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Clinical Study

Risk of growth in unruptured intracranial aneurysms: A retrospective analysis

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ABSTRACT

This study sought to define the growth of unruptured intracranial aneurysms, in particular the frequency of growth and the characteristic factors predictive of growth. Two hundred and eight patients with 285 unruptured aneurysms were followed. Electronic records and angiographic films were obtained for measurements of aneurysm size. The mean follow-up duration was 21.8 months (range 1.1–137.3 months). Growth was identified in 95 of the 285 aneurysms (33.3%). The cumulative incidence of growth predicted using the Kaplan-Meier method was 22.7% at 1 year, 35.2% at 2 years, and 47.7% at 3 years. Aneurysm growth was significantly associated with a patient history of excessive alcohol consumption ($p = 0.04$). A high incidence of growth can be seen in conservatively managed aneurysms with time. Consequently, continual follow-up is recommended to monitor for aneurysmal growth.

1. Introduction

Despite considerable advances in diagnosis, treatment and management, the overall outcomes associated with subarachnoid haemorrhage (SAH) remain poor, with mortality rates of 40–50%, and significant neurological impairment and disability in one-third of patients who survive.[1–5] As 85% of SAH is caused by aneurysmal rupture, treatment of unruptured intracranial aneurysms may be a definitive method to reduce the high mortality and morbidity rates.[5]

Identification of aneurysms that would benefit from treatment requires consideration and recognition of risk factors for aneurysmal rupture. Many studies have considered risk factors such as aneurysm size, location and cigarette smoking,[6–12] but few have examined the growth of an intracranial aneurysm.

The growth of an aneurysm has been associated with rupture;[10,13,14] however, evidence is limited due to the few clinical studies available. A further in-depth understanding of growth and its characteristics is necessary in investigating risk factors for aneurysm rupture.

This study sought to retrospectively analyze the growth of unruptured intracranial aneurysms in a multicultural Australian population.

2. Materials and methods

2.1. Identification of patients

The records of patients with verified intracranial aneurysms managed at the Royal Melbourne Hospital over the 10 years between January 1997 and December 2006 were reviewed.

Unruptured intracranial aneurysms that had not been treated with any neurosurgical or endovascular intervention were included. Aneurysms with a history suspicious of haemorrhage were excluded if no documentation existed to prove otherwise. All intracranial aneurysms, including extradural, were included. Mycotic, neoplasic or traumatic aneurysms were excluded, as well as aneurysms lacking follow-up angiography.

2.2. Data collection and follow-up

Data were collected for all patients regarding: location of aneurysm in relation to the parent artery, aneurysm size at diagnosis, patient age at diagnosis, patient gender, history of previous or current cigarette smoking, documented hypertension or use of antihypertensive medication, previous history of aneurysmal SAH, family history of verified intracranial aneurysms in first degree relatives, and excessive alcohol consumption.

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Aneurysm size was followed up using electronic reports and angiographic films, until subsequent aneurysm rupture, treatment, patient death or until last contact.

2.3. Study population

The study included 208 patients (54 male and 154 female) with 285 unruptured intracranial aneurysms. A total of 150 patients had one unruptured aneurysm, 48 had two aneurysms, five had three aneurysms, two had four aneurysms, two had five aneurysms, and one had six aneurysms. The age of the patients at the beginning of follow-up ranged from 14.0 years to 80.5 years (mean 51.1 years).

2.4. Location and initial size of aneurysms

The unruptured aneurysms were located in the following sites: the cavernous segment internal carotid artery for 24 aneurysms, the distal internal carotid artery and posterior communicating artery for 104 aneurysms, the anterior communicating artery for 34 aneurysms, the anterior cerebral artery for 11 aneurysms, the middle cerebral artery for 64 aneurysms, the posterior cerebral artery for 8 aneurysms, the basilar artery and superior cerebellar artery for 24 aneurysms, and the vertebral artery and posterior inferior cerebellar artery for 16 aneurysms.

