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Original Article

Difference in aneurysm characteristics between ruptured and unruptured aneurysms in patients with multiple intracranial aneurysms

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Abstract

Background: The risk of aneurysmal rupture is dependent upon numerous factors, however, there are inconsistencies in the results between studies, which may be due to confounding factors. This can be avoided by comparing the characteristics of ruptured and unruptured aneurysms within the same patient. We sought to analyze the aneurysm characteristics of patients with acute aneurysmal subarachnoid hemorrhage (SAH) and multiple intracranial aneurysms.

Methods: We reviewed our prospectively maintained institutional database, between 01/10/2007 and 01/01/2017, for all patients with confirmed SAH and >1 aneurysm. We recorded the size, location, and morphology and calculated secondary geometric indices such as bottleneck factor and aspect ratio.

Results: During the study period, a total of 694 patients with aneurysmal SAH were admitted to our institution. We identified 113 patients (74.3% female, average age 51.7 ± 12.3). The majority of patients had only one associate unruptured aneurysm (79.6%). The average unruptured aneurysm was 3.1 ± 1.5 mm and the average ruptured aneurysm was 5.7 ± 2.7 mm ($P < 0.001$). In the multivariate analysis, aneurysm location, aneurysm morphology, and size were independently associated with rupture. A complex aneurysm morphology was the strongest risk factor for rupture (OR, 29.27; 95% CI 14.33–59.78; $P < 0.001$) with size >7 mm (OR, 17.74; 95% CI 4.07–77.35; $P < 0.001$), and AcomA location also showing a strong independent association.

Conclusion: Size plays an important part in determining rupture risk, however, other factors such as location and in particular morphology must also be considered. We believe that the introduction of vessel wall imaging will help to risk stratify aneurysms.

Key Words: Aneurysm morphology, aneurysm, aspect ratio, bottleneck factor, lobulation, subarachnoid hemorrhage

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INTRODUCTION

Approximately 2–3% of the population harbours an unruptured intracranial aneurysm, and approximately 30% of the patients have multiple aneurysms.[11,18,36,58] With increased utilization of noninvasive imaging, the detection of these aneurysms has become commonplace. Following the detection of an incidental unruptured aneurysm, an evaluation must be made as to the likely rupture risk, and this needs to be weighed against the potential risk of any treatment strategy. However, accurate prediction of rupture risk is difficult and inaccurate. A recent pooled analysis by Grieving *et al*.[17] highlighted several predictors of rupture including geographic region (Finnish, Japanese), age, hypertension, history of subarachnoid hemorrhage (SAH) from another aneurysm, and aneurysms >7 mm, and aneurysms originating from the vertebrobasilar arteries, with the anterior or posterior communicating arteries carrying the highest risk.

Identifying which aneurysms, regardless of size, are prone to rupture is the key to optimizing management. A variety of different factors such as aneurysm shape, size ratio, and flow angles[4,5,13,26,29,30,35,37,45,46,55,59,62,65,66] have been identified as playing a possible role in rupture risk; however, the results between studies are not always consistent. More recently it has been shown that irregular shape has the strongest association with rupture risk.[8] Beyond anatomical classification, advanced imaging techniques may provide further enlightenment regarding the underlying pathological processes occurring in the aneurysm wall that may precede rupture.[6,7,15,19,21,38]

An inability to control for confounding factors may cause much of the difficulty when using a case-control design when analyzing patients with ruptured aneurysms to those with unruptured aneurysms. This can be avoided by comparing the characteristics of ruptured and unruptured aneurysms within the same patient.

We sought to analyze the morphological characteristics of ruptured and unruptured aneurysms within the same patient from a single institution.

MATERIALS AND METHODS

Study population

We reviewed our prospectively maintained institutional database, which includes consecutive patients with confirmed SAH. We extracted all patients who presented with acute aneurysmal SAH confirmed by computed tomography (CT) or magnetic resonance imaging (MRI). We included all patients between 01/10/2007 and 01/01/2017 with confirmed SAH and more than one intracranial aneurysm confirmed on diagnostic subtraction cerebral angiography (DSA). We excluded patients without confirmed aneurysmal SAH (missing CT/MRI or DSA), patients presenting with fusiform, dissecting, mycotic, and partially thrombosed aneurysms, as well as likely pseudoaneurysms secondary to trauma.

