> However, the mechanism by which the location of aneurysm increases this risk of rupture remains unknown. Further long-term follow-up studies of UIAs will help us understand the mechanism of posterior circulation affecting aneurysm growth.



Although the optimal angiographic follow-up interval for monitoring the growth rate is unclear, the 2015 American Heart Association and American Stroke Association guidelines<sup>24)</sup> suggest that intermittent imaging studies at regular interval to follow diagnosed UIAs conservatively (class I; level of evidence B). This recommendation is based on the understanding that aneurysmal growth may increase the risk of rupture. The importance of continual follow-up was confirmed by aneurysms that continued to show growth at times after 1 year. The first follow-up study at 6 to 12 months after initial discovery is recommend, followed by subsequent follow-up yearly (class IIb; level of evidence C). Our retrospective study included cases from 2011. Some of these cases could not follow the guideline. Also, some cases had no regular follow-up intervals, depending on their specific clinical situations. However, most cases from 2015 were followed at 6 to 12 months after initial diagnoses.

This study has some limitations. First, it was a single-center, retrospective study. In order to minimize error, patient records in this study were reviewed with predefined definitions. However, analysis in this study was limited by data available retrospectively. Also, because it was not a randomized study, patient selection bias cannot be ruled out. To further understand aneurysm growth, a multicenter prospective study with a long-term follow-up is important to minimize the bias due to patient selection. Another limitation was that different aneurysm imaging methods including MRA, CTA, and DSA were used. Because studies of aneurysm growth had different image modalities by available and suitable diagnosing methods, the scale of geometrical change can be underestimated in lower resolution image techniques. In the future, a consistent modality study could be valuable to understand aneurysm changes.

## CONCLUSION

We found that history of stroke, posterior location, and multicity of aneurysm were independent risk factors for aneurysm growth of UIA. Of them, diffuse growth pattern in aneurysm growth was the most common. It could explain why both aneurysmal wall thickening and wall hemodynamic stress can influence the growth pattern of aneurysm. Considering the risk of growth, patients who had stroke or have multiple aneurysms located in the posterior circulation may require additional attention during follow-up.

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