Table 1
Patient and aneurysm characteristics at the beginning of follow-up

Characteristic	
Patient	
No. of patients	208
Total no. of aneurysms	285
Age (years)	
Mean	51.1
Range	14.0–80.5
Sex (No. (%))	
Male	54 (26.0)
Female	154 (74.0)
Cigarette smoking (No. (%))	61 (14.9)
Hypertension (No. (%))	76 (36.5)
Prior aneurysmal SAH (No. (%))	63 (30.3)
Family history of aneurysms (No. (%))	5 (2.4)
Excessive alcohol consumption (No. (%))	6 (2.9)
Aneurysm	
Location of aneurysm (No. (%))	
Cavernous segment ICA	24 (8.4)
Distal ICA + PCoA	104 (36.5)
ACoA	34 (11.9)
ACA	11 (3.9)
MCA	64 (22.5)
PCA	8 (2.8)
BA + SCA	24 (8.4)
VA + PICA	16 (5.6)
Aneurysm size (mm)	
Median	4.0
Range	<2.0–24.0
Aneurysm size (No. (%))	
<2.0 mm	61 (21.4)
2.0–4.9 mm	152 (53.3)
5.0–9.9 mm	49 (17.2)
10.0–14.9 mm	13 (4.5)
15.0–19.9 mm	5 (1.8)
20.0–24.9 mm	5 (1.8)
⩾25.0 mm	0 (0.0)

ACA = anterior cerebral artery, ACoA = anterior communicating artery, BA = basilar artery, CI = confidence interval, ICA = internal carotid artery, MCA = middle cerebral artery, PCA = posterior cerebral artery, PICA = posterior inferior cerebellar artery, PCoA = posterior communicating artery, SAH = subarachnoid haemorrhage, SCA = superior cerebellar artery, VA = vertebral artery.

The study included aneurysms with initial diameters ranging from <2.0 mm to 24.0 mm. The median diameter of the 285 aneurysms was 4.0 mm (Table 1).

2.5. Statistical analysis

The incidence of growth was calculated as the number of aneurysms that grew divided by the number of aneurysms in the study. The cumulative incidence of growth was estimated by the Kaplan-Meier product limit method; with censoring of aneurysms that subsequently ruptured, received treatment, or did not exhibit growth at time of last contact. The univariate association of variables was tested by Fisher's exact two-tailed tests, with p values below 0.05 considered indicative of statistical significance.

3. Results

3.1. Follow-up duration and endpoints

The total follow-up duration was 6228.8 months (519.1 years). The individual follow-up for aneurysms ranged from 1.1 to 137.3 months (mean 21.8 months), with 147 aneurysms (51.6%) followed for 12 months, and 91 (31.9%) followed for 24 months. In 121 aneurysms (42.5%) follow-up terminated due to receiving treatment; 70 aneurysms receiving neurosurgical and 51 endovascular interventions. Three aneurysms ruptured during follow-up, and there were no patient deaths from haemorrhage or other causes.

3.2. Incidence of aneurysm growth

During the follow-up period, 95 of the 285 aneurysms (33.3%) increased in size; nine aneurysms (3.2%) decreased in size.

In the 95 aneurysms that increased in size, the mean time between initial imaging and angiographic documentation of growth was 15.9 months (range 0.5–91.0 months). The cumulative incidence of growth estimated using the Kaplan-Meier method was approximately 22.7% at 1 year after initial imaging, 35.2% at 2 years, and 47.7% at 3 years (Fig. 1).

3.3. Magnitude of aneurysm growth

The mean magnitude of growth for aneurysms was 47.7% (range 2.5–300.0%).