Imaging

All patients underwent either CT or MRI to confirm the presence of SAH and CT or MR angiography to confirm the presence of an aneurysm. All patients presenting with SAH underwent DSA with complete 6-vessel angiography. In addition to the standard Towne's and lateral projections, dedicated projections of all aneurysms were performed as per our standard practice.

Aneurysmal location, measurements, and morphological characteristics

The location of the ruptured and unruptured aneurysms was categorized into internal carotid artery (ICA), anterior cerebral artery territory (ACA), anterior communicating artery (AcomA), posterior communicating artery (PcomA), middle cerebral artery (MCA), vertebral artery (VA), posterior inferior cerebellar artery (PICA), basilar artery (BA), and the posterior cerebral artery (PCA).

The maximum neck width, dome width, and dome height were recorded from the DSA using standard techniques. We calculated secondary geometric indices including the aspect ratio (AR) – the ratio of the dome height to the neck width, the height to width ratio, and the bottleneck factor – the ratio of dome width to neck width.[20,37]

Aneurysm shape was categorized as spherical (if the width was at ≥80% of the dome height), lobulated (where the lobules were smooth and of approximately the same size), or complex/irregular (when the lobules were asymmetric or multiple lobules were seen).

Statistical analysis

Statistical analysis was performed using Stata/IC 14.2 for Windows (StataCorp LP, 4905 Lakeway Drive, College Station, TX 77845, USA). Numeric variables were presented in the form of mean ± SD (min − max) and categorical variables as frequencies. Correlative analyses were performed using the Mann–Whitney U test, Fisher's exact test, or the Chi-square test. P values less than 0.05 were considered statistically significant.

RESULTS

During the study period, a total of 694 patients with aneurysmal SAH were admitted to our institution. We identified 113 patients who met our inclusion and exclusion criteria. The majority of the patients were female (n = 84, 74.3%). The average age of the patients was 51.7 ± 12.3 years (range 21.8–85.6 years).

The majority of the patients had only one associate unruptured aneurysm (79.6%), but up to 5 associated unruptured aneurysms were recorded. The total number of associated unruptured aneurysms was 148. The number of associated aneurysms is shown in Table 1.

Aneurysmal size, location, and morphology

The average size of the unruptured aneurysms was 3.1 ± 1.5 mm (range 1.0–9.5 mm), and the average size of the ruptured aneurysms was 5.7 ± 2.7 mm (range 1.8–19.0 mm). There was a significant difference in the size of ruptured and unruptured aneurysms ($P < 0.001$). The unruptured aneurysms were overwhelmingly <7 mm (n = 146, 98.6%), with the majority being <5 mm (n = 131, 88.5%). Similarly, the majority of the ruptured aneurysms were also <7 mm (n = 91, 80.5%) and close to half were smaller than 5 mm (n = 52, 46.0%). The AR was significantly larger in ruptured aneurysms (1.8 ± 0.7, range 0.6–3.8 vs. 1.5 ± 0.5 range 0.4–2.9, $P < 0.001$) between the two cohorts. Similarly, the bottleneck factor was also significantly larger in ruptured aneurysms (1.7 ± 0.6, range 0.7–3.8 vs. 1.3 ± 0.4, range 0.1–3.0, $P < 0.001$).

The majority of the aneurysms were located in the anterior circulation (n = 227, 86.9%) with the majority of the ruptured aneurysms located in the anterior circulation (n = 94, 83.9%). The most frequent location for both the unruptured and ruptured aneurysms was the MCA (n = 54, 36.0% and n = 33, 29.5%, respectively), with the ICA representing the second most frequent location of unruptured aneurysms and the AcomA representing the second most frequent location for ruptured aneurysms.

The majority of the unruptured aneurysms were smooth and had a regular morphology (n = 113, 76.4%) compared to only 15.9% of ruptured aneurysms. Conversely, a significant majority of ruptured aneurysms were irregular (n = 87, 77.0%) with a minority of unruptured aneurysms having an irregular morphology (n = 20, 13.5%). The aneurysm characteristics are shown in Table 2.

In the multivariate analysis and after matching for age and sex, aneurysm location, aneurysm morphology, and size were independently associated with rupture. A complex aneurysm morphology was the strongest risk factor for rupture (OR, 29.27; 95% CI, 14.33–59.78; $P < 0.001$) with size >7 mm (OR, 17.74; 95% CI, 4.07–77.35; $P < 0.001$) and AcomA location also showing a strong independent association. Interestingly, although a lobulated appearance showed an increased risk, this did not reach statistical significance (OR, 3.45; 95% CI, 1.27–9.37; P < 0-001 0.015), suggesting that an increasingly irregular morphology is important in the risk of rupture. The characteristics of the two cohorts after matching for age and sex are shown in Table 3.

Table 1: The number of associated unruptured aneurysms seen in patients with at least one ruptured saccular intracranial aneurysm

No. of ass. aneurysms	Female (n=84)	Male (n=29)	Total (n=113)
1	67 (79.8%)	23 (79.3%)	90 (79.6%)
2	12 (14.3%)	5 (17.2%)	17 (15.0%)
3	1 (1.2%)	0 (0%)	1 (0.9%)
4	3 (3.6%)	1 (3.4%)	4 (3.5%)
5	1 (1.2%)	0 (0%)	1 (0.9%)

Table 2: Aneurysm location, size, and morphological characteristics

	Unruptured (n=148)	Ruptured (n=113)	OR*	95%-CI*	P*
Location					
ICA	32 (21.6%)	14 (12.5%)	Ref		
PcomA	26 (17.6%)	19 (17.0%)	1.67	0.70-3.96	0.244
MCA	54 (36.5%)	33 (29.5%)	1.40	0.65-3.00	0.391
AcomA	9 (6.1%)	24 (21.4%)	6.10	2.26-16.42	<0.001
ACA	12 (8.1%)	4 (3.6%)	0.76	0.21-2.78	0.680
PICA	2 (1.4%)	3 (2.7%)	3.43	0.51-22.84	0.203
Basilar artery	10 (6.8%)	15 (13.4%)	3.43	1.24-9.48	0.018
PCA	3 (2.0%)	0 (0%)	-	-	
Location					
Anterior circulation	133 (89.9%)	94 (83.9%)	Ref		
Posterior circulation	15 (10.1%)	18 (16.1%)	1.70	0.81-3.54	0.158
Morphology					
1 regular	113 (76.4%)	18 (15.9%)	Ref		
2 lobulated	15 (10.1%)	8 (7.1%)	3.35	1.24-9.03	0.017
3 complex, blebs	20 (13.5%)	87 (77.0%)	27.32	13.63-54.77	<0.001
Morphology					
Regular	113 (76.4%)	18 (15.9%)	Ref		
Nonregular	35 (23.6%)	95 (84.1%)	17.05	9.07-32.03	<0.001
Size					
≤7	146 (98.6%)	91 (80.5%)	Ref		
>7 mm	2 (1.4%)	22 (19.5%)	17.67	4.06-77.01	<0.001
Size					
≤5	131 (88.5%)	52 (46.0%)	Ref		
>5 mm	17 (11.5%)	61 (54.0%)	9.05	4.84-16.92	<0.001

DISCUSSION

A variety of factors have been implicated in the rupture of aneurysms. Aneurysmal dome size is naturally one of the most widely recognized risk factors, and at the moment size still remains the most widely used geometrical factor when determining the decision to treat. Aneurysms over 10 mm carry a 1.9% per year risk of rupture; however, size alone cannot be used as the only measure upon which to base treatment decisions, and recent studies have shown that size alone is not a good predictor.[14,42] In the anterior circulation, the ISUIA II investigators recommend a size threshold of 7 mm as the starting point from which intervention should be considered.[56,61]

Table 3: The characteristics of ruptured and unruptured aneurysms after age and sex matching

	Unruptured (*n*=148)	Ruptured (*n*=113)	OR*	95%-CI*	*P**
Location					
ICA	32 (21.6%)	14 (12.5%)	Ref		
PcomA	26 (17.6%)	19 (17.0%)	1.78	0.74-4.31	0.199
MCA	54 (36.5%)	33 (29.5%)	1.44	0.67-3.11	0.351
AcomA	9 (6.1%)	24 (21.4%)	6.22	2.30-16.81	<0.001
ACA	12 (8.1%)	4 (3.6%)	0.77	0.21-2.81	0.693
PICA	2 (1.4%)	3 (2.7%)	3.89	0.56-26.75	0.168
Basilar artery	10 (6.8%)	15 (13.4%)	3.58	1.28-9.99	0.015
PCA	3 (2.0%)	0 (0%)	-	-	
Location					
Anterior circulation	133 (89.9%)	94 (83.9%)	Ref		
Posterior circulation	15 (10.1%)	18 (16.1%)	1.72	0.82-3.58	0.151
Morphology					
1 regular	113 (76.4%)	18 (15.9%)	Ref		
2 lobulated	15 (10.1%)	8 (7.1%)	3.45	1.27-9.37	0.015
3 complex, blebs	20 (13.5%)	87 (77.0%)	29.27	14.33-59.78	<0.001
Morphology					
Regular	113 (76.4%)	18 (15.9%)	Ref		
Nonregular	35 (23.6%)	95 (84.1%)	0.12	0.04-0.32	<0.001
Size					
≤7	146 (98.6%)	91 (80.5%)	Ref		
>7 mm	2 (1.4%)	22 (19.5%)	17.74	4.07-77.35	<0.001
Size					
≤5	131 (88.5%)	52 (46.0%)	Ref		
>5 mm	17 (11.5%)	61 (54.0%)	9.06	4.84-16.95	<0.001