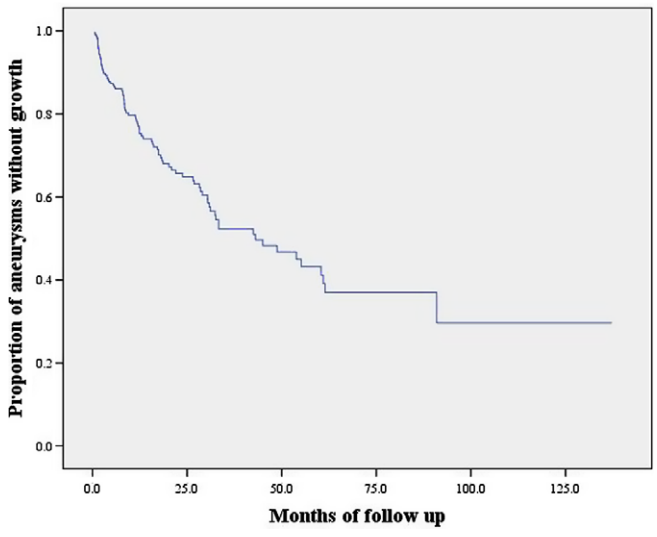

Fig. 1. The Kaplan-Meier analysis of growth of unruptured aneurysms.

3.4. Risk factors for aneurysm growth

Univariate analysis revealed excessive alcohol consumption to be a significant risk factor for aneurysm growth ($p = 0.04$). Growth was detected in 71.4% (5 of 7) of aneurysms associated with excessive alcohol consumption, compared to 32.4% (90 of 278) of aneurysms without.

The mean age of patients whose aneurysms enlarged was 49.6 years (range 16.9–76.3 years). These patients tended to be younger than those whose aneurysms did not grow; however, this difference did not reach statistical significance ($p = 0.06$).

The aneurysms that enlarged were located as follows: cavernous segment internal carotid artery for 10 aneurysms, distal internal carotid artery and posterior communicating artery for 35, anterior communicating artery for nine, anterior cerebral artery for three, middle cerebral artery for 19, posterior cerebral artery for three, basilar artery and superior cerebellar artery for 10, and vertebral artery and posterior inferior cerebellar artery for six aneurysms. Statistical analysis revealed that differing location was not associated with aneurysm growth.

Aneurysm growth was not significantly associated with female sex ($p = 0.6$), cigarette smoking ($p = 0.8$), hypertension ($p = 0.2$), prior aneurysmal SAH ($p = 0.5$), family history of intracranial aneurysms ($p = 0.7$), or aneurysm size of 10 mm or greater ($p = 0.4$) (Table 2).

3.5. Subsequent aneurysm rupture

During the 519.1 years of follow-up, 3 of the 285 aneurysms (1.05%) ruptured, resulting in an annual incidence of rupture of about 0.6%. Two of the ruptured aneurysms were located on the anterior communicating artery, and one at the origin of the superior cerebellar artery. These aneurysms were initially 8.0 mm, 1.0 mm, and 5.4 mm in size respectively. Only the 5.4 mm superior cerebellar artery aneurysm had increased in size prior to rupture.

4. Discussion

4.1. Incidence of growth

The study reports an overall incidence of growth of 33.3%, suggesting that a considerable number of aneurysms exhibit growth at some stage in their development. There have been few studies directly addressing the incidence of growth in unruptured intracranial aneurysms. Kamitani et al. previously reported a much higher overall incidence of 95%;[13] however, their study included previously ruptured and/or incompletely operated aneurysms, and it may be difficult to compare growth in these aneurysms to growth in typically unruptured aneurysms, which have not undergone any intervention.

Table 2
Aneurysm growth in relation to characteristics at the beginning of follow-up

Characteristic	No. of aneurysms with growth*/Total (%)	Odds ratio (95% CI)	*p* value
Patient			
Age (years)			
⩾51.1 (mean)	38/137 (27.7)	0.6 (0.4–1.0)	0.06
<51.1	57/148(38.5)	1.6 (1.0–2.7)	0.06
Sex			
Female	75/218 (34.4)	1.2 (0.6–2.2)	0.6
Male	20/67 (29.9)		
Cigarette smoking			
Yes	30/86 (34.9)	1.1 (0.7–1.9)	0.8
No	65/199 (32.7)		
Hypertension			
Yes	39/101 (38.6)	1.4 (0.9–2.4)	0.2
No	56/184 (30.4)		
Prior aneurysmal SAH			
Yes	26/87 (29.9)	0.8 (0.5–1.4)	0.5
No	69/198 (34.8)		
Family history of aneurysms			
Yes	4/10 (40.0)	1.3 (0.4–4.6)	0.7
No	91/275 (33.1)		
Excessive alcohol consumption			
Yes	5/7 (71.4)	5.2 (1.1–23.7)	0.04
No	90/278 (32.4)		
Aneurysm			
Location of aneurysm			
Cavernous segment ICA	10/24 (41.7)	1.5 (0.6–3.4)	0.4
Distal ICA + PCoA	35/104 (33.7)	1.0 (0.6–1.7)	1.0
ACoA	9/34 (26.5)	0.7 (0.3–1.5)	0.4
ACA	3/11 (27.3)	0.7 (0.2–2.6)	0.8
MCA	19/64 (29.7)	0.8 (0.4–1.5)	0.5
PCA	3/8 (37.5)	1.2 (0.3–4.7)	1.0
BA + SCA	10/24 (41.7)	1.5 (0.6–3.4)	0.4
VA + PICA	6/16 (37.5)	1.2 (0.4–3.3)	0.8
Aneurysm size (mm)			
⩾10.0	10/23 (43.5)	1.6 (0.7–3.7)	0.4
<10.0	85/262 (32.4)		

ACA = anterior cerebral artery, ACoA = anterior communicating artery, BA = basilar artery, CI = confidence interval, ICA = internal carotid artery, MCA = middle cerebral artery, PCA = posterior cerebral artery, PICA = posterior inferior cerebellar artery, PCoA = posterior communicating artery, SAH = subarachnoid haemorrhage, SCA = superior cerebellar artery, VA = vertebral artery.

* Within follow-up period of study.

The Kaplan-Meier method predicted a cumulative incidence of growth of 22.7% at 1 year after initial imaging, 35.2% at 2 years, and 47.7% at 3 years, indicating that the timing of growth is variable between aneurysms, possibly related to the presence or absence of risk factors, genetic differences and variable flow dynamics. Koffijberg et al. recently constructed a mathematical model of aneurysm growth.[15] This model suggests that aneurysm growth may be discontinuous, in which an aneurysm may have irregular episodes of growth, separated by periods of stability.

The importance of continual follow-up is confirmed by aneurysms that continued to show growth at times after 1 year. In this study, the longest interval to growth was 91.0 months after initial imaging, indicating that late changes can occur. Matsubara et al. recommended a follow-up period of at least 3 years for conservatively managed aneurysms.[16]

4.2. Risk factors for aneurysm growth

In this study univariate analysis identified excessive alcohol consumption to be significant for aneurysm growth. Excessive alcohol consumption may also be an independent risk factor for haemorrhagic stroke and aneurysmal SAH;[17,18] however, the role of alcohol consumption in aneurysm growth has not been previously recognised,[14] and the mechanism by which it may increase the risk of growth is unclear. Previous studies have reported an induction of tumour necrosis factor-alpha (TNF-alpha) in response to alcohol consumption.[19–21] TNF-alpha may contribute to aneurysm growth through activation of signalling pathways, with infiltration of inflammatory cells and mediators into the arterial wall.[19] Inflammation may progressively weaken the arterial wall, and thus contribute to aneurysm growth.