However, in just over one-third of the patients who present with SAH, the source of the bleed is an aneurysm that measures less than 5 mm in maximal diameter.[25] Furthermore, in other studies, even smaller aneurysms have been seen to rupture. For example in the study of Ishibashi *et al.*,[24] of 19 patients who had a documented rupture during the follow-up period, 14 aneurysms were 5 mm or smaller and of these 6 aneurysms were only 3 mm in maximal diameter. In the study of Backes *et al.*[3] that also looked at patients presenting with SAH with multiple intracranial aneurysms, in 36 of the patients (29%), the largest aneurysm was not the culprit and in 34 of these patients the aneurysm was <7 mm. In our series, the vast majority of ruptured aneurysms were <7 mm with nearly 50% of ruptured aneurysms being <5 mm (n = 52, 46.0%). Therefore, while aneurysmal size is no doubt important, the situation is more complex.[2,14,16,39,42]

The size ratio, introduced by Dhar *et al.*,[14] which is defined as the maximum height of the dome divided by the average parent vessel diameter, seeks to marry the size of the aneurysm and its location. In the study of Dhar *et al.*, this ratio was found to be a significant predictor of rupture with a sensitivity of 75% and specificity of 83%, and on multivariate logistic regression only the size ratio and undulation index were shown to remain significant. Rahman *et al.* have shown similar findings as have other investigators, and overall there is agreement that size ratio is an important estimator of rupture risk.[14,44,46,53] Although we did not assess the size ratio, the AcomA location has a significantly higher risk of rupture than many other locations and the size ratio of AcomA aneurysms has been proposed as an explanation for this tendency.[63] High AR is another feature associated with ruptured aneurysms.[31,37,47,55,60] One explanation that has been proposed is that the smaller neck seen in high AR aneurysms seems to reflect a lower intra-aneurysmal flow, and this subsequently raises the risk of rupture; however, because a low blood flow could also promote thrombosis, the real reason may be far more complex.[51,65] This was also seen in our data with a higher AR seen in the ruptured aneurysms than in the unruptured aneurysms. There is emerging evidence to suggest that high AR aneurysms are associated with low wall shear stress (WSS) and larger areas of low WSS within aneurysms, and these findings correlated with rupture.[41] Despite this we believe the true relationship between AR and rupture remains elusive and further work is required.

Irregular shape is another important variable linked to rupture. A Japanese observational study demonstrated that unruptured aneurysms with daughter sacs have a higher rupture rate than aneurysms with regular shapes,[54] and in the recent study of Björkman *et al.*[8] irregular shape showed the strongest association with rupture (Odds ratio 90.3; CI 47.0–173.5), which added to previous work published by this group demonstrating similar findings.[32] Other groups have shown similar associations between aneurysm irregularity and rupture.[1,23,33] The exact reason that irregularity is associated with rupture is still debated with some evidence to suggest that there is higher shear stress at or adjacent to blebs,[35,54] and an inherent weakness in the wall of the aneurysm at the site of the irregularity. Our results are similar with irregular morphology showing the strongest association with rupture.