This present study has shown a trend towards an association between aneurysm growth and younger patient age at the beginning of follow-up. However, excessive alcohol consumption, larger aneurysm size and other factors may have had confounding effects. As in the report of Juvela et al., younger patients have significantly larger aneurysms.[10]

Other studies have reported various risk factors for aneurysm growth: Juvela et al. reported cigarette smoking and female sex as significant risk factors for growth,[14] whereas Matsubara et al. found that growth was associated with location at the basilar artery bifurcation or the internal carotid artery, or an aneurysm size of $\geqslant$10 mm.[16] These factors were not found to be significant in the present study. This may be due to differences in the patient population, including racial or genetic characteristics, or differences in geographic location. These studies have been principally based in Japan and Finland; higher incidences of unruptured intracranial aneurysms and higher rates of SAH have been published for the Japanese and Finnish populations, and it is possible that differences in these patient populations may also apply to aneurysm growth when compared to the Australian population used in this study.

4.3. Association between growth and rupture

Aneurysm growth was not associated with rupture in this study. This finding was based on limited univariate analysis; only 3 aneurysms had ruptured in the study. The incidence of rupture in this study, approximately 0.6% per year, may have been lowered due to a relatively large proportion of smaller aneurysms. Wiebers et al. reported in 1981 that typically 80% of unruptured intracranial aneurysms are less than 10.0 mm in size, including 30% of 2.0 mm to 4.9 mm in size.[6] In comparison, most (91.9%) aneurysms in this study were initially less than 10.0 mm in size, and 53.3% were 2.0 mm to 4.9 mm in size. In addition, this study included no giant aneurysms (greater than 25.0 mm). Giant aneurysms have an exceptionally high rate of rupture and subsequent mortality: 43% to 50%.[22–24] In practice these aneurysms are frequently lost to follow-up or undergo surgical treatment, thus limiting their availability and potential for study inclusion.

For the three ruptured aneurysms, size measurements may have been underestimated at the time of rupture. An aneurysm may decrease in size at or shortly after the time of rupture, due to collapse or thrombus formation.[25] Thus, the three ruptured aneurysms might have had additional growth, unmeasureable at the time of rupture.

The surgical examination of aneurysms has revealed that fast-growing aneurysms generally have thinner walls, possibly indicating a predisposition of these aneurysms to rupture.[13] Clinically, little data are available: Juvela et al.'s study is one of the few clinical studies demonstrating an association between growth and rupture.[10] Other studies have not shown growth to be associated with rupture, due to rupture rates comparable to or lower than in this study.[16,26]

4.4. Selection bias

The results of this study may be substantially biased by its patient selection. The study does not represent all unruptured intracranial aneurysms that are encountered in daily practice. Notably, differences in aneurysm size have been observed in the patients, and it is likely that other characteristics – both those measured and those unmeasured in the study – may also be relevant. However, it is highly unlikely that a study will be conducted without selection bias of some kind, due to ethical and practical considerations.

4.5. Measurement bias

Measurements of aneurysm size are subject to interobserver differences when reading angiograms. However, due to standardised procedures established for angiogram measurements, these differences may be negligible. A study by Forbes et al. in 1996, utilizing standardised procedures to measure aneurysms, had reported a high correlation between different angiogram readers, throughout a range of aneurysm sizes.[27]

4.6. Usefulness of a retrospective study

In order to minimise error, patient records in this study had been reviewed with predefined definitions for key variables and case selection criteria. However, analysis in this study was limited by the data available retrospectively. The completeness of patient data, in particular patient characteristics and risk factors, is unknown and relies solely on recorded information. Scientific accuracy is also weakened by use of electronic records. To further evaluate the growth of aneurysms and the findings proposed by this study, large prospective studies would be ideal.

5. Conclusions

The present study demonstrates a high incidence of growth of unruptured aneurysms over time. The timing of growth varies between aneurysms, and continual follow-up is required for those lesions that have not shown growth in the short term; at a minimum, repeat imaging should be conducted annually. Excessive alcohol consumption may increase the risk of aneurysm growth; however, further studies are required to explore this association.

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