Applying the results of post-rupture morphological analysis to determine the risk of rupture relies on the premise that post-rupture morphology is not significantly altered from the pre-rupture state.[65] However, data from several small studies suggest that this assumption may not be accurate.[28,43,48,64] A recent nationwide retrospective review from Norway sought to further investigate this phenomenon.[49] In this study, Skodvin *et al.* retrospectively analyzed 29 aneurysms with a median time span of 12 months between the pre and post-rupture imaging. They showed that there was an increase in the size of the aneurysm post rupture but also that the ruptured aneurysms changed morphology with 59% of aneurysms demonstrating ≥1 daughter sac post-rupture compared to 31% demonstrating ≥1 daughter sac pre-rupture ($P = 0.005$). There was a similar change in the aspect ratio of aneurysms with median aspect ratio posture of 1.9 compared to 1.5 pre-rupture. The authors concluded that the results do not support the assumption that post-rupture morphology is representative of pre-rupture morphology and that the post-rupture morphology will reflect any recent changes in the size or shape that occur prior to rupture. These findings concur with others suggesting that aneurysms grow over time, with periods of stability and potentially rapid growth, and a nonconstant risk of rupture over time.[9,12,50] Given that aneurysm growth and morphological changes are strong risk factors for rupture and that the increase in rupture risk may be between 12 and 24-fold greater,[10,52,57] it is important to determine which aneurysms are unstable from those that are stable. One promising technique to determine which aneurysms are unstable is contrast-enhanced vessel wall MRI.

Routine imaging with MRI or CT angiography is the accepted standard of care for patients with small aneurysms with treatment considered if there are signs of growth. There is an increasing awareness that imaging of the wall may help to delineate which aneurysms are at risk of growth and rupture prior to any actual morphological change. One technique that shows early promise is contrast-enhanced black blood vessel wall MRI. Several cases and case series have been published that have shown a high accuracy in determining which aneurysm has ruptured in cases of multiple aneurysms.[7,27,34] Omodaka *et al*.[40] recently published their series that sought to identify whether aneurysms wall enhancement could identify the site of rupture in patients with multiple aneurysms. Contrast-enhanced black blood vessel wall MRI was performed in 26 patients with SAH harbouring 62 aneurysms. They showed that aneurysm size (OR 3.62, 95% CI 1.17–11.24), high aspect ratio (OR 15.81, 95% CI 2.07–120.58), irregular shape (OR 21.08, 95% CI 2.78–159.61) and contrast-enhancement (OR 16.65, 95% CI 2.19–126.50) were all associated with rupture status. Furthermore, they showed that after adjustment for aneurysm size contrast enhancement, irregular shape, and high AR remained strongly associated with rupture status. In the series of Nagahata *et al*.,[38] 15 patients demonstrated contrast enhancement at the apex or on a bleb of the suspected ruptured aneurysm. Seven of these 15 cases underwent surgical clipping and in all cases the rupture point correlated with the point of enhancement, and this study showed that not only can this imaging method demonstrate the culprit aneurysm but perhaps even the point of rupture. Although this information is no doubt useful, the need to potentially identify unruptured aneurysms prior to rupture would undoubtedly be more useful. Edjlali *et al*.[15] used black-blood vessel wall MRI to evaluate stable and unstable aneurysms. Unstable aneurysms were defined as those that were symptomatic or evolving in comparison to previous imaging, e.g., showed an increase in size, new lobulations etc., None of the aneurysms were ruptured at the time of recruitment into the study. In these unstable aneurysms, circumferential aneurysmal wall enhancement (CAWE) was seen in 79% of the cases ($n = 14$) whereas CAWE was seen in only 28.5% of patients with stable aneurysms (22/77) ($P < 0.0001$). Similarly, Hu *et al*.[22] showed that there was a strong correlation between aneurysm wall enhancement and symptomatic status on contingency table tests.

Our study is limited by the inherent weaknesses of a retrospective study design and the fact that visual confirmation of the ruptured aneurysm was not obtained in all aneurysms. A further limitation is that the measured variables such as irregularity and size may be a result of aneurysm rupture rather than a cause. We believe that future prospective studies should include aneurysm wall imaging preferably with black blood contrast-enhanced MRI. These studies may help to highlight the potential to detect inflammation and wall changes prior to rupture in aneurysms irrespective of size, location, etc., and help to risk stratify patients appropriately.

CONCLUSION

Aneurysm size is important in determining the risk of rupture; however, the morphology of aneurysms is also extremely important, and as others have reported the shape of an aneurysm may be more important in determining its rupture risk. We believe that rather than relying on size alone we must consider a larger number of features when determining the treatment strategy for our patients. As has been shown the pre and post-rupture appearance cannot be assumed to be the same, and a pre-rupture evaluation of the aneurysm wall is essential in accurately risk stratifying patients.

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Conflicts of interest
There are no conflicts of interest.

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